POULSSON'S TEXT-BOOK

OF

PHARMACOLOGY

AND

THERAPEUTICS

Second English Edition thoroughly Revised

by

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LONDON

WILLIAM HEINEMANN

(MEDICAL BOOKS) LTD.

1938

ABBREVIATIONS

B.P. . . .	British Pharmacopœia.
U.S.P. . . .	United States Pharmacopœia.
B.P.C. . . .	British Pharmaceutical Codex.
N.F. . . .	National Formulary of the American Pharmaceutical Association.

Printed in Great Britain

PREFACE TO SECOND EDITION

THE revised edition of this book is based upon the British Pharmacopœia, 1932 (including the Addendum to the B.P. published in 1936) and the United States Pharmacopœia XI (1936). This has necessitated considerable changes in the lists of official preparations.

While important advances have been made with new drugs, ideas have changed concerning many of the older remedies. In so far as revision has been necessary to include these changes, the book may no longer be typical of what the late Professor Dixon termed "the Continental atmosphere." Nevertheless, I have constantly endeavoured to preserve the Author's original style and to leave intact his lucid exposition of the principles of pharmacology.

A large number of non-official remedies have been retained. Frequently this has been justified by their intrinsic value, and, in any case, it is hoped that their inclusion will add to the value of the book as a work of reference for the practitioner. On the other hand, students beginning to read pharmacology are advised to omit these parts and to concentrate on the more important official remedies which are printed in heavy type.

It is a pleasure to acknowledge the help which I have received from my wife, and from my colleague, Dr. Andrew Wilson, whose wide knowledge of pharmacy has always been at my disposal.

STANLEY ALSTEAD.

GLASGOW.

PREFACE

OUR knowledge of the action of drugs and of the indications for their therapeutic employment has been gained in various ways. Clinical experience was originally the only guide. Subsequently an invaluable means of assistance was found in animal experiments, in which the fundamental actions are more clearly apparent and more readily analysed than at the bedside. Many of the more recent valuable contributions to our knowledge are also due to the constantly increasing employment of laboratory methods in clinical research. I have here endeavoured to bring together in a text-book of moderate dimensions such parts of this wide subject as are of most importance to the physician. In its preparation I have, in addition to periodical literature, made use of a number of manuals and text-books. In several chapters my statements are based in all essentials upon Schmiedeberg's classical work, "*Grundriss der Pharmakologie.*"

E. POULSSON.

CHRISTIANIA.

INTRODUCTION

CLASSIFICATION OF DRUGS

THE raw materials from the animal and vegetable kingdoms, artificially prepared products, and simple natural substances, with which the study of pharmacology is concerned, are so numerous, their nature is so varied, and their action often so composite, that a simple and rational classification is difficult to find. This is very soon apparent on a glance at a few text-books on the subject. It will then be seen that the classification varies in a multiplicity of ways, and that practically each author constructs a system of his own. A few have given up all endeavour to find a rational system, and simply follow the alphabet. The *natural-order classification*, which arranges the drugs according to the vegetable and animal families from which they come, has also had its adherents. That systems such as these are unsatisfactory is obvious. One plan of classification that is frequently met with in recent works is the *chemical*, which arranges the drugs in strict accordance with their position in the chemical system. This method is very attractive, but at present can be only imperfectly worked out, as some drugs contain widely different chemical substances, and the active constituents of others are not yet so accurately known as to allow of their being assigned a definite place. Moreover, it is not always the purely chemical configuration that determines the effects. Mannite, for instance, is an alcohol, but pharmacologically belongs to the laxative mineral salts, and is no more intoxicating in its action than the ordinary alcohol is laxative. The *therapeutic classification* is obvious, and is much used, but is certainly not the best. By this system remedies that are employed for various purposes must be mentioned in as many places. Caffeine, for instance, must appear among both heart and kidney remedies; and very frequently substances with essentially different actions are united simply because the external results are similar in appearance. In the group Diuretics the most heterogeneous substances are brought together, the only property they have in common being that of producing increased diuresis, while the manner in which this result is obtained is very often not a matter of indifference in the treatment of the patient. Such a system gives far too little insight into the mutual relationship and peculiar nature of

the remedies, and rather encourages a superficial view and treatment.

The so-called *pharmacological systems* represent an important advance towards a more perfect arrangement. They seek to collect the various remedies in natural groups according to their characteristic fundamental effects, just as modern zoology and botany arrange animals and plants in natural families according to their interrelationship, irrespective of superficial differences and similarities. In the strychnine group or family there are gathered, in accordance with this principle, those bodies whose predominant action is to produce spasms by increasing the reflex irritability; round cocaine as the centre are grouped those substances which have a paralysing action upon the sensory nerves; with curarine are placed poisons which have a corresponding action upon the terminations of the motor nerves; the chapter in which chloroform and alcohol appear also treats of those chemical compounds of which the characteristic feature is that they act in an especial manner, typical of all the members of the group, upon certain parts of the central nervous system so as to produce sleep and narcosis, etc., etc. In systems such as these, the new substances that are continually being admitted into the field of pharmacology allow, as a rule, of being easily classified, and their position is not altered too readily by changing therapeutic uses. It will be easily understood without further explanation that the classification of this enormous and heterogeneous mass of substances in natural pharmacological families or groups can hardly be perfect in every detail. This is especially true of the remedies that are not pure compounds, but raw products or drugs, such as leaves, bark, roots, of which the effects depend upon a mixture of sometimes unknown substances. In the case of remedies such as these, recourse must be had to purely practical-therapeutical points of view, and groups that are not very homogeneous must be formed (*e.g.* anthelmintics). For the rest the purely pharmacological classification frequently coincides with the chemical and therapeutic.

In this book the pharmacological system developed by Schmiedeberg will be followed in the main. The drugs will be divided into the following few principal sections:—

I. Organic remedies acting specifically after absorption.
II. Organic remedies acting locally.
III. Salts of light metals, alkalies, acids, halogens, oxidising media, etc.
IV. Heavy metals.
V. Ferments and foodstuffs.
VI. Antitoxins and bacterial products.

The first great section, to which many of the most important remedies and poisons belong, includes organic substances that are characterised by their specific effects after absorption on the nervous and muscular systems, while local effects are, as a rule, altogether absent or insignificant. A good many of the compounds belonging to this section, even when present in minute quantities, act injuriously upon all living tissues, and are then called protoplasmic poisons.

To the second main section belong numerous organic remedies that principally act locally, *i.e.* at the point of application, while the action after absorption is unimportant or, at any rate, is not utilised in medicine. Many of these remedies act, however, not only at the seat of application, but also at the seat of excretion, as there they once more acquire a sufficient concentration, whereas in the blood they are far too dilute to be capable of exerting any influence. They may be compared with the galvanic current, which has a great density where it enters and leaves the body through the electrodes, but within the body divides into innumerable current-loops.

The third and fourth main groups contain the inorganic bodies. The inorganic compounds differ from the organic, whose activity is due to the unchanged entire molecules, in that to a great extent they are subjected to dissociation ; it is most frequently through the products of dissociation that the characteristic action is brought about.

The fifth section is formed by digestive ferments and foodstuffs. Of these, pharmacology is concerned only with the few that are prepared for therapeutic purposes and prescribed in fixed doses.

The sixth section is concerned with antitoxins and bacterial products. Important advances have been made in our knowledge of these substances in the past few years, and serum and vaccine therapy now rank amongst the most important methods of treating and preventing disease.

I.—ORGANIC REMEDIES ACTING AFTER ABSORPTION

1. NARCOTICS OF THE METHANE SERIES

General Characters

Innumerable compounds of the fatty series (*methane derivatives*), if they are absorbed from the intestinal canal or volatilise at an ordinary temperature, and in the form of gas can be absorbed through the lungs, exhibit a uniform action upon the organism, namely, *a paralysis of the central nervous system produced in a particular manner and occurring in a definite sequence.*

First—in many cases after a preliminary stage of excitement—the *brain* is paralysed, drowsiness, unconsciousness, sleep, and cessation of spontaneous movement supervening. Sensibility to pain continues as long as consciousness remains. In this way the substances of the fatty series differ markedly from morphine, which also paralyses the cerebrum, but in another manner, the feeling of pain being dulled or ceasing, while the rest of the cerebral functions are still almost unaffected.

Paralysis of the *spinal cord* then occurs, characterised by the cessation also of the reflex movements ; and by degrees the action extends to the *medulla oblongata*, so that all blood-vessels become relaxed, and the respiration is feeble or ceases. Finally, as a rule, the *action of the heart* also ceases, the motor ganglia situated in the heart being paralysed in the same manner as those of the central nervous system.

From this general action, as sketched above, there may be several variations, but the fundamental features are always the same. The paralysis of the sections of the central nervous system in this consecutive order—brain, spinal cord, medulla, oblongata—is the constantly recurring tale with all these compounds, the only variation being that the above order is not always strictly adhered to, the effect sometimes appearing in other parts of the central nervous system simultaneously with the commencement of the brain narcosis. Vaso-dilatation, in particular, commences very early in the case of many substances.

The usefulness of this group of compounds for therapeutic purposes depends upon the clearness with which the limit of their action upon the various sections of the central nervous system is

defined, so that there is a sufficient interval between the doses that are necessary to develop the desired effect upon the brain or spinal cord and those that endanger life by paralysing the important centres of the medulla oblongata and the heart. The interval between these two limits is called the *latitude of the therapeutic action* of a remedy. By this is understood not always the absolute quantity of a drug, but, as regards the volatile substances, that concentration of the vapours which is required in order to reach a particular stage of the action. A number of investigators, independently of one another, have found that the concentration of ether and chloroform just sufficient for a safe narcosis is the same for man as for various herbivorous and carnivorous animals. From this it appears that the action of these substances upon the nervous system stands in no relation to the development of the brain : this, once more, is in marked contrast to morphine, which acts so much more powerfully on the highly developed brain that a human being is killed by doses that are quite harmless to many small mammals.

The hydrocarbon groups contained in the compounds are responsible for the narcotic action. By the introduction of other groups or single elements the action may be modified in various directions. The halogens, chlorine and bromine, strengthen the narcotic properties, but at the same time increase the toxicity of the new substances for the heart and vessels, and also alter metabolism. Thus non-poisonous marsh gas, CH_4, with chlorine, becomes chloroform, $CHCl_3$; the feebly acting ethane, C_2H_6, the narcotic ethyl chloride, C_2H_5Cl ; and the still more weakly acting aldehyde, CH_3COH, the very powerful chloral, CCl_3COH. If the NH_2 group be introduced, the reverse sometimes takes place ; the action is weakened in every respect, and the respiration often becomes even deeper. The group O—NO causes the narcotic action to become insignificant before the peculiar vasodilator action which accompanies this group, whether it is combined with an alcohol radical, as in amyl nitrite, or with a metal, as in sodium nitrite.

It is not only the presence of certain atomic groups or elements, however, that determines the action, but it is also their relationship to one another, which gives to the entire molecule its character. Thus trimethylamine, $N(CH_3)_3$, notwithstanding the numerous hydrocarbon groups, has no narcotic action, but according to its constitution, belongs to the ammonia derivatives. Concerning the laws which here assert themselves, little, unfortunately, is known as yet. Many a carefully prepared body has proved to have a totally different action from that anticipated ; and the reasons why one compound has a narcotic action and another has

not are in many instances just as obscure as is the cause of the physiological narcosis, sleep.

The facts that have up to the present been brought to light by numerous investigations are the following:

Among the **paraffins,** methane appears to be practically inactive, and ethane to possess little activity, while pentane and octane are recommended as anæsthetics for short operations, but have not won approbation. Among the unsaturated paraffins are pental, $(CH_3)_2=C=CH-CH_3$, which has been tried as an anæsthetic, and the technically important acetylene, $CH\equiv CH$, also with narcotic action. The higher, insoluble and non-volatile paraffins are quite inactive.

The monovalent **alcohols,** which are derived from the paraffins by the substitution of OH for an H, are very active, and their activity increases at first with an increase in the number of carbon atoms. Thus methyl alcohol is weaker than ethyl alcohol, and the latter, in its turn, is weaker than alcohols with from 3 to 5 carbon atoms. With a higher number of carbon atoms the solubility diminishes, and with it the action. While the activity is increased by one hydroxyl, it is weakened, or made almost to disappear, when the compound contains two, and is wholly lost in the polyvalent alcohols, *e.g.* glycerin.

The **ethers** (anhydrides of the alcohols) are still more active than the alcohols. The ordinary ethyl ether, $C_2H_5—O—C_2H_5$, is even a rival of chloroform. If an alcohol radical of the methane series in an ether is replaced by an aromatic radical, *e.g.* $C_2H_5—O—C_6H_5$, the action often becomes altogether that of the benzol derivatives.

The **aldehydes,** the first oxidation stage of the alcohols, are also active as is shown by ordinary aldehyde, $CH_3—COH$, and its polymer, the well-known hypnotic, paraldehyde, $(C_2H_4O)_3$.

If the alcohols are oxidised entirely to **acids,** then, practically speaking, all narcotic action disappears, but may to some extent be restored by halogen. Acetic acid, $CH_3—COOH$, for instance, is not soporific, while trichloracetic acid, $CCl_3—COOH$, produces drowsiness. The higher fatty acids are inactive, and, as ingredients of the fats, are among the most important foodstuffs.

The **compound ethers** or **esters** (anhydrides of alcohol and acid), again, are active, *e.g.* acetic ether, $C_2H_5—O—CH_3CO$.

Theory of Narcosis. Several theories have been advanced concerning the manner in which the methane derivatives produce narcosis, but only that which is generally held will be mentioned here.

The *cause of narcosis* has long been sought in *an affinity of the narcotics* for certain constituents of the body, especially the *fatty substances or lipoids, lecithin, cholesterin and others,* which form a considerable portion of the nerve-substance. Earlier investigators were of opinion that chloroform, ether, etc., which are good solvents for lipoids, injure the nerve-cells by simply taking from them a part of their fat. This view is at once seen to be untenable, because the rapid recovery after narcosis excludes any such important change. The "lipoid theory" acquired a more

modern form and a firmer foundation through the investigations of Overton and H. H. Meyer (1889–1901), who, conversely, directed their aim towards the solubility of narcotics in the lipoids. The last-named started with the view that if the narcotic action of the methane derivatives was dependent on their solubility in the fat of the nervous system, the strength of their action must be regulated, on the one hand, by their affinity for fat (lecithin, cholesterin), and, on the other, by their affinity for the other constituents of the body, *i.e.* principally water, which in the blood conveys the absorbed narcotic to the nerve-centres. In order to learn whether any such conformity to law existed, the *partition coefficient* (*i.e.* the relative proportion in which a substance divides itself between the two solvents, fat and water) was determined for a large number of methane derivatives with narcotic action. This revealed a striking parallel between large partition coefficients (*i.e.* considerably greater solubility in fat than in water) and intensity of action. According to this theory, the important point about the narcosis is not that chloroform, etc., deprive the nerve-cells of fat, but that the narcotics enter the cells because they are dissolved in the lipoids, and the narcosis is accordingly a consequence of the change thereby occasioned in the cell-lipoids and the entire structure of the protoplasm. The theory has proved to be extremely suggestive, and has also been applied to other actions besides that of the narcotic remedies. According to later research, however, it appears that it must be to some extent modified, as the lipoids engage the narcotics not by solution, but by adsorption, whereby a loss of permeability is brought about. In all such changes, in whatever way they may be produced, it is obvious that all the vital processes of the cell will suffer ; among other things, the exchange of gas in the cells is interrupted and their consumption of oxygen diminished. This, however, can hardly be adduced, as is done by another theory, in support of the view that the essence of narcosis is deficiency of oxygen, or asphyxia, but will more naturally be taken as a symptom of the presence of the narcotic in the nerve-cells.

As already mentioned, all the narcotic compounds of the fatty series have in the main the same action, although this assumes various forms according to the rapidity with which the compounds are absorbed and leave the body. If a substance, owing to its volatility, is absorbed very rapidly and again quickly eliminated, the action commences very soon, but is not of long duration. Such compounds are employed to produce a narcosis which is brief, but so deep that operations can be performed painlessly, and they are called *anæsthetics*. If, on the contrary, the absorption and elimination are slower, the action also extends over a

longer period. The compounds of this kind may be employed to produce a narcosis which is lighter, but continues for several hours, and they are called *hypnotics* or *soporifics*.

In the following pages these two groups will be discussed in the above order. A special chapter will be devoted to *alcohol*, which is employed as a beverage for the purpose of inducing a slight, incipient narcosis.

Ether and Chloroform

Ether and chloroform, the two anæsthetics whose rival claims have so often been discussed, were discovered, as narcotic remedies, at about the same time.

Ether was produced about 1540 by Valerius Cordus, tutor in materia medica at Wittenberg; but it was not until 300 years later, in 1841, that its anæsthetising properties were discovered, quite accidentally, by Jackson in Boston, when, after the explosion of a vessel containing ether, the laboratory assistant was found anæsthetised. The very next year ether was tried as an anodyne in operations by Crawford Long in Athens, North America; but as he did not carry the narcosis beyond the excitement stage, he found it unsatisfactory and gave up his experiments. In 1846, for the first time, a patient was completely anæsthetised, by the American dentist Morton, and in the same year the first surgical operation (removal of a tumour on the neck) during ether narcosis was performed by Warren.

Chloroform was discovered in 1831 simultaneously by Soubeyran in Paris and Liebig in Giessen. In 1835 the new fluid received its name, and its composition was elucidated by Dumas; and in 1847 Simpson published in Edinburgh a number of observations on its effects in childbirth.

Effects. The Course of the Narcosis. The effects produced by the inhalation of ether and chloroform vapour mixed with air may be divided into various stages.

The first effects observed are such as result from **local irritation** and reflexes arising therefrom. The heavy vapours fall from the mask upon the face, and cause irritation to the mucous membranes with which they come in contact. From the eyes tears flow; in the mouth and throat is felt the sweet taste of the chloroform, or the burning sensation from the ether, which promotes salivation and the secretion of mucus. The nasal mucous membrane is also irritated, and gives rise, through the trigeminal nerve, to the same reflex that serves as a defence against other foreign vapours, or irritating gases, namely, slow, shallow respiration, or even complete cessation. This preliminary respiratory condition, which must not be confounded with

paralysis of the respiration, which may occur later in the narcosis, ceases when the patient is told to take deep breaths or when more air is allowed to enter. The respiration then once more begins ; the vapour passes down into the bronchial tubes and irritates the sensory vagus branches of the lung ; and now a new reflex appears, which leads to the opposite result, the respiration becoming more frequent, the patient thus accelerating his own narcosis. The increase in the frequency of the pulse often occurring at this period is also of reflex origin.

The ether and chloroform vapours are taken up from the lungs into the blood, gaining, through the pulmonary veins, the left auricle and thence the left ventricle, and pass through the aorta into the arteries. The effects of absorption now immediately begin. They are divided into *three stages, answering more or less to the paralysis of the brain, the spinal cord and medulla oblongata, and the heart.*

First Stage. A feeling of warmth is diffused throughout the body, and there is often a pricking sensation in the hands and feet ; the reflexes arising from irritation of the mucous membranes cease, and a feeling of heaviness and helplessness heralds the approach of paralysis of the brain. Soon consciousness is dimmed, and dream pictures and hallucinations alternate in the mind, sometimes cheerful, sometimes sad. The patient laughs, sings, speaks in a foreign language, or has indistinct ideas that he is in danger, and gives vent to his uneasiness in violent movements, which may be tranquillised by gentle restraint, while rough treatment only causes increased efforts to be made. The face now often becomes flushed, the skin being warm and damp, and the pupils begin to contract. Vomiting frequently takes place, especially if the patient has recently partaken of food. This restless period is called the *stimulation stage*, a name which may be retained for the sake of convenience, although there is no stimulation in the true sense of the word. The whole process is only—as will be more fully explained in describing the corresponding stage in alcohol narcosis—a consequence of the circumstance that all the regions of the brain are not paralysed simultaneously nor to an equal extent. The sensory and intellectual functions are first affected, while the motorial functions, not held in check by the mind, for a time carry on an irregular activity. Sooner or later, however, the conditions change. The unrestrained movements subside, the disconnected speech ceases, and only a few inarticulate sounds indicate that a feeble dream-life is still going on. Soon these too are silenced ; a deep sleep supervenes, and spontaneous movements cease ; but the infliction of pain, or touching the eye, immediately produces reflexes.

The "stimulation stage" is of very varied intensity and duration. With children, women and delicate persons, it is easy and brief, or altogether absent, but is generally exceedingly violent and lengthy with persons addicted to alcohol. The latter may scream and make a noise and behave like maniacs for a quarter of an hour, this condition often suddenly passing into the final stage of the narcosis. The explanation of this is that the brain, accustomed to the allied narcotic, alcohol, is reduced to a state of tranquility only by such large doses of ether and chloroform that the paralysis of the medulla oblongata is already far advanced. Another important cause of the sudden transitions is the weak heart of such persons which often fails suddenly. Thus *addiction to alcohol limits the latitude of the therapeutic action of kindred remedies.*

Second Stage (*tolerance stage*). With continued inhalation the reflexes are also abolished, so that touching the cornea no longer produces closing of the eyelids. The patellar reflex, which at first is increased, ceases early, while reflexes from the nasal mucous membrane are not abolished until far on in the narcosis. The striated voluntary muscles are relaxed, the muscles of mastication last. There may still be spasm of the masseter and tightly clenched teeth after the other muscles are relaxed. Even short operations in the mouth, therefore, often require a deep narcosis, one of the causes of the not infrequent narcosis fatalities attending the extraction of teeth. When all the muscles are relaxed, and all the reflexes abolished, the stage favourable for the surgeon's undisturbed work has been reached. There is now complete analgesia, last of all in the forehead and the temporal region ; the severest and most painful operations, the dividing of nerves, the sawing and chiselling of bone, can be performed without reaction on the part of the patient. It appears that analgesia may be developed without complete anæsthesia, for when the narcosis is over the patient may sometimes have retained an impression of being touched, but not of pain. Some who have been very restless during the first stage may continue to cry out for a long time, and yet on waking have no recollection of suffering. During deep narcosis the pupils are greatly contracted, the pulse slow and regular, the respiration also slow, often stertorous, owing to paralysis of the soft palate and the falling back of the tongue through relaxation of the lingual and pharyngeal muscles. In ether narcosis the face is flushed or cyanosed ; under chloroform it is pale. By carefully conducted administration of the anæsthetic the second stage may be maintained for hours.

Third Stage. When the narcosis has developed thus far, the brain and spinal cord no longer function, and the medulla oblongata and the heart do not act quite normally, since both respiration and circulation—as already indicated and shortly to be further discussed—are slightly depressed even in a normal

narcosis, but not so much as seriously to endanger life. If, on the other hand, the inhalation is continued too long, both the medulla oblongata and the heart are greatly affected, the respiratory movements become more and more superficial, irregular and slow, the skin and mucous membranes cyanotic, the radial pulse small, intermittent, and at last imperceptible, and death supervenes from respiratory or cardiac paralysis. This last stage is entitled the *stage of collapse* (*période bulbaire*).

If the inhalation ceases in the second stage, the sequence of events described above is rapidly carried out in reversed order; reflexes and manifestations of pain reappear, a brief "stimulation stage" may occur, and after from 5 to 15 minutes the patient has so far recovered that he reacts when addressed. After being conscious for a short time, he often falls asleep again, but there is no danger in this. Few persons feel perfectly well after fully regaining consciousness; the majority suffer from various after-effects, such as indisposition, headache and vomiting. Sometimes after chloroform the urine acquires a yellow colour, and there is not infrequently a temporary albuminuria after both ether and chloroform.

Above we have described the paralysis of the central nervous system in the consecutive order, brain, spinal cord, medulla oblongata. We may now turn to *the action upon the various functions and organs, and the differences between ether and chloroform.*

Circulation. At first, as a consequence of the mucous membrane reflexes, the pulse may be irregular, and the blood-pressure fall or rise a little. As soon as the real narcosis has commenced the pulse becomes regular, often rather slow, full and soft. In ether narcosis the blood-pressure remains at about the original height, while in chloroform anæsthesia it is always lowered, the reason being that chloroform, like most of the remedies containing halogens, acts more powerfully on both vessels and heart. Pohl found in the blood of dogs in deep anæsthesia 0·035 per cent. chloroform, Nicloux 0·05 per cent. chloroform, and in ether narcosis 0·13—0·14 per cent. Thus on the brain chloroform is from 3 to 4 times as effective as ether, but for the heart the relative toxicity is quite different. From experiments with isolated hearts of mammals, through which blood containing chloroform (Sherrington and Sowton) or ether (Leeuwen and Made) was made to flow, it appeared that in order to bring the heart to a standstill the concentration of ether required was about 21 times as great as that of chloroform. While ether, in the concentration employed in surgical anæsthesia, has little effect upon the heart, chloroform, even during the normal narcosis, perceptibly inter-

feres with its work. First the contraction of the auricles becomes weaker, then that of the ventricles ; the heart does not empty itself completely, and sometimes during the narcosis the pulsation of the jugular veins may be observed, probably denoting a tricuspid insufficiency caused by acute dilatation of the right ventricle.

In experiments with isolated hearts of mammals in which the heart was made to drive the blood through a system of glass tubes instead of through the yielding arteries and veins (thus obtaining the simple action of the heart, uninfluenced by the changes of pressure consequent on the variations in the vascular contraction), Bock always found chloroform produce a distinct fall of the pressure in the rigid system of tubes, accompanied by diminished pulse-frequency, while ether occasioned only a slight fall, if any, and the number of contractions remained unchanged. In the vessels a similar difference asserts itself. Ether paralyses only those parts of the vascular nerve-centre which correspond to the face and the cortex of the brain ; the face is therefore congested, and the pulsations of the carotids and the temporal arteries can be seen. Chloroform, on the other hand, dilates comparatively early the entire vascular system, so that the total blood-pressure falls and the face becomes pale. As long as the heart still works more or less vigorously every systole sends a great wave into the relaxed vessels, and thereby gives rise to the characteristic well-filled, but at the same time soft, pulse. To sum up briefly, ether and chloroform both act in the same direction upon the circulation, but the action of chloroform begins much earlier, that is to say, with a weaker concentration. This quantitative difference is of great practical significance.

Respiration. When the initial irregularities mentioned in the description of the narcosis are over, the respiration is somewhat slow, but is otherwise satisfactory. When the sleep has commenced, the movements of the chest are regular and the excursions almost of normal extent, even in deep anæsthesia. If the respiration begins to be shallow, it is a sign that the patient is on the borders of the third stage. Ether has a weaker action on respiration than chloroform, but the difference is not so decided as with the circulation.

The condition of the eyes, especially that of the **pupil**, stands in a certain relation to the respiration. During the beginning of the narcosis the eyeball slowly turns upwards, so that the iris is covered by the upper eyelid. Subsequently nystagmus and squinting may occur. The pupils, which in the stimulation stage are dilated, become narrowed when the sleep begins, just as they are in the natural sleep, but still react for a long time to impres-

sions from without, such as a needle prick, loud noises, etc. In deep narcosis they are greatly contracted, and do not react to light or any operative procedure. On vomiting and on reawakening they dilate. Dilatation of the pupil in deep narcosis is an ominous symptom, which immediately precedes dangerous asphyxia. All this refers principally to chloroform ; in ether narcosis the condition of the pupil is less regular.

Is respiration or circulation the first to cease ? Ether follows the ordinary course of the methane derivatives as given in the preceding chapter, according to which the respiratory centre is paralysed earlier than the ganglia of the heart. Great disagreement has prevailed as to the order in which these functions are extinguished during chloroform inhalation, and the question has been discussed by specially appointed Commissions, which have had abundant material to work upon. From the numerous experiments on animals made by these Commissions, more especially by the Anglo-Indian "*Hyderabad Chloroform Commission*" (1890), which, in order to get as near as possible to man, also experimented with monkeys (70 monkeys and 430 dogs), it was considered proved that chloroform also, when inhaled slowly and sufficiently diluted with air, first paralyses the respiration, for in all the animals experimented on the breathing ceased first, while the heart still went on beating for from 1 to 11 minutes longer. With regard to man the case appears to be otherwise, as perhaps more than half the number of deaths occurring during chloroform anæsthesia are due to the arrest of the heart. This will be discussed more fully under "Deaths during Anæsthesia."

The **motor nerves and muscles** are paralysed when they are directly exposed to the vapour of ether or chloroform, but not in the ordinary narcoses.

The **temperature** always falls a little, on an average about 0·5°, but in deep and long chloroform anæsthesia it may fall as much as 3° or even 5°. The cause of this is partly increased radiation of heat through the dilated skin vessels, partly the decreased heat-production in consequence of the cessation of all muscular movement.

Metabolism. *Chloroform*, in the body, is absorbed not only by the nerve-cells, but also by the blood-corpuscles, and is probably taken up into many other cells. In the majority of cases, however, the connection is soon dissolved, the foreign substance is eliminated, and for all practical purposes the action ceases with the conclusion of the narcosis. In certain cases, while it is impossible to assign any definite cause, dangerous effects may appear in the form of acute fatty degeneration of the heart, muscles and liver, and injury to the kidneys (fatty degeneration and swelling

of the epithelium in the tubules), with excretion of albumin and casts in the urine. The excretion of nitrogen and sulphur is increased, but the quantity of the oxidised sulphur (sulphates) decreases, and is replaced by certain unoxidised compounds, this indicating increased protein destruction and reduced oxidation. Jaundice is seldom seen, acetonuria frequently. It has also been observed in diabetic persons that coma has followed chloroform anæsthesia, that the excretion of sugar may increase, and that latent diabetes may be made manifest. Further, hæmatoporphyrinuria, accompanied for several days by increased pulse-frequency and cyanosis, has been described. Chloroform thus acts as a *protoplasmic poison*, and accordingly also possesses antiseptic action. Various pathogenic micro-organisms die quickly in both chloroform water and vapour. *Ether* does not cause very great alterations in the metabolism, but is yet not quite without action. Wood found renal congestion in dogs that were killed immediately after ether anæsthesia, and on microscopic examination swelling of the epithelium. In man, apart from a brief glycosuria, concerning the frequency of which after ether narcosis nothing certain is known, no great changes in the metabolism have been demonstrated.

The **excretion** of ether and chloroform takes place in the expired air. As soon as the supply of anæsthetic ceases a rapid excretion from the blood begins into the lungs. When the concentration in the blood lessens, the narcotic substance is diffused from the brain back to the blood, and is once more excreted from the lungs; and within a short time the concentration has fallen so much that the narcosis passes off. According to Haggard, ether is not oxidised in the tissues. Practically all the ether that is not excreted in the expired air can be recovered in the other excretions. Chloroform is to some extent decomposed and excreted as chlorides, and a small quantity unchanged, in the urine.

Chronic poisoning has been observed in persons accustomed to frequent chloroform inhalations. The symptoms resemble those of serious alcoholism, namely, digestive disorders, loss of appetite, vomiting, emaciation, sleeplessness, hallucinations and mental maladies, most frequently in the form of periodical attacks of mania. A protracted period of ether-drinking or habitual inhaling of ether also produces symptoms similar to those of chronic alcoholism—morning vomiting, tremors, general debility. Records have been given of enormous doses: in one well-known case, described by Ewald, a man of 32, who, through a habit of years, had become passionately addicted to inhalations, consumed daily from 1 to 1¼ kilogrms. of ether.

Death during Anæsthesia. Death may occur at any stage of *chloroform anæsthesia*, and in various ways.

1. Early in the narcosis, often after only a few minutes' inhalation (the surgeon's "primary chloroform collapse"), the

heart fails; the patient suddenly turns deathly pale, the radial pulse disappears, all the muscles are relaxed, the heart ceases to beat in diastole, and after two or three short inspirations death supervenes. Embley explains deaths such as this, which may occur immediately after the placing of the mask, as a reflex arrest of the heart, caused by the irritant action of the chloroform on the mucous membranes. A normal heart reacts to such a reflex check with merely a slowed pulse, or at the most a stoppage of a few seconds; but the slight depression attending even the commencement of anæsthesia may prevent it from starting again. A more recent theory (Levy) considers ventricular fibrillation to be the cause of the sudden death. This action is not infrequently seen in various animals, *e.g.* the cat. A few of these very early deaths ought not perhaps to be ascribed to the chloroform, as even before the time of anæsthetics apparently healthy patients have been seen to die upon the operating-table before the operation was begun, and the post-mortem examination has afforded no explanation.

2. Deaths occur more frequently during deep anæsthesia, and may then be due to *paralysis* either *of the respiration or of the heart*, in the opinion of many surgeons most frequently the latter. In many cases cessation seems to occur almost simultaneously and it is difficult to decide whether the heart beats for a few seconds after the respiratory movements have ceased or *vice versâ*. The reason why paralysis of the heart on the operating-table is seen so much more frequently than animal experiments would lead one to expect is probably that the animals' hearts are healthy, whereas degeneration and infirmities of the most varied nature are frequently present in man without their revealing themselves in the clinical examination that has to be made before anæsthesia.

3. The delayed chloroform poisoning (protoplasmic action, acute fatty degeneration) occasionally causes death many hours or even days after the narcosis proper is ended, by a constantly increasing depression of the heart and collapse. This may be an immediate sequel to the narcosis, but more characteristically the onset is delayed and may occur any time within a week of the operation. A severe degree of acidosis develops accompanied by desiccation of the tissues and the appearance of ketone bodies in the urine. Hæmorrhages occur in the mucosa of the alimentary canal and blood is found in the vomit and in the stools. Later, jaundice develops and its intensity increases as the condition progresses to its almost invariably fatal end. Hypoglycæmia is a constant feature and is mainly due to the impairment of liver function. The autopsy has repeatedly shown advanced fatty degeneration of the heart.

Death during *ether* anæsthesia on the operating-table is of very rare occurrence. In the few cases that have been described, the cause of death seems always to have been *asphyxia*, while the primary paralysis of the heart, which is responsible for about half the deaths from chloroform, has not been observed with certainty in ether narcosis. Ether is also almost free from the injurious effects on the metabolism. On the other hand, *fatal bronchitis* or *pneumonia* may be developed several days after the narcosis, an after-effect which will be described more fully later.

Comparison between Ether and Chloroform. The Choice between them. In comparing the two anæsthetics, one is first struck by the fact that ether is a much weaker drug than chloroform. The very difference between the light chloroform mask, which permits of the free passage of air, and the often more or less close-fitting ether apparatus, shows that chloroform is evidently employed in a far less concentrated form than ether; and if the inhaling apparatus used allows the ether vapours to be greatly diluted with air, the anæsthesia is a long time in being accomplished, or has to be induced primarily by some other anæsthetic. The narcosis itself, moreover, with ether is not so deep, and the reflexes are not always completely abolished. The pulse is of a better quality than in chloroform narcosis, because the heart is not affected and the vascular paralysis is less pronounced. For the same reason the face, as already mentioned, in ether narcosis is flushed (cyanosed if a close-fitting mask be used), while in deep chloroform anæsthesia it is pale. The awakening from the anæsthesia is quicker after ether. As regards vomiting the two remedies are alike. Concerning the very important question as to the concentration with which ether and chloroform are able to produce anæsthesia, and that with which they act fatally, *i.e.* their *latitude of therapeutic action*, numerous investigations have been made, with the following results: The required concentration of chloroform vapour in the air inhaled for the production of anæsthesia is 1·2—1·4 per cent., that of ether vapour 4—6 per cent. With increasing concentration the toxic effect increases far more rapidly with chloroform than with ether. The lethal concentration of both ether and chloroform is about twice the anæsthetising concentration. The margin between the two limits is thus about 1 per cent. in the case of chloroform, and several per cent. in that of ether. Variations in the composition of the air inhaled are consequently far less dangerous with ether than with chloroform, or *ether possesses a far greater latitude of therapeutic action (narcosis latitude) than chloroform.*

The question "Ether or chloroform?" presented itself very soon after these two anæsthetics had been discovered. At first

ether was almost everywhere superseded by chloroform, which possessed such obvious advantages in the rapidity of its action, the depth of the narcosis it produced, and the convenience of its employment; but with the long anæsthesia required for some major operations made feasible by the use of antiseptics, the number of chloroform deaths increased rapidly. The anæsthesia question was therefore reopened, and an enormous amount of matter collected by investigations.

If the figures from the anæsthesia statistics of Roger Williams, Julliard-Carré, Gurlt, Mikulicz, and others, are brought together, they show 344 deaths in 878,148 cases of chloroform anæsthesia, and 38 deaths in 409,149 cases of ether anæsthesia, or a mortality of 1 in 2,550 under chloroform and 1 in 10,767 under ether. Thus the results of the statistics were in favour of ether. There was a temporary reaction in favour of chloroform when an investigation of the fate of patients in the period immediately following the anæsthesia showed that after ether bronchitis, pneumonia and pulmonary œdema occurred so frequently, and in so many cases ended fatally in the course of a few days, that the ultimate result was even less favourable for ether than for chloroform. These sequelæ were attributed to the highly irritating action of ether on the respiratory mucous membrane. Subsequently it was found by numerous animal experiments that after the longest periods of ether narcosis there is no great irritation in the bronchioles. On the other hand, ether, when the vapours are concentrated, often causes, both in man and in animals, a profuse secretion of mucus in the mouth and throat, which by aspiration may be the cause of the above-mentioned lung affections. By the employment of suitable precautions, however (lowering the head, wiping out the mouth and throat, the lowest possible concentration of the vapour), this may to some extent be avoided. By these improvements in the technique of ether anæsthesia the frequency of its sequelæ has quickly been reduced.

As a consequence of this there has been a general return from chloroform to ether, another great advantage of the latter being that with its employment the alarming deaths on the operating-table hardly ever occur. In diseases of the heart, chloroform ought not to be used; and even in bronchitis, where ether has been especially feared, it is now employed by many. When an operation has to be performed by artificial light (a flame fixed at a low level is especially dangerous, as ether vapour sinks), and also when galvano- or thermo-cautery is to be used, ether must be employed with great caution. In drunkards ether sometimes fails to cause narcosis, even after preliminary injection of mor-

phine ; and it is therefore often necessary to have recourse to chloroform, or, at any rate, to begin the inhalation with it. In operations on the face, too, many surgeons give the preference to chloroform, because the patient awakens from the narcosis if the mask has to be frequently removed in the case of ether.

Mixtures of the Anæsthetics. Many proposals have been made for a combination of various anæsthetics which should produce a deep and fairly safe narcosis. One of the best known is the English ACE mixture, which consists of 1 part alcohol, 2 parts chloroform and 3 parts ether. It appears doubtful, however, whether it has any special advantages, for animal experiments show that, as a rule, only cumulation of the effect is obtained if the component parts of a mixture, *e.g.* ether and chloroform, are closely allied to one another and have the same seat of action in the central nervous system. If, on the other hand, substances with different points of application be combined, *e.g.* narcotic alkaloids with ether or chloroform, an effect will often be produced that goes far beyond the result of a cumulation, and thus becomes a potentiation. Of this kind are the numerous narcotic mixtures now employed ; a hypodermic injection of morphine, or morphine and scopolamine, is given some time before the beginning of the inhalation. In a patient slightly anæsthetised with the alkaloids, quite a small quantity of ether or chloroform is, as a rule, sufficient to obtain a complete anæsthesia. The unpleasant stage of excitement is almost or altogether absent, and the scopolamine also has the advantage of lessening the above-mentioned secretion of mucus otherwise occurring in ether anæsthesia. In many places ether and chloroform are used in the apparatus, which makes it possible for the vapours to be inhaled mixed with oxygen instead of with air, it being supposed that thereby less injury is done to the respiration and circulation.

Therapeutic Uses. Inhalation. The introduction of ether and chloroform as *anæsthetics in operations* was one of the greatest advances ever made in the history of medicine. Anæsthesia not only frees the patient from pain, but, by inducing repose, greatly facilitates the work of the operator. Within six months of the discovery of ether anæsthesia the number of operations in the London hospitals was doubled, and many of the long, serious operations of the present day would be impossible without anæsthesia. It is, further, of the greatest value *in bloodless operations that require relaxation of the muscles, e.g.* in the reduction of dislocations and herniæ, and in examinations that would be rendered difficult by pain or muscular contraction ; but, as there is danger connected with all anæsthesia, its use should be restricted

as much as possible, and diagnosis can often be made by examining the patient in a hot bath. With regard to its employment during *normal labour* opinion is divided. A light narcosis ("semi-narcosis") towards the end of the labour, especially if ether be employed, is, without doubt, justifiable ("divinum opus sedare dolorem"), and does not retard the parturition to any marked extent; the mortality among new-born infants is not thereby increased. A long, deep chloroform anæsthesia, on the other hand, weakens the uterine contractions and lengthens the intervals; and chloroform is also said to cause a relaxation of the uterus and consequent tendency to retain the placenta and to hæmorrhage. It has sometimes been stated that children of mothers who have been chloroformed are frequently subject to icterus neonatorum. In deep chloroform anæsthesia, the low blood-pressure and imperfect respiration may also endanger the life of the child. Anæsthesia, or semi-anæsthesia, is employed as a *remedy for reducing spasms*, such as those of *strychnine poisoning*, *traumatic tetanus*, and also in *violent attacks of asthma*, *eclampsia*, the more serious forms of *chorea*, and incessantly returning *epileptic fits* (status epilepticus). Anæsthetics may also be indicated in continued *convulsions in infants*, and may bring about a longer interval between the attacks.

Internally *ether* is frequently prescribed as a stimulant, both in cases of *acute collapse* and in respiratory and, more especially, cardiac depression in *fevers*. Resuscitating and strengthening action upon the heart is ascribed to it, and the well-known 10—15 drops every one or two hours are prescribed in pneumonia, typhoid fever, etc. The pulse generally gains thereby in fulness, and thus gives the impression of being stronger, but it is exceedingly doubtful whether the action of the heart is really strengthened. The injection of small quantities of ether in animals, at any rate, has no influence upon the blood-pressure. The change of pulse should probably be interpreted as the effect of a slight vascular paralysis, inducing sufficient vaso-dilatation to weaken the peripheral resistance that has to be overcome by the heart, thereby facilitating its contraction. A small dose of ether can also often induce the very earliest stage of anæsthesia, and is readily taken by the patient as a beverage. In cases of acute collapse ether is injected hypodermically, as the severe pain caused by the injection acts reflexly upon the pulse and respiration. The point of the syringe should be placed in the subcutaneous tissue just beneath the skin; deep injections in the vicinity of the nerve trunks may occasion neuritis and local paralysis. In *indigestion*, *nausea* and *vomiting*, ether, like other pure, strong-tasting local irritants, gives relief. In the stomach, of which the

temperature is 2° or 3° C. higher than the boiling-point of ether, the ether immediately begins to boil, and the stomach is greatly distended. It follows, therefore, that ether must not be used in cases where the resistance-capability of the walls of the stomach is impaired, *e.g.* with ulcer or corrosion. Chloroform is only occasionally employed internally for *vomiting*, *abdominal pain* and obstinate hiccough, and also as an intestinal antiseptic for *diarrhœa* and *tapeworm*.

Externally chloroform is used mixed with equal or a greater number of parts of cotton-seed or olive oil, or as a component part of analgesic liniments and poultices. Less frequently it is used pure, as, for instance, a few drops on cotton wool in a hollow tooth for toothache: the brief effect is probably due partly to the anæsthetic action of the cold, and partly to the paralysis of the sensory nerves by the penetration of the chloroform. When applied to the skin in a fine spray (Richardson's ether spray), ether, by its rapid evaporation, produces cold and anæsthesia, but has now been superseded by the more active ethyl chloride.

Practical Anæsthesia. Precautions against, and Treatment of, Poisoning. The primary condition for regularity in the course of an anæsthesia is that *the drugs* employed *shall be pure*. As regards ether, it is of the greatest importance that it shall not contain aldehyde, hydrogen peroxide, nor other substances that irritate the bronchial mucous membranes; as regards chloroform, that it shall not contain allied, but dangerous, chlorine compounds, nor the poisonous carbonyl chloride or phosgene, $COCl_2$. Both ether and chloroform undergo changes when exposed to air, light and heat, and should therefore be prescribed and preserved in small quantities, and remains that have stood for some time in half-filled bottles should not be used. During long chloroform anæsthesia by gaslight frequent airing of the room is necessary, as chloroform is decomposed by a naked flame into gases of a very irritant nature, principally hydrochloric acid, a little free chlorine, and possibly phosgene.

The patient must be examined, especially as regards the heart and lungs. Valvular disease and degeneration of the heart contra-indicate an anæsthetic only when there is marked insufficiency. Considerable fatty degeneration absolutely forbids chloroform, and any form of anæsthesia is, on the whole, undesirable. In pronounced atheroma it has been feared that the raising of the blood-pressure during the "stimulation stage" of ether might cause apoplexy. All diseases in which the area of respiratory surface is diminished demand great caution, as do also great weakness, anæmia and extreme old age; children may be chloroformed from birth. Untreated diabetes, above all when the

urine contains an abundance of acetone bodies, contra-indicates anæsthesia as being liable to induce coma (see Nitrous Oxide, p. 58).

The technique of anæsthesia must be learnt from practice, and will here be only treated with brief directions. To avoid vomiting, the stomach should be empty, and it is best to give the patient a light meal three or four hours before the anæsthesia. To anæsthetise in the morning before the patient has partaken of food is not good, as the long fast is weakening. Before the anæsthetic is given the mouth should be empty (false teeth, tobacco plug), and all clothing that might hinder free movements of the chest removed ; but the body must be well covered to prevent a fall of temperature. At first a low concentration of the anæsthetic is employed, as in this way it is less unpleasant, incites less struggling, and elicits feebler reflexes from the mucous membranes. If the respiration nevertheless ceases, more air is given, and the patient is told to breathe or count aloud. It is of the greatest importance in administering chloroform that *the vapours shall be diluted with air*, for if the pulmonary veins convey to the heart blood containing too large a proportion of chloroform, the heart may very quickly be paralysed. The goal to be constantly striven for is an anæsthesia with air which contains the anæsthetising vapours in the minimal efficient concentration. In animal experiments it has long been proved that in this way it is possible to obtain a safe anæsthesia of many hours' duration, and that a far lower concentration is required for the maintenance of the anæsthesia than for its induction. Unfortunately no apparatus has yet been constructed that is sufficiently convenient for general practice, and we are therefore in the meantime reduced to the necessity of having to regulate the dose by the depth of the anæsthesia and the appearance of the patient. The administration therefore requires *uninterrupted attention*, and the anæsthetist ought to have nothing else to occupy him—a requirement which doctors in isolated positions have to forego. As a rule, the operation is not begun until the corneal reflex is abolished. It has often been recommended, in operations in which complete relaxation of the muscles is not necessary, to use the semi-anæsthesia more than is now done, for even if the patient reacts to the operative procedure, or cries out, all recollection of pain is obliterated on reawakening. Opinion is here divided, however. It is urged that the half-anæsthetised patient is more liable than the completely anæsthetised to the sudden arrest of the heart that was known, even before the time of anæsthetics, as the cause of sudden deaths on the operating-table. In animal experiments, ventricular fibrillation occurs upon irritation of sensory nerves in light anæsthesia.

If breathing is obstructed by *the falling back of the tongue*, the lower jaw must be gently dislocated forward. In addition it may be necessary to secure the tongue with forceps and draw it out. In *vomiting*, the head must be turned to one side and the mouth cleansed, so that nothing shall be inspired. In ether narcosis, the head is placed so low that the glottis is higher than the nasopharynx, and the mouth and throat are carefully cleansed. From all that has been said above concerning the action it will be seen that it is to the respiration and pulse, the colour of the face, and the condition of the pupil, that attention must be given.

If the respiration ceases, artificial respiration should be instantly commenced by faradisation of the phrenic nerves, or, still better, by one of the well-known mechanical methods, and the doors and windows of the operating-room opened to free the air from the anæsthetising vapours, and thus promote excretion by the lungs.

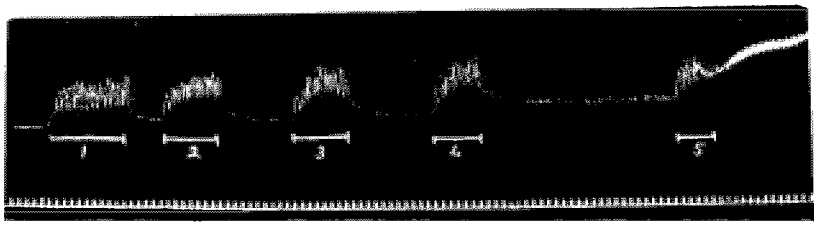


FIG. 1.—Rabbit. Arrest of the heart during chloroform narcosis, treated with intermittent heart massage. After massage repeated five times the heart begins to beat normally, and the blood-pressure rises rapidly. Uninterrupted massage is less effective. (Gunn and Martin.)

At the first signs of respiratory paralysis the condition is often at once improved by lowering the patient's head.

The situation is one of far greater danger when *the heart ceases to beat*. The early arrest ("primary chloroform collapse") is generally quite hopeless, while the later, gradual weakening of the heart is more amenable to treatment. The means to be adopted are massage of the heart, consisting of short, sharp blows over the cardiac area—about 120 per minute—and slinging up or raising the lower extremities and the pelvis, whereby the heart is filled passively and the dilatation may act as a mechanical stimulus and elicit contraction. An intravenous injection of from 1 to 2 litres of hot (40°—41° C.) physiological solution of common salt acts in a similar way.

Successful *antidotes* to ether and chloroform are not known. Many remedies have been suggested, but experience has shown that substances which, in the unnarcotised animal or person, have a stimulating effect on respiration and heart, fail to act on the paralysed ganglion cells. The following is a general rule very

important in the prognosis and treatment of poisoning : Of two antagonistic substances, *i.e.* substances which act upon the same cells in different ways, the victor is the one which has a paralysing action. Camphor, in the form of one or more hypodermic injections of camphorated oil, may be tried as a remedy that not only acts upon the nervous system, but also upon the cardiac muscle. In animal experiments, the low blood-pressure may be raised by camphor, the condition being, however, that the remedy must be employed at a fairly early stage ; for if the circulation is already greatly impaired there will be no absorption. It has not yet been sufficiently proved whether the power possessed by adrenalin of raising blood-pressure can be utilised during anæsthesia.

Preparations and Doses

Chloroformum, Chloroform (B.P., U.S.P.), $CHCl_3$. A clear, colourless liquid, with a sweetish aromatic odour and burning taste, sparingly soluble in water, readily in alcohol and in fixed oils. The official preparation contains a little alcohol, which increases its keeping quality. *Dose*, 6—30 centimils, 1—5 mins. (B.P.) ; 0·3 mil, 5 mins. (U.S.P.).

Various Kinds of Chloroform. The ordinary chloroform is formed by the heating of alcohol with chlorinated lime. Among other kinds may be mentioned *Chloroformum anglicum* (Chloroformum e Chloralo), which is produced by the decomposition of chloral by soda, and is reputed to be very pure. The same is said of *Chloroformum medicinale* (Pictet), which is prepared by the cooling of chloroform to from −70° to −80° C., when the pure compound $CHCl_3$ crystallises out, and the fluid remaining is said by Du Bois-Reymond to be a stronger poison than ordinary chloroform. Another good preparation is *Chloroformum Anschütz*, which is obtained from salicylid-chloroform, a chemical compound which contains chloroform held in the same manner as water of crystallisation, and when heated gives it off in pure condition. All these preparations are much more expensive than the official preparations.

Spiritus Chloroformi, Spirit of Chloroform (B.P., U.S.P.). *Dose*, 3—20 decimils, 5—30 mins. for repeated doses ; for a single dose 25—30 decimils, 30—40 mins. (B.P.) ; 2 mils, 30 mins. (U.S.P.).

Aqua Chloroformi, Chloroform Water (B.P., U.S.P.). Internally for nausea and cardialgia ; a pleasant gargle for inflamed sore throat.

Linimentum Chloroformi, Chloroform Liniment. A mixture of chloroform and camphor liniment (B.P.C.) or soap liniment (U.S.P.). Externally rubbed in to relieve pain. A more lasting effect is obtained by a poultice of chloroform mixed with 2 parts of a fixed oil, *e.g.* olive oil or cotton-seed oil.

Æther (B.P.), **Æthylis Oxidum** (U.S.P.), Solvent Ether, $(C_2H_5)_2O$. A clear, colourless, mobile liquid, with a refreshing odour and burning taste, sparingly soluble in water, freely in alcohol and fixed oils. The official preparation contains a small percentage of alcohol and water. *Dose*, 1—4 mils, 15—60 mins. (B.P.).

Æther Anæstheticus, Purified Ether (B.P.), **Æther** (U.S.P.), meets the more rigorous demands for purity. Employed for anæsthesia.

Æther Aceticus, Acetic Ether (B.P.C.), $CH_3COOC_2H_5$. A transparent

liquid with pleasant, refreshing odour. Prescribed with the same indications and in the same doses as ether.

Spiritus Ætheris, Spirit of Ether (B.P.), Hoffmann's Anodyne, an old, popular mixture of ether and spirit, a household remedy for fainting, debility, etc. *Dose*, 1—4 mils, 15—60 mins.

Other Anæsthetics

An action similar to that of chloroform is possessed by numerous allied compounds of the halogens chlorine and bromine with methane and ethane. When the first deaths in anæsthesia occurred shortly after the introduction of chloroform, many such compounds were tried in the hope of their proving less harmful, but without the desired result. Special attention was directed to the nearest allies of chloroform, the rest of the chlorine substitution products of methane. *Methyl Chloride* (CH_3Cl) and *Dimethyl Chloride* (CH_2Cl_2) were both employed for a short time, but again abandoned. *Tetrachloride of Carbon* (CCl_4) is far too dangerous, as there is little difference between the therapeutic and the lethal dose. *Bromoform* acts analogously to chloroform, but is more poisonous, while *Iodoform*, from the very fact that it is a solid body, cannot be compared with these volatile compounds, although certain of its toxic symptoms recall its chemical relationship to narcotics of the fatty series. Among the halogen compounds of ethane, *Ethyl Chloride* (C_2H_5Cl) and *Ethyl Bromide* (C_2H_5Br) have attained practical importance, and will be mentioned below. Among the halogen-free remedies no serviceable anæsthetic except ether has hitherto been found.

Ethyl Bromide (not official)

Ethyl bromide was recommended as an anæsthetic by Nunnely as early as 1849, but it attracted little attention until of late years, when it came to be employed in cases of short anæsthesia.

Its *action* differs from that of ether and chloroform in the extraordinary rapidity with which analgesia is produced while touch is still appreciated. Consciousness is frequently not quite lost, and the reflexes and muscular tone are still present up to the moment when the respiratory paralysis commences. When 10—20 grammes of ethyl bromide are poured at once, after the usual manner of procedure, upon a mask covered with an impermeable material, analgesia supervenes, without or almost without excitement, in the course of about 20 seconds, and lasts, even when the mask is still held to the face, at the most only a few minutes. As the corneal reflex cannot be used as a guide, the patient is tested with needle-pricks or something similar. He reawakens a few seconds after the removal of the mask, feeling perfectly well. The very brief anæsthesia is attended with little danger. Deep anæsthesia, on account of the threatened respiratory paralysis, cannot be employed, and may also, judging from animal experiments, prove fatal in its after-effects, which seem to

be due to decomposition of the compound and retention of bromine. It appears that ethyl bromide may readily undergo change in the organism, from the fact that even after the short anæsthesia the patient's breath may smell of onions for a day or two.

Before the anæsthesia the heart and lungs must be examined and the same contra-indications maintained as with ether and chloroform. When the preparation is pure, the fatalities are certainly very few, statistics from 1891 to 1895 showing 2 deaths in 9,000 cases of anæsthesia, and from 1889 to 1891 in 20,000 cases no death for which the drug could be certainly said to be accountable. A few deaths may be traced to contamination with the highly poisonous ethylene bromide, $C_2H_4Br_2$.

The *indications* for ethyl bromide are easily given by the effects ; it is suitable only for *short operations, e.g. teeth-extraction, incisions, thermo-cautery,* and other minor surgical operations that do not require relaxation of the muscles nor the abolition of the reflexes.

Ethyl Chloride

Ethyl chloride is also one of the remedies that were tried in the eager search for anæsthetics which the discovery of ether and chloroform anæsthesia had aroused.

Flourens, as early as 1847, called attention to its anæsthetising properties, but little account was taken of it, as it was deemed to be greatly inferior to chloroform. In 1890 it was introduced as a local anæsthetic by Reddard, and in 1894 its narcotic action was discovered for the second time by the Swedish dentist Carlson, who observed that certain of his patients, when the ethyl chloride jet was directed towards the gum, fell into a brief sleep during which several teeth could be extracted painlessly. Subsequently extensive experiments have proved that it acted like ethyl bromide. A few cubic centimetres of ethyl chloride on a more or less close-fitting mask produces, in from ½ to 2 minutes, complete anæsthesia, which may last for several minutes, and from which the patient awakens to consciousness feeling perfectly well, or in rare cases with headache or some similar ailment ; muscular relaxation is incomplete, and reflex movements are present. It is said to be a pleasanter narcosis than others, and, like ethyl bromide, it is employed as the introduction of ether anæsthesia or in *short operations,* especially the extraction of teeth. As with ethyl bromide, however, anæsthesia with ethyl chloride has been almost entirely superseded by local anæsthesia.

The low boiling point of ethyl chloride, 12·5° C., causes it to evaporate so rapidly on the warm skin that in the course of a few seconds great cold is produced, and *local anæsthesia*. For this purpose it is supplied in glass capsules terminating in a capillary tube furnished with a lid. If the hand is closed round the tube, its warmth is sufficient to cause the liquid to shoot from the narrow point in a strong jet, which, when turned upon the bulb of an ordinary thermometer, rapidly sends the quicksilver down to — 20° C. or lower. When the jet impinges on the skin, the first feeling is one of burning, the hairs are covered with rime, and the skin soon becomes white and frozen to a slight depth. Small surgical operations that require only a few minutes, or extraction of teeth, can now be performed without pain. By repeated application of the jet to the spots tender to pressure the pain in superficially situated nerves, *e.g.* in intercostal neuralgia, may be relieved and sometimes quite cured. To insure against gangrene, which, however, very rarely occurs, the skin should previously be rubbed with vaseline or fat. Ethyl chloride is very inflammable.

Methyl Chloride (not official)

Methyl chloride is a colourless gas with an ethereal odour, which condenses into a liquid at — 23° C. This evaporates with extreme rapidity on the skin, producing anæsthesia by the intense cold ; but its employment is far less convenient than that of ethyl chloride, as in an ordinary temperature it only liquefies under a pressure of 5 atmospheres, and has therefore to be kept in strong, tightly-closed, metal cylinders.

Bromoform (not official)

Bromoform, resembling chloroform in all its properties, was at one time recommended, but soon after abandoned, as an anæsthetic ; it has of late years been much employed internally as a remedy for *whooping-cough*, and often seems after a few days to diminish the severity of the paroxysms and shorten the course of the illness. Its action is probably not specific, but being depressant it suppresses the paroxysms of coughing. A number of cases of poisoning have been recorded, the principal symptom being a deep narcosis, which, after doses of several grammes, has a dangerous appearance, but ends as a rule in recovery, as bromoform is excreted rapidly through the lungs. The treatment consists in washing out the stomach and for the rest proceeding as in chloroform poisoning.

Preparations and Doses

Ethyl Bromidum, Ethyl Bromide, C_2H_5Br. A colourless, clear liquid, with a pleasant, ethereal odour. Boiling-point, 38°—40° C. It is very liable to decomposition, and should therefore be kept in small, brown bottles that contain only sufficient for use at one time, any that remains being thrown away. Ordinary inhalation dose, about 15 mils.

Æthylis Chloridum (B.P., U.S.P.), Ethyl Chloride, C_2H_5Cl. A colourless, clear, very volatile liquid of an agreeable odour, boiling at 12°—13° C. From 3 to 5 mils is required for inhalation. For local anæsthesia it is supplied in the above-mentioned glass capsules with capillary tubes. It is also called "kelene." *Anestile* is a mixture of ethyl chloride and methyl chloride.

Addenda

Petroleum or **Rock Oil** (*Oleum petræ*). The crude, unrefined petroleum is a thick, brown, oily liquid, probably originating in the decomposition, under high pressure, of the animal remains of former periods, perhaps marine fauna more especially. It gushes out in natural springs, or is obtained by boring, and occurs in greatest abundance in North America and in regions on the western shores of the Caspian Sea (the peninsula near Baku), but is also found in many other places, *e.g.* in Austria, Italy, Egypt and the East Indies. Its chemical composition varies somewhat with its geographical origin. The American petroleum, which rules the market in Western and Northern Europe, contains principally hydrocarbons of the methane series, from the lowest members, which are gaseous at ordinary temperatures, up to the hard paraffins. By fractional distillation of the crude oil, which in its natural condition is unsuited for illuminating purposes, a number of different products are obtained, which are put to various technical uses. The following are also of interest from a medical point of view :—

Petroleum Ether (*Petroleum Spirit*), which, together with chloroform and ether, is employed for inhalation, consists of various very volatile hydrocarbons, principally pentane (C_5H_{12}) and hexane (C_6H_{14}). Boils at 50°—60° C. Highly inflammable.

Petroleum Benzine, or *Benzine* (not to be confounded with the aromatic hydrocarbon benzol, C_6H_6, which is known commercially by the name of benzene), consists of the paraffins that boil at 60°—80° C., principally hexane and heptane (C_7H_{16}), and is often used to remove stains, as it is a good solvent of fat. It is occasionally employed as a liniment to relieve pain, as an antiparasitic for pediculi, and still more rarely internally for bronchitis, and as an antiseptic and preventive of fermentation in the intestine. Highly inflammable.

The illuminating liquid, *refined petroleum*, which consists of the paraffins which boil between 150° and 250° C. (the Caucasian petroleum contains principally aromatic hydrocarbons) is of toxicologic interest. According to investigations made by *Lewin* in the district of the American oil-springs, the petroleum-saturated air appears to have no injurious effect upon the *employés* who work in the open air. In the factory rooms, on the other hand, various skin-diseases are to be seen, and after many years at the work bronchial catarrh with dyspepsia and anæmia. It is only on remaining in the great "tanks" that acute absorptive effects appear, which are analogous to those of other volatile methane derivatives, namely,

a feeling of excitement, of lightness and freedom, soon passing into drowsiness and subsequently into fully developed narcosis, with contracted pupils, cyanosed face, and vomiting. Large internal doses produce violent symptoms of poisoning, consisting in burning pains in the throat and abdomen, vomiting, inflammation of the stomach and intestine, loss of consciousness and narcosis ; but even as much as 1 litre (attempted suicide and criminal abortion) does not seem to be fatal to adults. In children, fatal poisoning is described as loss of consciousness, weakening of respiration and circulation, coma, and death. As a drug, petroleum was formerly used for bronchitis and cystitis, and more recently in France, under the name of *huile de Gabian*, also as an anti-asthmatic.

After the volatile constituents of crude petroleum have been distilled off, thick liquid and semi-solid products are obtained, of which *liquid paraffin*, *hard paraffin* and *vaseline* will be mentioned among the fats.

Hypnotics

There is no essential difference between anæsthetics and hypnotics (see p. 7). The fundamental action is the same, the only difference between these two groups of drugs being that a slight paralysis of the cerebrum is all that is required of the hypnotics, while not merely the medulla oblongata, but also the spinal cord, shall be affected as little as possible, and that the effect shall be of much longer duration than that of the anæsthetising drugs. While, therefore, gases, or very volatile liquids that are rapidly absorbed and excreted, are employed as anæsthetics, less volatile liquids or solid bodies that remain in the organism for a longer period, and may continue to act for many hours or an entire night, are employed as hypnotics. In the present day synthetic chemistry can supply an unlimited number of narcotics, but, in order that they may be suitable for use as hypnotics, they must, as far as possible, fulfil certain *general requirements*.

The first requirement is that they shall produce sleep of sufficient depth without secondary action, especially on respiration and circulation. Among the hypnotics, too, those which contain chlorine prove to be more depressant to the circulation and respiration, and have a narrower latitude of action than halogen-free substances ; but in considering the utility of these drugs from which no very deep narcosis is required, this is of far less importance than in the case of the anæsthetising substances.

It is an advantage that the sleep shall be quickly induced, *e.g.* within half an hour. This depends mainly upon the degree of ease with which the drugs are dissolved and absorbed.

The action shall further be of sufficient duration, but on the whole be concluded after the lapse of 6 to 8 hours ; that is to say, the substance chosen as the hypnotic should be one that will be more or less rapidly excreted, or converted in the body

into an inert combination. Much recent experience (see under "Sulphonal") shows that this is of great practical importance. If the excretion takes place too slowly, continued use causes cumulative action to commence.

The necessity of employing hypnotics during a long period makes it desirable that no habit should be formed. This requirement is difficult of fulfilment, for with most hypnotics, as with their ally alcohol, continued use necessitates increase of the dose. Sulphonal forms an exception from all others.

As regards their employment, it should be noted that the methane derivatives and morphine are types of two different classes of hypnotics. The choice between them is governed by the difference in their action. If *sleeplessness* has its cause in mental strain and unrest, troubles or other psychic cause ("nervous sleeplessness"), chloral hydrate or some other hypnotic of the fatty series is prescribed. If pain or some other sensory irritant, cough or dyspnœa, is the cause of the sleeplessness, morphine is the sovereign remedy, while hypnotics of the fatty series are less valuable, as it is only by very large doses that their analgesic effect is produced. The great advantages that the methane derivatives have over morphine are that they do not cause constipation, that children can take them well, and that the danger of becoming habituated to them is far less.

Chloral Hydrate

Chloral hydrate was discovered by Liebig in 1832, and in 1869 introduced by Liebreich as a hypnotic, a very valuable addition to materia medica, which at that time had no effective hypnotic except morphine.

Action. In normal persons, chloral hydrate, in doses of 1—2 grammes, induces after 10 to 15 minutes a pleasant languor and drowsiness, which very soon passes into a quiet sleep of several hours' duration. The action is of a nature altogether similar to that of chloroform. The higher psychic functions, consciousness and notice of surroundings, are the first to be dulled; but, in favourable contrast to chloroform anæsthesia, the chloral sleep begins in the great majority of cases without any previous excitation stage. Very occasionally an atypical action is to be seen, consisting of a preliminary long period of restlessness, or, instead of sleep, the occurrence of an intoxication which takes the form of excitation and delirium. The normal chloral sleep is quiet and deep, but is often accompanied by dreams. The sleeper is awakened without difficulty by being spoken to or

touched, and, as a rule, on awakening feels quite well and clear in mind. After-effects in the form of indisposition, vomiting and headache are of rare occurrence. The pupil, which is contracted during the sleep, dilates with the reawakening. In appearance light chloral narcosis exactly resembles natural sleep, but even after ordinary doses the action is not confined to the brain alone, for the respiration seems to be a little slower than during ordinary sleep, as also the pulse ; and the blood-pressure falls a little as a rule. The face is often a little flushed, and the temperature falls 0·5°—1° C., the reason for this not inconsiderable fall being partly a greater loss of heat (vascular dilatation), partly a diminished production of heat. *In therapeutic doses* chloral hydrate does not noticeably affect the heart or respiration, and its use is not contra-indicated by diseases of the cardiovascular or respiratory systems.

After very large doses of chloral, *e.g.* 5—10 grammes, the sleep assumes the character of chloroform anæsthesia. No operative procedure is felt, all reflexes are abolished, all voluntary muscles relaxed, and respiration and pulse still further weakened. The ultimate cause of death is in most cases respiratory paralysis, or rarely sudden cardiac paralysis.

Locally chloral has a strongly irritant or almost escharotic action, and if the solution is not sufficiently dilute, produces, when taken internally, a burning sensation in the epigastrium. When applied to the skin as an ointment or poultice, it causes pain, redness and vesicles, and on wounds a white corroded surface-crust.

Fate in the Organism and Excretion. Chloral hydrate is excreted in the urine, partly unchanged, partly after reduction to trichlorethyl alcohol, which combines with glycuronic acid to form urochloralic acid, the last-named being the reducing substance in the urine, which formerly led to the erroneous supposition that chloral induced glycosuria.

Habituation and Chronic Poisoning. Nearly all sedatives and soporifics have, as already mentioned, the unfortunate property that sooner or later their effect becomes weakened, so that if their employment is continued they have to be administered in ever-increasing doses. In this respect, chloral hydrate is one of the best remedies. Habituation to it is not nearly so quickly acquired as to alcohol or morphine, but does sometimes occur. In time the doses have to be increased, and may at last rise to quantities that would be fatal to the normal person, *e.g.* 16 grammes or more. The degree of tolerance for large doses seems to differ greatly in different cases, and in some persons *chronic chloralism*—a very polymorphous type of disease—is very soon formed, in others

only after many years. From its powerful local action it will be easily understood that all kinds of digestive disturbances are among the early symptoms. Many kinds of skin-diseases (which, if there is idiosyncrasy, may appear after the very first dose), such as urticaria, petechiæ, œdema of the skin and transient erythema, may suddenly appear from various predisposing causes, *e.g.* drinking something hot (coffee) or alcohol. A pricking sensation at the edges of the eyelids sometimes occurs, usually accompanied by suffusion of the conjunctivæ and troublesome lachrymation. More disturbing symptoms are attacks of extreme dyspnœa, which may even end in death from asphyxia. Here, too, alcohol plays a part as a predisposing cause. Finally, a number of symptoms resembling those of chronic alcoholic poisoning are seen—general depression, both mental and physical, peripheral paralysis, and psychosis.

Therapeutic Uses. For ordinary sleeplessness chloral hydrate and veronal are the best remedies. Chloral is given from the first in small doses, which may often be sufficient to induce a condition of dulness which is the precursor of sleep. More serious psychic conditions of excitement, and *mental diseases*, require larger quantities. In *delirium tremens*, which was formerly treated with very large doses, some caution is requisite, as serious collapse may be a consequence of the action of massive doses of chloral hydrate on the heart weakened by alcohol. In *fever delirium* chloral hydrate is not used, but, when a sedative is to be administered, opium or morphine. As an antispastic remedy chloral hydrate, when given in large doses, has an undoubted effect in *traumatic tetanus*, and also in *strychnine poisoning*. With suitably large doses administered gradually, it is possible to reach the point at which the spasms almost cease, or are, at any rate, alleviated, before the narcotic action has arrived at a dangerous depth. Strychnine, however, does not act to any extent worth mentioning upon the medulla oblongata, when this organ is paralysed by chloroform or chloral; it has often been tried for these kinds of poisoning, but is without satisfactory results. In *epilepsy* chloral is not to be recommended, but in the *eclampsia of childbirth* it is indicated in large doses; in prolonged and violent *chorea* protracted chloral sleep (1·2 grammes chloral and 0·6 gramme potassium bromide, a good meal on awakening, and the dose then repeated) is recommended. In *sea-sickness* chloral is sometimes effectual. *Externally* it is employed in a 2—3 per cent. solution on wounds.

Contra-indications. Chloral is contra-indicated in all ulcerous complaints and inflammatory processes in the alimentary canal, especially in the stomach. In hysterical and in alcoholic subjects the atypical action, excitement instead of sleep, is often to be

observed. Neurasthenic and hysterical persons are those most apt to become habituated.

The *treatment of chronic poisoning* consists in a gradual breaking of the habit. *Acute poisoning* is treated by washing out the stomach (emetics have no effect when once the patient is in narcosis), diuretics, and for the rest as in chloroform poisoning. In advanced asphyxia the prognosis is far worse than in chloroform narcosis, because the elimination of chloral takes a far longer time. The lethal dose is stated to average 10 grammes, but varies within wide limits; death has been known to occur after 5 grammes, and recovery after 30 grammes.

Chloral Formamide (Chloralamide) (not official)

Intravenous or subcutaneous injections of ammonia raise the blood-pressure and have a stimulant action upon the respiratory centre. This gave Schmiedeberg the idea of combining an amido group with a hydrocarbon group with narcotic action, and thus producing a hypnotic—the *urethane* mentioned later—which should be without depressant action on the circulation and respiration. This principle has since been frequently utilised, *inter alia*, in the chloral formamide introduced by von Mehring, which, as the name implies, is a product of the combination of chloral with formamide. The amido group, however, is only capable of weakly asserting itself beside the powerful chloral. Chloral formamide, therefore, behaves more like a dilute chloral. As regards hypnotic effect, 1·5 grms. of chloral formamide may be reckoned equal to 1 grm. of chloral hydrate.

As might be expected, trial has been made of many of the substances that are closely allied to chloral hydrate. **Bromal hydrate,** $CBr_3.CH(OH_2)$, is far more poisonous than chloral hydrate. **Chlorbutol,** a condensation-product of acetone and chloroform which has been known for many years as a local anæsthetic, acts as a hypnotic in somewhat smaller doses than chloral hydrate, but *in animals* has a far narrower latitude of therapeutic action than chloral, and in hypnotic doses occasions a considerable fall of the blood-pressure. Another hypnotic belonging to the chloral group is **Isopral,** or trichlorisopropylalcohol, which, according to present experience, is very nearly related to chloral hydrate in its pharmacological action. **Aleudrin** (the carbamic acid ester of a dichlorisopropylalcohol), like chloral formamide, contains the amido group, and is said to have only a slight influence upon respiration and circulation; it is recommended as a sedative and soporific, and is also said to possess analgesic properties. A further group of new hypnotics is characterised by inclusion of the amido group, but using bromine instead of chlorine. This plan of construction is common to the following remedies, which, as the chemical names given to them signify, are all nearly related to one another. It is probable that many similar substances will be produced. **Neuronal** (bromodiethylacetamide) has been used as a hypnotic and also as a sedative in mental diseases and conditions of excitement. **Carbromal** (bromodiethylacetylurea) is a hypnotic and sedative of medium strength, often acting well. As it is quickly eliminated, there is no cumulation, but the action appears to become weaker with continued use. **Bromural** (bromisovalerianylurea) is a hypnotic and sedative of weak action, but with the advantage of possessing very little toxicity. It can also be given to

children. **Hedonal** (methylpropylcarbinol urethane) is a similar compound with a dose of 0·3–0·6 grm. 5–10 grs. (not official).

Paraldehyde

Paraldehyde, $(CH_3COH)_3$, which was introduced by Cervello, is considerably weaker and less reliable than chloral hydrate, but probably the least toxic of all hypnotics. It is frequently prescribed for the insomnia of febrile and toxæmic illnesses, *e.g.* pneumonia and typhoid fever. Its most important use, alternating with other remedies, is in mental diseases, where the long-continued use of hypnotics is often necessary and variety is desirable.

Paraldehyde possesses a great advantage in having little toxicity. (Two mentally deranged patients, who had each drunk 50 grms. of pure paraldehyde, merely fell into a sleep which lasted in the one case for 14, and in the other for 19, hours; and even 104 grms. produced no other result than a sleep of 32 hours' duration.) On the other hand, it has several less favourable characteristics. It is a strong local irritant, and is therefore contra-indicated in gastric and intestinal diseases; its pungent odour, which quickly causes coughing, prevents its use in bronchitis and pulmonary diseases; and, finally, it imparts to the breath, during its excretion through the lungs, an unpleasant odour which continues for a long time. Further, paraldehyde is not suitable for alcoholists, who soon discover its affinity to alcohol, and accustom themselves to its misuse. The chronic poisoning which occurs from the habitual consumption of large doses, *e.g.* 20—30 grms. daily, closely resembles alcohol poisoning.

Amylene Hydrate (not official)

Amylene hydrate, or tertiary amyl alcohol $[(CH_3)_2 . C . C_2H_5 OH]$, stands, as regards action, between paraldehyde and chloral hydrate. Over the former it has the advantage of having a pleasanter taste, and being better tolerated by the stomach; and it is preferable to chloral from its being less toxic in large doses. From 2 to 4 grammes of amylene hydrate, as a rule, produces a quiet sleep of some hours' duration, without any distinct action upon respiration or circulation.

Sometimes, as with all hypnotics, there may be after-effects in the form of headache, giddiness, feeling of indisposition and vomiting. Amylene hydrate is probably only dangerous in very large doses, judging from a case in which 27 grms. produced nothing more than a long narcosis of somewhat suspicious appearance. *Dormiol*, a combination of amylene hydrate and chloral, is recommended as being of rapid action, and in most cases reliable. It is considered by many to be one of the best hypnotics, and is said to produce after ¼—½ hour a sleep of from 5 to 8 hours, rarely followed by unpleasant after-effects.

Avertin (tribromethyl alcohol) is available dissolved in amylene hydrate; 1 mil of the solution contains 1 gramme of avertin. This is diluted to 2·5 per cent. strength before it is used. The drug is given per rectum about half an hour before the operation. It is mainly valuable as a *basal anæsthetic*, *i.e.* to render the patient unconscious by the administration of a non-volatile anæsthetic prior to using a minimal quantity of a volatile anæsthetic to induce surgical anæsthesia. Avertin is said to be somewhat depressing to the respiration and to lower the blood-pressure. *Dose*, 0·1 gramme per Kg. body-weight.

Sulphonal and Methylsulphonal (Trional)

Sulphonal, produced by Baumann in 1885 and introduced in therapeutics in 1888, was one of the most frequently employed hypnotics for a good many years.

Sulphonal really possesses many of the properties required in a good hypnotic. As a rule it produces a quiet sleep of several hours' duration without any previous stimulation stage, has no unpleasant taste, and does not irritate the mucous membranes of the alimentary canal as do paraldehyde and chloral, nor does it, like opium and morphine, cause constipation; it is more or less free from unwelcome secondary effects on respiration and circulation; and, finally, it has the very great advantage of being one of the very few hypnotics for which tolerance is not acquired, and thus the doses have not to be increased with long-continued use. One drawback to its employment is that the action is produced slowly, often not before an hour or even more has passed. This slowness of action is due to the tardy solubility of the drug, and the consequent slow absorption; but this can to some extent be overcome by practical methods of prescription. Slow in its absorption, sulphonal is also slowly eliminated from the organism, and the action therefore extends over a somewhat longer period than is desirable in the form of weariness and drowsiness the next morning. One advantage in connection with the slow elimination is that it occasionally has a welcome after-effect, namely, an inclination to sleep on the evening of the second day also.

Sulphonal is employed for *ordinary nervous sleeplessness*, and as a sedative and hypnotic in *mental diseases*. In consumptive patients it to some extent *reduces night sweats*; it may also be administered in moderate doses, *e.g.* 0·6 gramme, in cases of *acute fever*.

That which chiefly contributed to the placing of sulphonal among the most highly prized hypnotics was its apparently

almost non-poisonous character. In the few known cases of fatal acute poisoning, the doses were about 30 grammes (smallest dose, 16 grammes); but even far larger quantities did not necessarily prove fatal. Neisser, for instance, describes a case in which a young man, after taking 100 grammes, became unconscious in the course of three-quarters of an hour, had slight spasms, slept for 5 days and nights, and then recovered. Increased experience of sulphonal, however, quite altered the views regarding its harmlessness as far as a lengthened use was concerned. A dose of 1·00 –1·50 grammes every evening for only a few weeks may induce a very *serious chronic poisoning*, of which the characteristics are marked disturbances of the metabolism and nutrition. The most distinctive symptom is *hæmatoporphyrinuria*. The urine becomes scanty, assumes a dark claret colour, in reflected light almost black (hæmatoporphyrin and methæmoglobin), has a very strong acid reaction, and often contains albumin, casts and red blood-corpuscles. There are disturbances of the digestive functions, with obstinate vomiting, abdominal pains and diarrhœa or constipation. Finally, there are symptoms emanating from the *central nervous system*: prolonged condition of drowsiness and confusion, monoplegia, *e.g.* ptosis, ataxia and motor weakness of the lower extremities. If there are only slight symptoms from the nervous system, such as drowsiness and uncertain gait, recovery is possible; but as soon as the change in the urine has commenced the prognosis is very doubtful and death often ensues after steadily increasing emaciation and weakening of the heart. Sulphonal is decomposed in the organism, and is excreted in the urine as a sulphonic acid (ethylsulphonic acid); but the decomposition and excretion proceed so slowly that, even with daily doses of only 1 gramme, they do not keep peace with the supply. The cause of the poisoning must therefore be looked for in the cumulation of the unchanged substance in the body. The lesson that this teaches is that sulphonal must not be given daily for longer than, say, a week at a time. In cases where hypnotics are required constantly for months together—*e.g.* in mental cases —the use of sulphonal must be intermittent, with intervals in which the organism can be given the necessary time for elimination. Anæmia and chronic constipation have proved to be especially predisposing causes to poisoning. If the poisoning has begun, the bowels should be regulated, and an abundance of alkaline water (*e.g.* Vichy water) given, as also bicarbonate of soda, which promotes the excretion.

The formula for sulphonal is $\begin{matrix}CH_3\\CH_3\end{matrix}>C<\begin{matrix}SO_2C_2H_5\\SO_2C_2H_5\end{matrix}$. Baumann

and Kast, in their investigations as to which of its components were associated with its hypnotic action, found that only such sulphones as were decomposed in the organism and also contained ethyl groups were active, while those that contained only methyls were inactive. An attempt was therefore made to improve sulphonal by substituting ethyls for one or both of the methyl groups, the new bodies being called trional and tetronal. Of these the latter proved to be of little use, **trional,** on the contrary, of great efficiency. As regards strength of action, it is very much like sulphonal, but is absorbed somewhat more readily, and is decomposed and excreted in the form of sulphonic acid more rapidly. Sleep is therefore induced sooner, the after-effects on the following day are less pronounced, and, more important still, it appears to be attended with less danger of chronic poisoning than sulphonal, although the difference in this respect is not very great. A good many cases of poisoning of the same dangerous character as chronic sulphonal poisoning have been described, and it would therefore be wise to observe the same caution as with sulphonal.

Urethane (not official)

Urethane is founded upon the idea (see under " Chloral Formamide," p. 32) of producing a hypnotic that is indifferent to circulation and respiration by combining an amido group with a narcotic hydrocarbon group. The hypothetical carbamic acid, a near ally of urea, was chosen as the amido compound, and with it was combined an ethyl group, $NH_2—CO—OC_2H_5$. In animal experiments the new compound, urethane, seemed likely to fulfil all expectations, as the blood-pressure remained approximately at the normal height, and the respiration was strong and regular, even after doses that produced a narcosis of 24—28 hours' duration ; but in man the hypnotic action has unfortunately proved uncertain. One of its secondary effects is that it is often slightly diuretic. The result of numerous clinical experiments may be summarised in the statement that urethane is a mild remedy which fails in conditions of great excitement, but is worth a trial in slight degrees of sleeplessness and in cases in which the employment of other hypnotics is undesirable. It has no analgesic action, and in certain cases its use is prevented by nausea. Demme and v. Jaksch recommend it as a certain and safe hypnotic for children. The idea represented by urethane has encouraged attempts to produce more effective compounds by substituting other alcohol radicals for ethyl (see Preparations and Doses).

Diethylbarbituric Acid, Veronal, Barbitone

Diethylbarbituric acid (diethylmalonylurea), or veronal, $(C_2H_5)_2C(CONH)_2CO$, is also one of those nitrogenous remedies which have their origin in urea. It was introduced by Emil Fischer and v. Mehring in 1903, and for the time being has largely superseded all the earlier hypnotics. As regards its sleep-inducing properties, it is about twice as active as chloral hydrate. It is not a local irritant and does not affect digestion. In therapeutic doses it has no toxic effect upon the heart or respiration. The sleep, which is induced on an average half an hour after the administration of a dose of 0·50 gramme, is, as a rule, deep, dreamless, and refreshing, rarely followed by unpleasant after-effects. Among the secondary effects that have been observed are weariness and drowsiness the next day (a consequence of the slow elimination, concerning which more will be said hereafter), giddiness, headache, nausea, vomiting, diarrhœa, and various exanthemata (urticaria, pemphigus, measles-like rash), accompanied by itching, and sometimes also by fever. All these secondary effects, however, are comparatively rare. Veronal occupies a favourable position also as regards its *latitude of therapeutic action*, as there is a considerable interval between the effective and the dangerous dose. The fatal quantity may be put at 8—10 grammes.

In acute veronal poisoning there is usually a preliminary phase of confusion and restlessness. Deep sleep supervenes and progresses to a state of coma which may last several days according to the amount of drug ingested. At this stage there is almost invariably present a serious degree of myocardial degeneration accompanied by congestion of the bases of the lungs. These effects of veronal combined with depression of the vital centres in the medulla account for the cyanosis usually present in acute poisoning. In patients who survive, extreme depression, muscular weakness and low blood-pressure are found. Memory is impaired and there are difficulties with articulation. Ocular complications include nystagmus and paresis of the extrinsic muscles. Morbilliform and scarlatiniform eruptions are fairly common and careful nursing is required to prevent sores developing at the pressure-points.

The *indications* for veronal are like those for the other hypnotics, namely, *ordinary nervous sleeplessness*, *mental diseases*, etc. It compares favourably with the other remedies of the fatty series in having a slightly analgesic action, and can therefore be employed where the cause of the sleeplessness is some slight somatic affection, such as moderate pains or coughing. Veronal is recom-

mended as a sedative in illnesses of the most varied character, *e.g. delirium tremens, nightly epilepsy*, for *tremor* in *Parkinsonism*, and after *operations on the eye*, where perfect repose is desirable ; and it is also said to be useful in the *vomiting of pregnancy* and for *sea-sickness*. Like sulphonal, it also checks the *night sweats* in *phthisis*.

As already mentioned, the employment of veronal has increased with extraordinary rapidity ; but the abundant experience thereby gained has shown that it is not so innocent as it at first appeared to be. Its weak point is that its excretion takes place slowly, a character that must always give ground for some caution. Veronal passes for the most part through the body unchanged, about 70 per cent. being found in the urine ; but even after a single dose of 0·50 gramme the excretion takes several days. The consequence of this is that after continued use of the ordinary doses for a comparatively short time cumulative effects may appear in the form of a continuous slight intoxication with confusion and uncertain gait. After continued use for a long period a serious *chronic poisoning* begins, which manifests itself by emotional and intellectual depression. Numerous nervous syndromes may be simulated including general paralysis and Parkinsonism. Oculo-motor pareses, pyramidal symptoms and ataxia of gait and speech are observed in a high proportion of cases. Alimentary disturbances, *e.g.* anorexia, vomiting, constipation, etc., are usually present. Anæmia and hæmatoporphyrinuria are also recorded. Thus, although less dangerous in this respect than sulphonal, veronal must also be used only for a short period—*e.g.* 1 week—at a time and then put on one side in order that complete elimination may take place. The danger of cumulative action is reduced by giving the drug dissolved in a large quantity of hot liquid, whereby diuresis and excretion are promoted, and absorption and action are more rapidly achieved.

The principle of the mixture of narcotics (the potentiation of the action of drugs with different points of attack, see p. 18) is, of course, applicable to hypnotics. Small doses of morphine, for instance, or codeine, may be combined with small doses of veronal, and thus attain an action that is distinctly beyond their added result.

Treatment of Veronal Poisoning. Treatment of acute poisoning aims at rapid removal of the drug from the body. This is accomplished by thoroughly washing out the stomach and by draining off the cerebrospinal fluid by lumbar and cisternal puncture. An ounce of kaolin or animal-charcoal should be introduced into the stomach through a stomach-tube and washed down with about a pint of strong black coffee. Strychnine hydrochloride in

full doses (8 milligrms.) should be injected subcutaneously every hour until the reflexes return. Coramine (1 ampoule of 5·5 mils) should be given intravenously as a cardiac stimulant and may be repeated hourly until 20—30 mils have been injected. Leschke advises the intra-thecal administration of 2 mils of ordinary camphorated oil (10 per cent.) which ascends through the cerebro-spinal fluid to the ventricles of the brain and stimulates the respiratory and vasomotor centres. In *chronic poisoning* attempts are made to promote excretion of the drug by means of alkaline mineral waters and other diuretics ; further, symptomatic treatment on the lines indicated above.

Veronal can be varied in several ways. In **Luminal** an ethyl group is replaced by C_6H_5. The introduction of the phenyl group is accompanied by greater stability of the drug, and although phenobarbitone is more powerful than barbitone (veronal), its sedative action is relatively slower and somewhat prolonged. Hence it is most suitable for use in neuroses and in epilepsy where a sustained action is required. On the other hand, when the *iso*-amyl group, C_5H_{11}, is introduced to replace an ethyl group, the compound is broken down rapidly in the tissues. Thus sodium amytal produces its effects rapidly, but they are of short duration. Accordingly, this and similar preparations are selected for producing *basal anæsthesia*. The sodium salts of barbitone and phenobarbitone are official preparations ; they are soluble salts and can therefore be administered in aqueous mixtures or parenterally. Sodium phenobarbitone should not be prescribed with ammonium bromide nor with hydrochloric acid. The bromides of sodium and potassium are, however, compatible with the soluble barbiturates.

About sixty derivatives of diethylbarbituric acid are available and many more can be synthesised. A number of the better known preparations are mentioned under Preparations and Doses.

Preparations and Doses

Chloral Hydras (B.P.), **Chloralis Hydras** (U.S.P.), Chloral Hydrate, $CCl_3.CH(OH)_2 + H_2O$. Colourless crystals of a refreshing, melon-like odour and disagreeable, sharp, stinging taste, very readily soluble in water. *Dose*, 3—12 decigrms., 5—20 grs. (B.P.) ; 0·6 grm., 10 grs. (U.S.P.). On account of its highly irritant properties, it cannot be injected subcutaneously. It is best given internally with some sweet flavour corrective, *e.g.* in the form of the following preparation. In tetanus and eclampsia, 2 grms. as an enema every 2 hours until effective.

Syrupus Chloral (B.P.C.), Syrup of Chloral, 20 per cent. *Dose*, 2—8 mils, 0·5—2 fl. drs.

Chloral Formamidum (B.P.C.), Chloral Formamide, $CHCl_3.CH—(OH).NH.CHO$. Colourless and odourless crystals, readily soluble in water. *Dose*, 1—3 grms., 15—45 grs.

Butyl-Chloral Hydras (B.P.C.). $CH_3.CHCl.CCl_2.CH(OH)_2$. Action similar to that of chloral hydrate over which it has no notable advantages. *Dose*, 0·3—1·2 grms., 5—20 grs.

Chlorbutol, Chloretone, (B.P.), **Chlorbutanol** (U.S.P.), Chloretone, $(CH_3)_2.CCl_3.COH. + \frac{1}{2}H_2O$. Colourless crystals with a camphoraceous odour, slightly soluble in water. *Dose*, 0·3—1·2 grms., 5—20 grs. (B.P.); 0·6 grm., 10 grs. (U.S.P.). Externally as a dusting powder or ointment (5—10 per cent.) in pruritus and other skin conditions. A saturated solution of chlorbutol in oil of Clove is an effective obtundent. In commerce, in 1—2 per cent. solution, under the name of Aneson or Anesin.

Isopralum, Isopropylalcohol, $CH_3CCl_3.CH.OH$. Colourless prisms with a camphoraceous odour and aromatic, biting taste, freely soluble in water. *Dose*, 0·5—1·5 grms., 8—25 grs. Is very volatile, and therefore best prescribed in tablets or in solution.

Carbromalum (B.P., U.S.P.). A sparingly soluble, white crystalline solid. *Dose*, 3—6 decigrms., 5—15 grs. (B.P.); 5 decigrms., 8 grs. (U.S.P.). Given in average doses of 1 grm. as a hypnotic, and in half-doses, for instance thrice daily, may be used as a sedative in conditions of nervous excitement. This also applies to *Bromural*, *Aleudrin*, *Neuronal* and *Adalin*. *Dose*, 3—10 decigrms., 5—15 grs., in powder or tablets. They have often proved good remedies in cases of slight sleeplessness.

Paraldehydum (B.P., U.S.P.), Paraldehyde, $(CH_3.COH)_3$. Transparent, colourless liquid of aromatic odour and first burning, afterwards cooling, taste, soluble in about 9 parts of water. *Dose*, 2—8 mils, 0·5—2 fl. drs. (B.P.); 2 mils, 30 mins. (U.S.P.). Is prescribed in 10 per cent. aqueous solution with the addition of sugar, or in brandy and water.

Amyleni Hydras, Amylene Hydrate, $(CH_3)_2.C.C_2H_5OH$. Clear, colourless liquid of aromatic odour and burning taste. *Dose*, 2—6 mils, 0·5—1·5 fl. drs. Is prescribed in the same way as paraldehyde.

Dormiol, Amyl Chloral, an oily liquid, with camphoraceous odour and at first burning, then cooling, taste. *Dose*, 5—30 decigrms., 8—50 grs., in capsules or as a 10 per cent. solution in milk.

Sulphonal (B.P.), Sulphonal, $(CH_3)_2.C.(SO_2C_2H_5)_2$. Colourless crystals, inodorous and tasteless, almost insoluble in cold water, soluble in 15 parts of boiling water. *Dose*, 3—12 decigrms., 5—20 grs. (B.P.). Given in a glass of hot water or with alcohol (whisky) in which it is soluble, as this hastens the absorption and action.

Methylsulphonal (B.P.), **Sulphonethylmethanum** (U.S.P.), Trional, $C_2H_5.CH_3.C.(SO_2C_2H_5)_2$. Colourless, shining, acicular crystals, with slightly bitter taste, soluble in 320 parts of cold and in 10 parts of boiling water. *Dose*, 6—12 decigrms., 10—20 grs. (B.P.); 0·75 grm., 12 grs. (U.S.P.). Given, like sulphonal, in hot water.

Æthylis Carbamas, Urethane, $NH_2.CO.OC_2H_5$. Colourless crystals, without taste and smell, very readily soluble in water and in alcohol. *Dose*, 1 grm., 15 grs. Larger doses generally required, *e.g.* for adults 2—4 grms., for children under 2 years 2 decigrms., and for children of 2—3 years 5 decigrms.

Barbitonum (B.P.), **Barbitalum** (U.S.P.), Diethylbarbituric Acid, Veronal, $(C_2H_5)_2.C.(CONH_2)_2.CO$. Colourless crystals of slightly bitter taste, sparingly soluble in cold water. *Dose*, 3—6 decigrms., 5—10 grs. Given best in a glass of hot water or tea. For infants 25 milligrms.; for older children 5—7 centigrms. The sodium salt, **Barbitonum Solubile** (B.P.), **Barbitalum Solubile** (U.S.P.), *Sodium veronal* or *Medinal*, which is

soluble in 5 parts of water, may be given as injections or subcutaneously. Doses similar to those of veronal.

Proponal, Dipropylbarbituric acid. Colourless crystals, sparingly soluble. *Dose*, 2—5 decigrms., 3—8 grs. *Dial*, diallylbarbituric acid. A colourless crystalline powder, very slightly soluble. A strong remedy. *Dose*, 1—3 decigrms., 2—5 grs.

Phenobarbitonum (B.P.), **Phenobarbitalum** (U.S.P.). Luminal, Gardenal, Phenylethylbarbituric acid. A white crystalline powder with bitter taste, almost insoluble in water. *Dose*, 3—12 centigrms., ½—2 grs. (B.P.); 3 centigrms., ½ gr. (U.S.P.). In epilepsy the smallest doses that prove to be effectual, *e.g.* 1 decigrm. two or three times a day, or 1—2 decigrms. in the evening, are given for an indefinite period.

Phenobarbitonum Solubile (B.P.), **Phenobarbitalum Solubile** (U.S.P.). The sodium salt of the above. Administered in aqueous solution orally or parenterally. *Dose*, as with phenobarbitone.

Sodium Amytal, sodium iso-amyl-ethyl barbiturate, a structural isomer of Nembutal (see below). A white crystalline powder, soluble in water. Small doses are hypnotic, larger doses act as basal anæsthetics. Usually administered orally or per rectum, but a very rapid action results from intravenous injection. Unconsciousness lasts 4 to 6 hours and major operations can be carried out with minimal quantities of ether or other volatile anæsthetic. *Dose*, hypnotic: 0·06—0·2 grms., 1—3 grs.; anæsthetic: 0·2—0·6 grms., 3—10 grs.; anæsthetic dose per rectum: 0·015 grm. per Kg. body-weight administered in 3 per cent. solution. *Nembutal*, pentobarbitone, sodium ethyl-methyl-butyl barbiturate. Uses in general resemble those of amytal but effects are of shorter duration and nembutal is said to be less depressing to the heart and respiration. In combination with chloral hydrate it is extensively employed in parturition on the same principle as Morphine-Scopolamine narcosis (p. 117). *Dose*, 1—2 decigrms., 1½—3 grs., by intravenous injection: 2—3 decigrms., 3—5 grs., in 10 mils (120 mins.) water. *Evipan* is N-methyl-C-C-cyclohexylmethylmalonylurea. Hypnotic *dose*, 0·25—0·5 grm. 4—8 grs. or more. *Evipan Sodium*, the sodium salt of the above. Intravenous injection rapidly produces general anæsthesia. *Dose*, 7—10 mils 10 per cent. solution in water. For technique of administration, indications and contra-indications, special literature should be consulted.

Nirvanol, Phenyl-ethyl-hydantoin, $\begin{matrix}C_6H_5\\C_2H_5\end{matrix}\!\!>\!C\!<\!\!\begin{matrix}CONH_2\\NHCO\end{matrix}$, hypnotic and sedative. Used also in chorea, for a child, 0·3 grm. (5 grs.) daily for about 10 days until "Nirvanol sickness" occurs, characterised by pyrexia and a morbilliform eruption, when the drug should be discontinued. The treatment has not been attended by conspicuous success. Slightly soluble, white crystals. *Dose*, 5 decigrms., 8 grs.

Alcohol

Ethyl alcohol, known as a beverage from prehistoric ages in the form of various fermented liquors, is obtained by fermenting glucose, cane sugar, or starch that has first been converted into sugar. In addition to the ordinary method of production, it is formed in great quantities in the working of bakers' dough, but is almost entirely dissipated by the heat of the oven. (In new

bread there is about 0·3 per cent. of alcohol, after 24 hours much less.) Alcohol is also produced in many ways besides the typical fermentation. It is to be found, for instance, in rich mould, passes, as a product of dry distillation, into coal-tar and animal oil (*oleum animale*), and, finally, is found to exist in certain plants and in most of the organs of various animals (dog, horse, guinea-pig, rabbit, calf, ox), perhaps originating in the decomposition of the carbohydrates in the intestine by ferments or bacteria. According to Schweissheimer, human blood contains 0·03 per cent. alcohol.

Action. The **general type** of alcoholic action is so well known that there will be no need for more than a mention of its principal features. In small doses alcohol produces, in most cases, a sensation of mental and physical well-being, and a contented, benevolent, communicative state of mind. If the dose is increased, this develops further into what is called an animated condition, a certain psychical instability, which causes the individual to react more readily than is normal for him, and produces a freer, more untrammelled behaviour than is usual with him. A very general and very characteristic symptom is talkativeness even in persons who are otherwise very reserved and embarrassed; if speeches are made, the speakers are very well pleased with what they themselves say, also a pathognomonic symptom. At this stage of the action the head feels hot, the face is congested, the carotids throb, the pulsation of the temporal arteries is visible, and the radial pulse is about 100 and well filled. Soon it will be observed, especially in working men, that there is a tendency to commit impulsive, unpremeditated acts, and to boast of their physical strength. The brain-worker is better able to maintain an appearance of dignity, but is affected in the same way: his self-esteem is generally greatly increased (rarely the reverse), he believes he can overcome many difficulties that make his daily life commonplace, feels himself on the whole to be a highly endowed man, and shapes his speech and actions accordingly. It is this condition which forms one of the greatest allurements in the indulgence in alcohol, and ascribes to the bottle the credit of being a friend in adversity. If indulgence is continued beyond this stage, intoxication, or acute alcoholic poisoning, ensues rapidly. The mental balance is completely lost, all kinds of meaningless actions are performed, the gait becomes unsteady, the utterance is indistinct, and the previous animation gives place to drowsiness and inclination to sleep. Nausea and vomiting frequently make their appearance, and the flushed condition of the face is superseded by pallor. After very large doses the action becomes similar to ether or chloroform anæsthesia. There is com-

plete insensibility and narcosis, muscular relaxation, soft pulse, lowered temperature, stertorous breathing, cyanosis, and, finally, death from respiratory paralysis. Even after many hours' narcosis, however, acute poisoning nearly always ends in awakening and recovery attended by the well-known after-effects—physical and mental depression, vomiting and throbbing headache.

The whole of the above description shows that alcohol, like its chemical allies, chloroform, ether, and all the hypnotics mentioned in the preceding chapter, acts upon the central nervous system in the consecutive order—brain, spinal cord, medulla, oblongata, and that the subsequent stages of the action consist in paralysis. There is a difference of opinion, however, regarding the nature of the initial action of alcohol. Binz and his pupils, in numerous treatises, maintain the old-time theory that alcohol first acts as a stimulant on the nervous system, and then paralyses, while Schmiedeberg has established the new doctrine that from the very first the action of alcohol is purely narcotic, and that the stimulation is only apparent, elicited by the previous paralysis of certain cerebral functions that play a controlling part, and give a character of self-restraint to the behaviour of the individual in everyday life. He ascribes all the above-mentioned symptoms, the altered manner, the spontaneous behaviour, and the confident expression of opinion on all possible subjects, however little understood at other times, to the fact that it is the finer shades of judgment, reflection and, more than all else, self-criticism, that are first of all lost, while other, more subordinate, functions carry on an uncontrolled activity for some time longer.

This latter view seems to find support in the more extended acquaintance with the **psychical action** of alcohol that recent years have brought. Numerous writers have endeavoured, by the aid of experimental-psychological methods, to make a quantitative analysis of the influence of alcohol on various kinds of brain-work, such as the addition of figures, learning by heart, forming an opinion, judging of time, choosing promptly, perception of sound, light, etc. The results show that an altogether favourable effect, without subsequent lowering of the achievements, is only seen after very small doses, *e.g.* 5 grammes, whereas even moderate doses have in the majority of cases a pronounced paralysing action, and that the easiest, least complicated, work suffers least. Skill in adding up, for instance—in the main a matter of routine—is not greatly diminished by even large doses (80 grammes), whereas the memory, measured by the ability to learn rows of figures by heart, is distinctly impaired by a foregoing consumption of even 20—40 grammes. After the same doses the power of perception (tested by the reading of syllables and words that

are shown quickly to the eye through a narrow slit) suffers greatly. The association of ideas, *i.e.* the association that the subject of the experiment is able to attach to a given word, is changed by replacing the more valuable inner association, or thought-association (*e.g.* stream as water), with an external association in which similarity of sound, rhyme and the like, play the principal part (*e.g.* stream, seam). After small doses (7·5—10 grammes) work that is connected with some motor action is at first made easier by the shortening of the time of reaction, but the accuracy of the work suffers. If the subject of the experiment is required to perform as quickly as possible, at a given signal, one of two movements previously agreed upon, *e.g.* either with right or with left hand (choice-reaction), he responds more quickly to the signal under the influence of alcohol, but the number of mistakes increases. The sum of many and varied experiments shows that the cerebral activity suffers more the more it demands an intellectual adaptation of the impressions received. The subjects of the experiments are themselves, however, always of opinion that under the influence of alcohol they have done better work—a very characteristic feature of which a parallel is met with in ordinary life in the form of enfeebled self-criticism after drinking alcohol. Taken all together, the interesting phenomena which these experiments have brought to light are, when carefully considered, only a reproduction on a reduced scale of the symptoms which, at the beginning of intoxication, are to be seen more coarsely pronounced. The shortening of the reaction period and the easier performance of movements answer exactly to the proneness of the intoxicated man to impulsive actions, and the predominance of the superficial association of ideas, to his empty eloquence ; and the whole is most naturally explained as a result of depression, not of stimulation.

The influence on **muscular work** has been investigated by letting a certain load be lifted at regular intervals until the muscle is no longer able to raise it, upon which follows a brief pause, then a fresh series of contractions, and so on, until complete exhaustion ensues. Elaborate experiments, made by Hellsten (1904) and others, show that alcohol, almost immediately after its consumption, increases the amount of work performed, but soon after (after 4 to 40 minutes) a diminution of working power of comparatively long duration (2 to 10 hours) takes place, so that the total amount of work performed after alcohol becomes less.

In these investigations the same feature is once more met with, namely, that the subject of the experiment has himself, even when his performances have been bad, the impression that

he does more with than without alcohol. The reason is that the feeling of fatigue is lessened, due to the narcotic action. Thus the result of exact muscular experiments is that alcohol may be favourable to a momentary and indiscriminate development of strength, but is distinctly detrimental to prolonged labour. This accords with the result of many experiments carried out with soldiers, which show that troops that have not taken alcohol do a longer day's march, and after going through exertion are in better condition than those that have had a moderate alcohol ration. Similar experience was long ago gained by professional athletes, who eschew alcohol when training.

How alcohol acts upon the **circulation** is at present far from clear. The facts recorded concerning *blood-pressure* are various. According to experiments initiated by Binz, who, as regards the circulation, maintains the theory of a direct stimulating action, the blood-pressure rises considerably in man after 50—75 c.c. of sherry. Other investigators have found, in animals and man, sometimes no distinct effect, sometimes a slight rise, which Dixon and Kochmann ascribe to contraction of the abdominal vessels. The *cutaneous arteries*, especially those of the face, are dilated in man even after small doses. The increased *pulse-frequency* occurring with the drinking of alcohol in company is a secondary effect, produced by the exhilarating environment and other similar subsidiary circumstances. If such extraneous factors be excluded by letting the subject of the experiment lie in bed and consume alcohol in peace and solitude, even large doses occasion no change in the frequency of the pulse.

In order to exclude the influence of the vessels, and obtain the simple *heart-action*, various experiments have been made with excised hearts of mammals. The result that several investigators obtained from these experiments is that the heart is not affected by small quantities of alcohol, and by large quantities is only injured. Others have found that a low concentration of alcohol acts beneficially, especially when the heart has previously been weakened by having worked for some time without sufficient nourishment, while the effect was absent or doubtful in normally working and well-nourished hearts. This condition of things, no traceable effect on the normal organ, but improved contractions in weakened heart-action, is also found with camphor, as will be mentioned in detail later. Fig. 2 illustrates the effect on the excised heart of a rabbit.

It is probably the vascular dilatation, which allows a greater quantity of blood than usual to gather in the surface arteries, that makes alcohol an **antipyretic.** The fall in temperature after the usual doses amounts, however, to only 0·5°—1° C. If an

intoxicated person when asleep be exposed to the cold of winter, his temperature, owing to the increased radiation of heat through the dilated cutaneous vessels, may fall very considerably—an occasional cause of death in northern latitudes.

The effect on the **respiration** is investigated by measuring its amount, *i.e.* the volume of the inspired and expired air in normal condition, and after varied quantities of alcohol. The experiments show that after moderate doses this increases a little in healthy, unfatigued persons, and far more in weary persons ; and that the kinds of ether which give to wine its bouquet have a considerable share in this effect. The question is now once more whether alcohol does directly stimulate the respiratory centre, or has the increased volume of respiration another cause, *e.g.* an endeavour to make good the loss of heat by increased oxidation, which

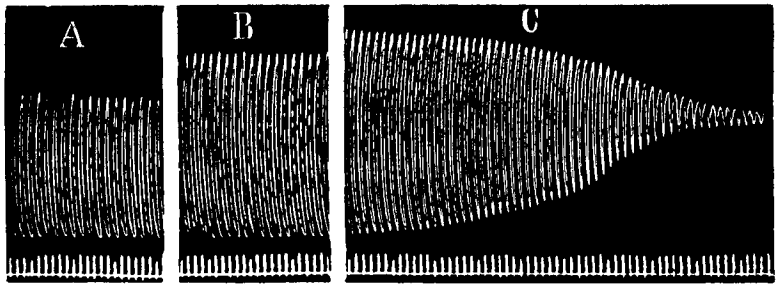


FIG. 2.—Excised heart of a rabbit perfused with Ringer-Locke's solution. *A*. Normal heart action. *B*. Improved systole after 2 minutes' perfusion with 0·4 per cent. alcohol. *C*. 0·8 per cent. alcohol : first still higher systole, but soon after toxic action. (Dixon.)

secondarily produces stronger respiration ; or is the latter only due to greater activity of the stomach and intestine, just as after an ordinary meal ? Numerous experiments have not made this clear. Endeavours have been made, for instance, to find a test for the irritability of the respiratory centre by determining the manner in which it reacts to inhalation of carbonic acid in a definite concentration, that is to say to an accumulation of carbonic acid in the blood. If its irritability were increased by alcohol, it would be expected to react more sensitively than in the normal condition. In such experiments Loewy found, however, in man after 35 c.c. no distinct alteration of the typical reaction. No positive proof that alcohol is a direct stimulant of respiration has been produced.

Fate in the Organism and Excretion. Is Alcohol a Food ? This important question has now, after much controversy, been settled. It was originally assumed that alcohol, after having circulated for a short time in the blood, was excreted from the

body unchanged, and therefore could not serve as a food. It was proved by Binz and others, however, that only a small percentage —according to Atwater and Benedict's investigations (1902), only 1—2 per cent.—is excreted unchanged through the kidneys, the lungs and the skin. The oxidation in the body requires a certain length of time, about 12 hours, in a normal individual after a single large dose, *e.g.* 100 c.c. (see Fig. 3, p. 50). Only very slight traces are found in the milk. In the case of a woman who received 60 c.c. of brandy, only 0·009 c.c. of alcohol was found in the milk evacuated after 3 hours (46 grammes). Thus the greater amount undergoes combustion in the body. It is further shown, by the fact that the carbonic acid excretion and the absorption of oxygen after the administration of alcohol are but little increased in man, that alcohol does not undergo combustion uselessly, but is oxidised in the place of other substances, which it thus spares, as they would otherwise, during the same period, have undergone combustion ; and the common experience that drinkers become fat leads to the conclusion that it is fat in the first place that is spared.

The last point, which is of the greatest interest and has been most actively discussed, is the question whether alcohol, like fat and carbohydrates, can, by its combustion, economise protein. This may be tested in two ways : alcohol may be added to an already sufficient diet, and then, if alcohol spares, *i.e.* protects, protein from combustion, the nitrogen elimination in the urine must decrease ; or a certain amount of the carbohydrates or fat of the food may be replaced by the amount of alcohol equivalent to it in combustion value, when, if alcohol can take the place of these substances, the excretion of nitrogen must remain unaltered. After the first experiments made in one or the other of these ways, it seemed as though alcohol had not the power of sparing protein ; but, notwithstanding that the experiments were carried out with irreproachable technical skill, their results were still incomplete, for it appeared that the alcohol-periods employed (a few days) were far too short. In an experiment that covered in all 35 days, Neumann (1899) arrived at a different result. After having first brought himself to nitrogenous equilibrium, he omitted 77 grammes of fat in the second period (4 days), during which time protein underwent combustion in the place of the fat, and an increase took place in the excretion of nitrogen. During a third period (10 days) 100 grammes of alcohol (answering to the deficit of fat) were added. For the first 4 days the loss of nitrogen continued, but in the remaining 6 days the nitrogenous equilibrium was restored. Exactly the same result has been given by all subsequent investigations, some of which were

made during fever (Ott). The explanation evidently is that large doses of alcohol act at first as a protoplasmic poison, which causes increased waste of protein; but after a few days, when the organism has become accustomed to alcohol, this deleterious influence ceases, and the protein is again economised. If the arrangement of the experiment is altered in such a way that in the first alcohol-days rather smaller doses are taken, no temporary toxic effect occurs, and the economising of protein is fully apparent whether it is carbohydrate or fat that is replaced by alcohol. The result of many laborious investigations is therefore that *alcohol, in moderate doses, as combustible material replaces isodynamic quantities of fat and carbohydrates, and economises protein on the same scale as is done by carbohydrates.* It is unnecessary to add that this is the matter regarded only from a chemical point of view, and that *the effects upon the nervous system most certainly deprive alcohol of all real value as a food for healthy persons.*

Digestion and Absorption of Foods. In dogs with gastric fistula, the gastric juice can be seen beginning to flow immediately after the introduction of a few drops of alcohol into the mouth or stomach. Small doses of the concentrated alcohols (spirits and liqueurs) sharpen the appetite, and by their pleasant taste and locally irritant effect upon the mucous membranes produce salivation and increased secretion of very acid gastric juice. The latter effect, however, is obtained only when the doses are so small that the concentration of alcohol in the contents of the stomach does not amount to more than 3 per cent. If it rises to 5 per cent., no effect is seen, and a concentration of more than 10 per cent. hinders the secretion. The effect on the digestion otherwise and on the absorption has been made the subject of many investigations and conflicting interpretations, which have lost their interest since the above-mentioned investigations of the metabolism by Atwater and Benedict. In these the utilisation of the food was investigated by determining the amount of nitrogen, fat and carbohydrates that passed out unutilised with the fæces in the normal periods and in the alcohol-periods; and it appeared that daily doses of 60—120 grammes of alcohol had no distinct influence upon the absorption of the foods. Large doses hinder, as already mentioned, the excretion of hydrochloric acid and the action of the pepsin; and long-continued abuse of alcohol in concentrated form produces gastric catarrh. The instinctive use of alcohol with fat foods, which was formerly taken as a proof that it promoted the digestion of the fat, has probably had its origin in the fact that the impression made on the gustatory nerves by concentrated alcohol is calculated to counteract the nausea that readily arises from the eating of large quantities of fat (*cf.* the

analogous employment of other substances with strong flavour, *e.g.* mustard).

No influence on the **metabolism** is known except that consequent on the circumstance that alcohol by its combustion spares other substances. As the consumption of alcohol by gouty subjects may produce, as is well known, acute attacks of gout, special attention has been paid to the uric acid ; but it has been found that its excretion in the healthy person is not changed. The **amount of urine** after both small and large doses of alcohol is somewhat increased. The reason of this is not exactly known.

Locally alcohol acts as an irritant, as it precipitates albumin and absorbs water. On the skin it produces by evaporation a feeling of cold ; but applied for some time as a poultice, closely covered, it causes redness, inflammation and vesicles. Spirit of more than 70 per cent. strength acts upon mucous membranes almost corrosively. Alcohol is **antiseptic,** but not to any great extent ; the fermentation of wine, as is known, does not cease until about 15 per cent. of alcohol has been formed. On bacteria 50—70 per cent. alcohol seems to be more effective than the concentrated alcohol, which perhaps has more difficulty in penetrating the bacterial bodies.

Habituation and Chronic Alcoholism. The individual reaction to alcohol varies greatly. With long use, tolerance for the acute effects may be so much increased that many persons are able to consume, with a certain degree of pleasure, amounts (*e.g.* 1 or 2 bottles of spirits daily) that in the unpractised person would produce dangerous poisoning. This is probably to be accounted for partly by " habituation of the nerve-cells," partly by the capacity, acquired by practice, of subjecting the alcohol to rapid combustion, for Schweissheimer found in drunkards after similar doses a smaller percentage in the blood, and disappearance from the blood in half the time required in normal persons (see Fig. 3). Animals, too, that have become habituated, free themselves more quickly from alcohol than normal control-animals.

Continued abuse of alcohol produces chronic poisoning, in which nearly all functions and organs are impaired. A detailed description of the symptoms is more the concern of a monograph, and only the most important features will be indicated here.

In the first place, the *central nervous system* suffers. The loss of intelligence, which is a transient effect during periodical excesses, becomes permanent with habitual abuse. Dulness and an impaired memory ensue, mental activity, elasticity, and all higher faculties of mind are lost, and the entire psychical life moves (in accordance with the simplified association of ideas, *cf.* p. 43) on to a lower plane, not only in the drunkards, but also in

the far greater number of those whose steady consumption of alcohol apparently leaves them unharmed. Inflammatory processes in the *peripheral nerves*, the recently recognised polyneuritis alcoholica, are the underlying cause of the well-known motor symptoms—tremor, paralysis and ataxic conditions (pseudotabes). After disorders of the nervous system the complaint of most frequent occurrence is *inflammation of the mucous membranes*. The local irritant action of alcohol occasions catarrh in the throat, and also more especially in the stomach, with the well-known symptoms : anorexia, muculent morning vomiting, and irregular bowels. Gastric catarrh, with consequent poor nutrition, appears earlier in proportion as the concentration of alcohol in the beverage consumed is greater ; dilution weakens

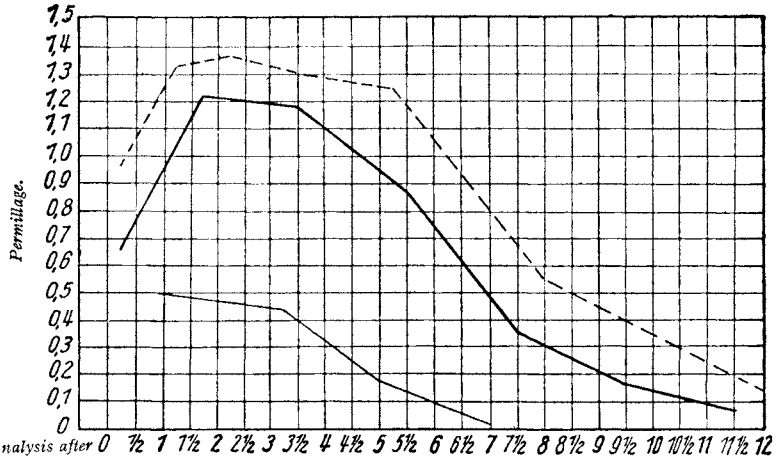


FIG. 3.—Alcohol in the blood after a single large dose (1·57 c.c. per kilo. of body-weight) : - - - - - - of abstainers, ——— of moderate drinkers, ——————— of drunkards.

this local action, and the alcohol appears in its *rôle* of economiser. The typical beer-drinker is therefore fat, the typical spirit-drinker thin. The face is turgescent, the nose and cheeks of a bluish colour due to the dilated vessels, and frequently there is acne rosacea ; in acute intoxication the colour becomes of a more fiery tinge (arterial dilatation). The changes that occur in *vessels, kidneys* and *heart* are of the greatest significance with regard to the length of life. Chronic alcoholic endarteritis is one of the most frequent causes of apoplexy. In the kidneys, the well-known shrinking of the interstitial tissue, Bright's disease, is found. The heart suffers, partly secondarily, as a consequence of diseases in the vessels or kidneys, partly primarily, from a chronic myocarditis with fatty degeneration and loss of muscular tissue. The heart-weakness consequent on this is often latent in

ordinary life (for the alcoholic shuns physical exertion), but is a very frequent cause of death when much strain is put upon the heart, *e.g.* in acute febrile diseases, and above all pneumonia. In addition to the alcohol, the great amount of liquid with which the heart is loaded in a large consumption of beer has a deleterious effect (hypertrophy of the heart, *Bierherz*). Chronic diseases also, especially epilepsy, syphilis, arthritis urica and diabetes, run a more dangerous course in alcoholists. In women, the *milk secretion* diminishes or ceases, infant mortality being thus indirectly increased.

The effects of an habitual use of alcohol are especially harmful to *children* (stunted bodily growth and mental development, neurasthenia, epilepsy). The *offspring* of habitual drinkers frequently present infirmities of the most varied nature—a circumstance that has not yet been sufficiently investigated. It is difficult, however, to unravel the causal conditions. A propensity to the abuse of alcohol is often a symptom co-ordinate with other abnormalities, and alcohol is therefore frequently blamed for consequences which in reality have nothing to do with it. The pairing of alcoholised guinea-pigs is, as a rule, either without result or produces abortion.

A very peculiar symptom of chronic alcoholism is *delirium tremens*, an acute mental disease, the characteristics of which are its generally rapid course and its being accompanied by very acute delirium and hallucinations of hearing and sight (the patient sees especially all kinds of small animals, such as flies, snakes, rats, etc.). The first attack generally ends, after a few days' illness, in recovery, while a relapse may pass into permanent mental disease or terminate in collapse and death. The outbreak of delirium can nearly always be traced to a definite cause, unusually great drinking-excesses ; but internal diseases (especially pneumonia) or serious injuries (fractures) predispose. Sudden withdrawal of spirituous liquor seldom, if ever, produces delirium.

In *dipsomania*, with its sharply-defined attacks and free intervals resembling epilepsy, and by many designated as a variety of that disease, the consumption of alcohol takes place in a way that differs from the ordinary forms of alcoholism. Dipsomaniacs (quarterly drinkers) are often persons who for months may lead a most exemplary life, until premonitions of an attack—in women sometimes coincident with menstruation—appear in the form of anxiety, cardialgia and great congestion, the whole sometimes concluding with a regular epileptic fit. Most frequently, however, this discharge does not take place, the anxiety increases, sleep vanishes, a deep depression develops, with restlessness and desire for movement, and, in an irresistible

craving for alcohol, the patient falls upon all spirituous liquors (wine, spirits, methylated spirits, eau de Cologne, etc.). The sufferer may continue to drink for several days without typical intoxication, without sleep, and without the next-morning headache. When the attack is over, the patient keeps his bed for several days with protracted after-effects, and then resumes his daily occupation, to which he may give his careful attention until the next attack. In close relationship to dipsomaniacs are neuropaths, dangerous persons who exhibit the pathological or *abnormal alcohol-reaction*. It is characteristic of these persons that alcohol produces in them, generally without the ordinary signs of intoxication, staggering gait, etc., a complete unconsciousness and confusion, frequently accompanied by the most violent impulses (desire to see blood, sexual pleasures), that are yielded to blindly. It is by such persons that many of the most horrible crimes are committed; and their perpetrators are subjects, not for prisons, but for criminal lunatic asylums.

Therapeutic Uses. Alcohol was formerly almost invariably prescribed in *acute febrile diseases*, upon the assumption that it had a stimulating action upon respiration and circulation, more especially the latter. For habitual drinkers this treatment seems to be beneficial, but with this exception opinion as to its usefulness has latterly been somewhat divided, and the premises for its employment are various. Many clinicians still consider alcohol to be a direct cardiac stimulant, and assume that in conditions of collapse it elicits more powerful contractions (*cf.* the previously mentioned experiments on its effect on a badly-working heart, p. 45). The dilatation of the peripheral vessels may perhaps give relief to the heart in cases where increased arterial tonicity offers too great a resistance to its contraction. In incipient acute feverish *cold*, alcohol taken with a large quantity of hot water seems to be beneficial. The explanation that has been given of this is that the congestion in internal organs diminishes when the blood is diverted to the skin.

A special significance is attributed to the energetic treatment of *septic fevers*, especially *puerperal fever*, in which alcohol has been credited with actual antiseptic action. A real bactericidal action in the blood cannot, however, be assumed, for alcohol is so weak an antiseptic that a concentration in the blood that would be injurious to bacteria is unattainable, even if enormous doses be administered. A direct answer to the question of the importance of alcohol in septic diseases has been sought in animal experiments. The results are varied. Laitinen examined in a large number of control-animals its effects on tubercle bacilli, anthrax bacilli and diphtheritic toxin, and found them to be only unfavourable.

Friedberger and C. Fränckel saw in rabbits after a single large dose, administered simultaneously with cholera vaccination, the immune bodies in the blood increase to $2\frac{1}{2}$ times their former quantity, but after continued use of similar doses decrease greatly. The general impression of these and other investigations of the bactericidal power of the blood, phagocytosis, and the resistance of the red blood-corpuscles, is that the influence of alcohol on infection and poisoning in febrile disorders is still a very obscure question.

It is in any case certain, however, that in acute febrile diseases alcohol may be considered useful as a *food* and a *beverage*.

The special value of alcohol as a *food* in these diseases, in which the activity of the digestive organs is in a low state, consists in its being absorbed, without requiring any digestive labour, rapidly and—in contrast to almost all other food—unchanged; in its complete combustion; and in having so great a heat of combustion that the body can thereby be supplied with a considerable proportion of the calories it requires. One gramme of alcohol yields 7·2 calories (1 gramme of fat 9·4, and 1 gramme of protein or carbohydrate about 4 calories). The requirements of a person confined to bed may be estimated, at the most, at 1,500—2,000 calories per diem. Even 50 grammes of alcohol, which can easily be taken in the form of wine or spirits, represents 360 calories, or between $\frac{1}{6}$ and $\frac{1}{4}$ of the needs of the 24 hours, a contribution which must be considered of great value to patients who are in a state of inanition. The question has been raised whether these doses may not also have deleterious effects that will neutralise their importance as food. It is scarcely possible to give any decided answer; in each case the fact of the patient's being habituated to alcohol or not must be taken into consideration.

Regarding the last feature of the action agreement is easy. Its narcotic properties make alcohol a very valuable *drink and anodyne in febrile diseases*. The incipient cerebral paralysis which even small doses induce allays the depressing feeling of weakness and illness, causes the heat, thirst and unpleasant sensations that accompany a heightened temperature to be felt less strongly, acts soothingly, and produces a certain dulness and feeling of well-being which may induce a beneficial sleep. As an anodyne small doses of alcohol may be very well indicated, but can to some extent be replaced by the newer antipyretics.

In *chronic diseases* alcohol was often until recently employed as an appetiser and nutrient and as a hypnotic during long convalescence for poorly-nourished and weak persons, for consumptives and for anæmic and neurasthenic patients. The risk of acquiring a habit, however, is great, and there is now, with reason,

a feeling in the direction of restricting as much as possible or giving up the use of alcohol in most chronic diseases. This is especially the case with its employment as an " exhilarating " remedy or hypnotic for neurasthenics, who very easily and quickly become alcoholists. The ordinary hypnotics, of which the use can better be controlled, are much to be preferred. As regards alcohol in the case of aged persons there need be little hesitation. Its employment for rickety and scrofulous children is quite improper.

In *anorexia* and *dyspepsia* alcohol in small doses generally has a good effect, but appears to be contra-indicated for hyperacidity and ulcer of the stomach. Concentrated alcohols must not be taken on an empty stomach, but during or after a meal, as concentrations of more than 10 per cent. in the contents of the stomach, as already mentioned, hamper digestion.

The injection of a few drops of 96 per cent. alcohol into a nerve causes interruption of conduction. By means of this now frequently practised treatment a cure, often lasting, of neuralgia is attained. The injection must not be made into sensorimotor nerves (motor paralysis), but only into purely sensory (*e.g.* in trigeminal or occipital neuralgia).

Externally alcohol is employed for a wash in the sweats of phthisis, for refreshing friction in fever, as a cooling poultice to allay itching, and as a component part of various liniments acting as anodynes and skin-irritants. For *disinfection* of the hands and the skin before operations, washing with alcohol or ether is done for the purpose of dissolving the fat which would prevent the penetrating action of aqueous antiseptics on the skin. For the same reason, the cleansing of instruments with alcohol is expedient. A spirit poultice (96 per cent., 24 hours) is now recommended for *lymphangitis*, *phlegmon*, *furunculosis*, *panaritium* and *erysipelas ;* the inflammation is often reduced, or at any rate its spread prevented, this being ascribed partly to the antiseptic action of the alcohol, partly to the hyperæmia induced, which is supposed to weaken the bacteria (*cf.* Bier's stasis treatment).

Treatment of Poisoning. In *acute* poisoning the stomach is emptied by the stomach-tube (emetics during deep narcosis are inactive). If the temperature has fallen very much, warmth must be restored ; in threatened respiratory paralysis, artificial breathing must be started ; as a stimulant to heart and brain caffeine is employed ; strychnine may also be tried. *Chronic alcoholism* is treated by breaking off the habit in a retreat, a subsequent protracted sojourn in the same institute, and after that total abstinence for life. All attempt to make of the actual drunkard a temperate man is wasted trouble. The withdrawal of the alcohol is better done suddenly, or at any rate in the course of

2 or 3 days ; in this there is little risk, as was formerly supposed, of delirium. Unlike the morphinist, the alcoholist suffers only for a few days from troublesome, but very seldom dangerous, abstinence symptoms, such as deep depression, anxiety, sleeplessness, increased tremor, anorexia and thirst for alcohol. These symptoms are combated by hot baths, light manual labour, hypnotics and bitters.

Preparations

Alcohol is official in the pharmacopœias, partly as Alcohol (various strengths) (B.P.) or Alcohol Dehydratum (B.P., U.S.P.), which must not contain more than 1 per cent. of water, partly in the form of various dilutions which are used in the concoction of extracts, tinctures and other pharmaceutical preparations. *Spiritus Methylatus Industrialis* (B.P.), methylated spirit, contains 95 per cent. of alcohol and 5 per cent. of wood naphtha.

Wine is the fermented juice of the grape. The most important of its component parts is ethyl alcohol, of which *Bordeaux wines* and *Burgundy*, as also the *Rhine wines*, contain from 7 to 10 per cent. Other products of the fermentation, in addition to alcohol and carbonic acid, are succinic acid and glycerine, which give a body to the wine, and higher alcohols and compound ethers of acetic acid, butyric acid and œnanthic acid, which give it aroma. Several of the compound ethers, like amyl nitrite, cause great congestion in the head. The red wines also contain tannic acid. Natural wines cannot have a greater alcoholic strength than 14 or 15 per cent., as the fermentation stops when the concentration becomes higher. The *heady wines*, port, sherry, Madeira and Marsala, with 16—23 per cent. of alcohol, have spirit added, and sometimes, to improve the taste, must, *i.e.* unfermented grape juice. *Champagne* is wine to which, when the fermentation has ceased, sugar is added, and the wine then once more fermented in bottles. It contains 10 per cent. of alcohol, and free carbonic acid ; the latter causes more rapid absorption and intoxication.

Spirits are obtained by distillation of fermented sugar syrup of varied origin. Most spirits contain about 50 per cent. of alcohol, which during distillation passes over together with water and volatile aromatic compounds. By cognac or *brandy* was originally understood only the distillation from the Charente and Charente-Inférieure departments, but the name has now been extended to include all grape-spirits. *Whisky* is made from barley, the peculiar smoke-flavour being from the peat used for firing. *Arrack* is distilled from fermented rice-sugar, and *rum*, the strongest of all spirits, containing up to 70 and 77 per cent. by volume of alcohol, from molasses, *i.e.* the syrup remaining after the cane-sugar has been crystallised out, this being diluted with water and left to ferment. The ordinary *grain spirit* is dilute spirit (25—45 per cent.), with bitter and aromatic substances added, or distilled with it.

Beer is made by the fermentation of malt. Bavarian beer contains 3—4½ per cent. of alcohol, the strongest English beers as much as 7—10 per cent. hop-constituents (bitter principles and ethereal oil), as also a small percentage of dextrine and sugar, and ½ per cent. of albuminous substances. Its nutritive value, contrary to the general opinion, is thus small. The dark-coloured beers, however, contain more malt ingredients.

Kumiss is made by the fermentation of the milk of the Kirghiz mares (9 per cent. of milk sugar, 2·5 per cent. of nitrogenous ingredients), as also free carbonic acid, which gives to the whitish beverage a refreshing taste, and, by promoting rapid absorption, makes it more intoxicating than the amount of alcohol would lead one to expect. The *kephir* of the Caucasians is a similar product, prepared from ordinary cows' milk, to which are added "kephir grains," yellowish lumps with an odour of cheese and rancid butter, and containing various micro-organisms. As the kephir fungus is an article of commerce, the preparation of kephir is easy. Both these milk-preparations, in doses of several tumblers daily, are used for tuberculosis and digestive disorders.

Yoghurt, a peculiar kind of sour milk that is a favourite article of food in the Balkan States, is prepared by condensing goats' or cows' milk to half its original volume, cooling to 50° C., and adding a special bacteria mixture called "*maya*," whereupon the whole is allowed to remain in the above-mentioned temperature for 12 hours. The result is a cheese-like, acid mass containing lactic acid, some alcohol, and albumin partly converted into peptone and albumose. It has been found that yoghurt is useful in diarrhœa for adults and children, probably by destroying harmful intestinal bacteria; it is also spoken highly of as a good food for weak digestions, though not for hyperacidity.

Addenda

Among univalent alcohols, ethyl alcohol is the only one that at present has any medicinal importance. The much talked-of *fusel oil*, which is formed simultaneously with alcohol by fermentation, varies in composition according to the material from which it is derived. The principal constituent is the ordinary *amyl alcohol*, a colourless liquid with a disagreeable, penetrating odour that is very irritating to a cough. It acts somewhat in the manner of ordinary alcohol, but is about 4 times more poisonous. The blame that is so often laid upon fusel oil for the unpleasant consequences of spirit intoxication is at the present time unjustifiable, because, owing to improved methods of spirit production, it does not, as a rule, occur in quantities of any importance.

Methyl alcohol, CH_3OH, which is found in the form of esters of acids in the unripe fruits of various umbelliferous plants, is obtained principally by dry distillation of wood, whence the name, *wood-spirit*. Methyl alcohol has of late years acquired great toxicological importance, because, on account of its cheapness, it is misused as a means of intoxication, and has proved to be much more dangerous than ordinary alcohol. In order to bring about intoxication, a larger dose is required than of ethyl alcohol, but the poisoning lasts longer, and is of a much more dangerous character. The cause of this must lie in the fact that methyl alcohol behaves differently in the body. In the next place it does not undergo complete combustion, but is only partly oxidised into formic acid and aldehyde. Moreover, methyl alcohol circulates very much longer in unchanged condition; in a dog, after a single dose of ethyl alcohol, the blood is already free from alcohol after 1 day, while methyl alcohol, after a similar dose, is still perceptible after 5 days. With repeated doses, a cumulative effect therefore commences. The more prominent symptoms of the poisoning consist in cardiac and muscular weakness, spasms, excitement, even paroxysms of madness, violent abdominal pains, shivering fits, failing sight, cyanosis and dyspnœa. Schmiedeberg is of the opinion that it is

a question of an acidosis resulting from the formic acid. Contrary to the ordinary alcholic intoxication, the narcosis often ends in death. After repeated poisonings (rarely after a single intoxication), permanent blindness occurs in a considerable percentage of cases, occasioned by neuritis and atrophy of the visual nerve. The lethal dose is estimated to be 50—75 grms., but cases of dangerous poisoning have been seen with very much smaller doses (11·5 grms.).

2. NITROUS OXIDE.

Although not organic, this compound will, from practical considerations, be mentioned here in connection with anæsthetics of the fatty series. Nitrous oxide was discovered in 1776 by Priestley, and analysed in 1799 by Davy, who became acquainted with its properties by experimenting with it on himself. In 1844 it was employed by the American dentist, Wells, as an anæsthetic —thus earlier than chloroform and ether—but it was not used in Europe until 1868. Our more intimate knowledge of this gas is due principally to Paul Bert's investigations.

Action. When the undiluted gas is inhaled the action begins instantly. There is buzzing and singing in the ears, consciousness is clouded, and analgesia commences, associated with slight cyanosis, all in the course of 1 minute. If the inhalation is now interrupted the anæsthesia last only from 20 to 30 seconds, and the patient wakes feeling perfectly well. If, on the contrary, the inhalation is continued, asphyxia follows, and death results in the ordinary manner. The time that elapses before death occurs is about the same as in the case of anyone breathing an indifferent gas, such as hydrogen or nitrogen, the only difference in the manner of death being that with nitrous oxide the asphyxial convulsions are absent or slight on account of the narcotic action.

There are two factors which here assert themselves. In the first place, nitrous oxide is a true *anæsthetic*, which paralyses the cerebrum. In the second place, it is an *irrespirable gas*, which only at a high temperature can be dissociated and serve as a source of oxygen. Glowing coal bursts into flame in an N_2O atmosphere, as in pure oxygen, but the sulphur flame, which burns with little heat, is extinguished. The blood is unable to obtain oxygen from N_2O, and hence the early commencement of asphyxia.

The symptoms are of a different character when nitrous oxide is inhaled mixed with as much oxygen (21 per cent. in volume) as the air contains. There is then no asphyxia, but on the other hand, N_2O is absorbed under a lower pressure—only $\frac{4}{5}$ of an atmosphere—and is not dissolved in the blood in sufficient quantity to produce complete anæsthesia: there is here only "happy intoxication," a lively flow of ideas, good spirits and

laughter (laughing gas). The feeling of pain is a little dulled, but complete analgesia is not attained.

To combine the advantages of the two conditions here described —the anæsthesia of the former with the freedom from danger of the latter—was the object of a series of ingenious experiments made by Paul Bert. He attained this by letting a mixture of 85 parts of nitrous oxide and 15 parts of oxygen be inhaled under an extra pressure of $\frac{1}{4}$ of an atmosphere. The blood thus received the necessary oxygen, and under the increased pressure enough N_2O was also absorbed to produce the full action. In this way the ideal anæsthesia aimed at could be attained ; but unfortunately the method is unpractical, as it requires an exceedingly elaborate apparatus, among other things an air-tight chamber large enough to contain patient, operator and assistants.

Uses. For short operations lasting a minute or so, pure nitrous oxide may be employed. To prolong anæsthesia, the gas is commonly administered by means of a mask fitted with a valve which enables the patient to breathe air at intervals, say one breath in four or five. More accurate adjustment of the proportion of gas and oxygen is possible with special apparatus. Thus, to begin with, pure or almost pure N_2O is used ; when anæsthesia supervenes, more oxygen is turned on, *e.g.* 6—8 per cent. ; if the patient reacts, the supply of oxygen is diminished, and so on. This technique increases the usefulness and safety of nitrous oxide anæsthesia. In order to establish a satisfactory degree of muscular relaxation in the course of a major operation, it is necessary to use ether in addition to gas and oxygen, but further modification of the apparatus is required for this purpose. The combination of ether with gas and oxygen is particularly valuable when major operations are carried out on diabetics. Prior to the operation the patient should receive about 50 grammes of glucose and half as many units of insulin. In childbirth, a few (3—6) inspirations of N_2O at the beginning of each pain are often sufficient to ensure a painless delivery.

When pure nitrous oxide is used the appearance of cyanosis is employed as a sign that the anæsthesia has commenced, as the reflexes are not abolished. The same rise of blood-pressure that accompanies all asphyxia also appears with inhalation of nitrous oxide, and limits its employment in the case of elderly persons suffering from arterio-sclerosis.

Wood once calculated that in North America there were annually 750,000 cases of anæsthesia with 3 deaths.

Ethylene is an unsaturated hydrocarbon of the olefine series, and has the formula C_2H_4. Its anæsthetic properties were discovered by Nunnely in 1849, but it was not commonly used

therapeutically until 1923. Loss of consciousness is induced rapidly by a mixture of 90 per cent. of ethylene and 10 per cent. of oxygen, and anæsthesia can be maintained by 80 per cent. of the gas with 20 per cent. of oxygen. It is superior to nitrous oxide in that muscular relaxation is almost complete and there is no dyspnœa, cyanosis or rise of blood-pressure. Ethylene has a slightly sweet taste and odour but is non-irritant to the respiratory tract. After discontinuing the anæsthetic, recovery occurs in 2 to 3 minutes. Headache and vomiting are fairly frequent after-effects ; there are no other complications. The only serious disadvantage in using ethylene is the formation of explosive mixtures with about 40 per cent. of oxygen, and special precautions are therefore necessary.

Propylene (not official), another olefine, having the formula C_3H_6, also acts as a general anæsthetic. The polymethylene cyclo-propane (not official), an isomer of propylene, has been employed extensively in the past few years. It rapidly induces surgical anæsthesia with a satisfactory degree of muscular relaxation, and has no toxic effect upon the heart. Respiration, however, is often irregular and may give rise to anxiety. A basal narcotic should be given beforehand.

Preparations

Nitrogenii Monoxidum (B.P., U.S.P.), Nitrous Oxide, N_2O. A colourless, odourless gas with sweetish taste, readily soluble in water. Is compressed, under a pressure of 30 atmospheres, or at −88° C., to a colourless liquid, which, on being still further cooled, congeals into an ice-like mass. It is supplied and employed compressed in cylinders.

Æthylenum (B.P., U.S.P.), Ethylene, Olefiant Gas, $CH_2.CH_2$. A colourless gas with a slightly sweet odour and taste. Inflammable and forms explosive mixtures with 40 per cent. oxygen. Like nitrous oxide it is stored in metal cylinders.

3. PRUSSIC ACID

Prussic acid occurs in the vegetable kingdom in a free state, or in the form of *glucosides*, of the decomposition of which it is a product. The best known is the *amygdalin* of bitter almonds, which, by the action of the accompanying ferment, emulsin, is broken up into prussic acid, oil of bitter almonds (benzaldehyde) and sugar. The same or similar glucosides are found in several plants belonging to this family, *e.g.* in the seeds of the cherry, plum, apricot and peach, in the *Prunus Laurocerasus* of Southern Europe, and in the wild bird-cherry. More recent investigations have shown that substances which yield prussic acid also occur in a surprisingly large number of other plants belonging to various families. The remarkable *Pangium edule* (*Bixaceæ*), a native of

the Malay Archipelago, even contains so large an amount that a single tree may produce 350 grammes of HCN. In the animal kingdom prussic acid is met with in certain millepeds (*Fontaria gracilis*), where it is probably a means of self-defence ; it occurs in distinct cutaneous glands, whence the secretion is expelled when the animal is touched.

Action. Prussic acid is *the most rapidly acting of all poisons.* There is therefore little to tell of the symptoms following large doses. Accounts of suicides, who, after having emptied a bottle of prussic acid, succumb almost immediately, merely state that the person falls to the ground " as if struck by lightning," utters a cry, and after a few deep respirations dies in convulsions, the whole lasting only two or three minutes. With less rapid action—for instance, after a teaspoonful of the official preparation, which contains only 2 per cent. of HCN—several phases may be observed in the poisoning. After a brief prodromal stage, in which there are great anxiety, pains in the region of the heart and a feeling of constriction in the chest, dyspnœa and respiratory spasms ensue—infrequent laboured respiratory movements with short inspirations and long expirations, followed by a pause. This is soon succeeded by the convulsive stage, in which there are violent, universal muscular spasms, partly clonic and partly tonic in character, increasing to tetanus. In conclusion there is an asphyxial stage, in which the respiration becomes irregular and shallow ; and at last there are long pauses between the feeble respirations, and death ensues. The result in this kind of poisoning is generally very quickly arrived at. If respiration still continues after 1 hour has passed, there is usually a rapid and complete recovery. The smallest lethal dose is about 0·06 gramme of HCN.

The symptoms described show that prussic acid first stimulates in the highest degree the respiratory centre in the **medulla oblongata,** and soon after paralyses it. It appears from animal experiments that the vaso-motor centre is affected in the same manner, and that the circulation exhibits changes corresponding to those in the respiration. If asphyxial death is prevented by artificial respiration, the falling of the blood-pressure will then be the cause of death.

Simultaneously with the effect upon the nervous system, there occurs a very peculiar **change in the metabolism,** described by Geppert, consisting in the cessation of the normal gaseous exchange in the body. During its passage through the capillaries the blood does not, as is usual, lose oxygen, but retains in the veins the same bright red colour, and about the same amount of oxygen as it has in the arteries. There is thus almost no consumption of

oxygen, oxidation is checked, and in consequence the production of carbonic acid is also reduced. With all this the oxygen is no more firmly combined with the hæmoglobin than under normal conditions, for outside the organism it is easily dissociated, and the blood assumes a venous character. Thus the cause of the reduced consumption of oxygen cannot lie in the blood, which contains the ordinary amount of available oxygen, but must be looked for in *the power of the prussic acid to deprive the tissues of their ability to absorb oxygen* (ferment paralysis). This is in accordance with the fact that prussic acid also acts as a *protoplasmic poison* towards lower organisms and plants, hindering fermentation and putrefaction (though not very energetically); the tentacles of the various species of the insectivorous *Drosera* cease their movements, and seeds cannot germinate, in the presence of prussic acid vapour. That blood, on being shaken up with prussic acid, loses its catalytic action upon peroxide of hydrogen, which is instantly broken up by normal blood-corpuscles into water and oxygen, is a phenomenon of the same nature. The action of colloid metals is also paralysed in the same way (see the introductory chapter to the Heavy Metals). Prussic acid forms compounds with pure hæmoglobin and methæmoglobin, to which, however, no significance as regards the poisoning can be attached, as in all essentials the action is the same in the "salt frog," whose blood has been replaced by normal saline, as in the normal animal.

Locally, prussic acid has an anæsthetic action. Even the sensitiveness of the skin is lessened, and, after being for some time in contact with the official 2 per cent. solution, the feeling of having a glove on may last for several days.

The quick commencement of the poisoning shows that prussic acid is exceedingly easily *absorbed*, and the strikingly rapid recovery after non-fatal doses that it is also rapidly rendered innocuous. It is probably partly *eliminated* through the lungs and partly transformed into comparatively harmless rhodanic compounds.

The toxicity of **other cyanic compounds** depends upon whether they give off prussic acid in the organism. *Potassium cyanide*, which has an odour of prussic acid, because the latter is driven out by the carbonic acid of the atmosphere, is very poisonous (lethal dose about 0·15 gramme), and, as it has technical uses and is more or less easily obtainable, is also the cyanide that most frequently occasions poisoning (suicide, attempted criminal abortion). It produces the symptoms of a rather slow prussic acid poisoning, as HCN in the stomach is gradually set free, and, moreover, being corrosive like caustic potash, violent pain and gastritis. If the cyanogen is not ionisable the compound becomes

innocuous. The *ferrocyanides* are thus, as a rule, innocent, and, as they are not affected by the very dilute hydrochloric acid of the stomach, produce even in large doses only diarrhœa like Glauber's salt. If, on the contrary, they are introduced into the stomach together with large quantities of strong acids, a prussic acid poisoning is brought about. *Bitter almonds* contain 3 per cent. of amygdalin, and produce each about 1 milligramme of prussic acid; about 60 almonds will thus provide the lethal dose.

The **therapeutic uses** of the prussic acid preparations are at present few. They are employed principally as *flavouring agents* and also for *nausea* and *vomiting*, and for *cardialgia*, where, by their locally anæsthetising action, they may serve as anodynes.

Treatment of Poisoning. In the most rapid cases, all treatment is too late. In slower cases, and in cyanide of potassium poisoning, the stomach is emptied with the stomach-tube, or an apomorphine injection is given and the stomach washed out with a dilute solution of potassium permanganate (1 : 500), which oxidises hydrogen cyanide into innocuous cyanic acid. A hot bath is also recommended, with cold sponging of the chest and back, artificial respiration, and camphor injections. The intravenous administration of about 50 mils of a 1 per cent. solution of methylene blue has been found to be of value. Also for poisoning with bitter almonds the first thing is the washing out of the stomach, after which hydrochloric acid (1 per cent.) is given to prevent the decomposition of the amygdalin.

Preparations and Doses

Acidum Hydrocyanicum Dilutum (B.P.), Diluted Hydrocyanic Acid, an aqueous solution containing 2 per cent. of hydrogen cyanide. *Dose*, 12—30 centimils, 2—5 mins. (B.P.); 0·1 mil, 1½ min. (U.S.P.).

Amygdala Amara, Bitter Almond, the ripe seed of *Prunus Amygdalus* var. *amara*. The bitter form is probably the original, the sweet variety being a product of cultivation (*cf.* wild and cultivated apples).

In the pharmacopœias of most countries there are still found various preparations containing prussic acid, to which no great medicinal importance is now attached, but which serve principally as flavouring agents.

A preparation frequently employed in expectorant mixtures is *Syrupus Pruni Serotinæ* (B.P.), prepared from the bark of the wild cherry. *Dose*, 2—8 mils, ½—2 fl. drs. *Aqua Laurocerasi* (B.P.C.), made from cherry-laurel leaves. *Dose*, 2—8 mils, ½—2 fl. drs. *Tinctura Chloroformi et Morphinæ Composita* (B.P.C.) also contains prussic acid (see under "Morphine").

The following are official in the United States Pharmacopœia: *Oleum Amygdalæ Amaræ*, containing 2—4 per cent. of HCN. *Dose*, 0·03 mil, ½ min. *Aqua Amygdalæ Amaræ*. *Dose*, 4 mils, 1 fl. dr. *Syrupus Pruni Virginianæ*. *Dose*, 10 mils, 2½ fl. drs.

Addenda

Essential oil of bitter almonds and *nitrobenzol.* The decomposition of the amygdalin takes place according to the following equation :—

$$\underset{\text{Amygdalin}}{C_{20}H_{27}NO_{11}} = \underset{\text{prussic acid}}{HCN} + \underset{\substack{\text{benzaldehyde (essential}\\ \text{oil of bitter almonds)}}}{C_6H_5COH} + \underset{\text{dextrose}}{2C_6H_{12}O_6}$$

The whole amount of prussic acid does not, however, become free by the decomposition, some of it appearing loosely combined with benzaldehyde. This " crude oil of bitter almonds," which may contain up to 14 per cent. of HCN, is naturally very poisonous. The pure oil or benzaldehyde, which is now produced synthetically, has, on the other hand, as regards action, nothing in common with prussic acid ; it is not very poisonous, and is said, in very large doses only, to produce spasms which resemble epileptic attacks. The quantities in which it often occurs in perfumes and liqueurs may be considered harmless. On the other hand, the oily, pale yellow **nitrobenzol,** also called *oil of mirbane,* or "*false oil of bitter almonds,*" is very dangerous. It has now acquired an extraordinarily great technical importance as a source of the production of aniline. The odour of nitrobenzol closely resembles that of the oil of bitter almonds, and being also a very inexpensive substance, it has acquired an extensive but highly improper employment in the manufacture of perfumes, as an addition to soap (" almond soap "), in confectioners' goods, and in spirituous liquors. Its toxicological importance has lately increased owing to the reputation it has gained among laymen for producing abortion. Toxic doses begin with as little as 1 grm. The poisoning presents two separate series of symptoms, one originating in changes in the blood, which turns a dark brown and loses its ability to absorb oxygen, the other a result of the action of the nitrobenzol on the central nervous system. The most important of the numerous symptoms are at first great indisposition and feeling of weakness, a burning in the mouth and throat, intense headache, later a characteristic greyish blue or almost blackish blue cyanosis of the face, lips and fingers, vomiting—the odour from the vomited matter making the diagnosis very easy—spasms and loss of consciousness passing into coma, which generally after a few hours ends in death. If the toxic action is prolonged, it may assume a peculiar, intermittent course with successive periods of coma. The patient lies in the deepest narcosis, is cyanosed, with dilated pupils and without reflexes ; there are tonic spasms, the pulse becomes very frequent and small, the mucous rattle begins, and, in short, death appears to be imminent. In a little while, however, there is an unexpected improvement ; the pulse gains strength, consciousness returns, and the patient wakes. The same thing may be repeated several days in succession, until at last the attacks cease, the cyanosis disappears, and convalescence commences. When the first coma has passed, the great danger is over. Abortion may occur. The prognosis is always very doubtful, as the symptoms appear so late (as a rule not for ½—1 hour) that complete removal of the poison from the stomach is not feasible. Even if several hours have passed, however, washing out the stomach must always be done and a purgative given, as nitrobenzol is absorbed slowly. Further, bleeding is recommended with subsequent saline infusion, hot bath with cold sponging, artificial respiration, hypodermic camphor injections. Fat (milk), alcohol, and ether, must not be given internally, as they dissolve nitrobenzol, and facilitate its absorption.

Carbon Monoxide

Another blood poison that is of no therapeutic importance, but of all the greater toxicological interest, is *carbonic oxide* or *carbon monoxide*, CO, which originates in the combustion of carbon with an insufficient supply of air.

In towns it is not unusual to meet with cases of poisoning with the ordinary illuminating gas, which contains about 7 per cent. of carbonic oxide, and for the rest consists mainly of hydrogen and methane (CH_4). Leakage from, or breakage of, gas pipes under asphalted streets, or in winter when the ground is frozen, is especially dangerous, as the gas is thus prevented from diffusing in the air. If it passes for some distance underground, the odoriferous constituents (heavy hydrocarbons, sulphur compounds) are absorbed, and the entrance of the gas into inhabited rooms is unnoticed. Many deaths were caused formerly by the old-fashioned stoves, where the draught was regulated by a damper, by the closing of which the fumes arising from the coal readily came out into the room, or by other unpractical heating-apparatuses, *e.g.* the so-called chafing-dish. Carbonic oxide is also found in many products of technical importance (water-gas, etc.), in the explosion-gas of various explosives, etc. In fire in closed rooms, *e.g.* a fire in a theatre, death is often due not to direct burning, but to carbonic oxide poisoning.

The great toxicity of carbonic oxide is due to its power of expelling the oxygen from the blood and forming with the hæmoglobin a very firm combination—carbonic oxide hæmoglobin. The blood loses the power of absorbing oxygen in the lungs and giving it off to the tissues, the result being an internal suffocation (asphyxia) as a consequence of the lack of oxygen, but without a simultaneous accumulation of carbonic acid. As the affinity of carbonic oxide for hæmoglobin is about 200 times as great as that of oxygen, the hæmoglobin takes up the carbonic oxide, even if it is present in the air in only very small quantities. The quantitative course of the reaction depends upon the mutual proportion of CO to O_2. If blood be shaken with air containing $\frac{1}{10}$ per cent. of carbonic oxide, 42 per cent. of the hæmoglobin passes over to carbonic oxide hæmoglobin, and with greater concentration the blood is almost completely saturated. In practice, not only the concentration, but also the time during which the poisonous gas has been inhaled, is of course of decisive importance. In man, death occurs when 60—70 per cent. of the hæmoglobin of the blood is saturated by carbonic oxide. To lower, hæmoglobin-free animals, CO is said to be harmless.

Symptoms. When an animal is made to inhale air containing much carbonic oxide, the poisoning develops very rapidly. The animal at once becomes restless, pulse and respiration frequent; spasms begin, and immediately after arrest of the heart and respiration. In man, in whom carbonic oxide almost always only acts in a much diluted state, the earliest symptoms, according to Kunkel, are a feeling of mental dulness, heaviness and throbbing in the head, congestion and violent headache. If the poisoning goes further, the face becomes pale, consciousness is lost and vomiting begins. With continued inhalation the respiration becomes irregular, the pulse frequent and small, the pupil is large and ceases to react, and involuntary passing of urine and fæces almost always takes place. If the patient is taken into the fresh air, he may still recover; otherwise, deep coma ensues, which, after some hours or days, ends in death. Recovery has, however, been observed even after a period of

unconsciousness lasting for several days. The urine often contains sugar. Recovery from the poisoning may have a number of sequelæ—inflammation of the lungs (perhaps in consequence of aspiration while vomiting), gangrene, pemphigus, pains and paralysis of the most varied kinds (of the bladder, rectum or extremities, blindness, aphasia), some due to peripheral neuritis, others of central origin ; diabetes, prolonged somnolence, mental diseases. A difference of opinion exists as to whether all these may be interpreted as consequences of the prolonged asphyxia of the tissues, or whether the carbonic oxide has an independent toxic action on other constituents of the body besides the hæmoglobin.

The post-mortem results after an acute carbonic oxide poisoning are very characteristic. The CO blood is not quite of the arterial colour, but has a tinge of pink, and does not after death assume a venous character. The dead body, therefore, retains a fresh appearance, livid spots are of a bright cherry-colour, and the blood in all the organs, even in the veins, is bright red. Even in life, the peculiar contrast between the difficult respiration and the fresh colour of the mucous membranes, may lead to the correct diagnosis. Carbonic oxide hæmoglobin can be demonstrated both spectroscopically and by chemical reaction.

The obvious *treatment* consists in taking the patient into the fresh air, and commencing artificial respiration, the carbonic oxide hæmoglobin being thereby dissociated. As the rapidity of the reaction—expulsion of CO by O_2—is in proportion to the tension of the oxygen, the inhalation of the latter is more effective than that of ordinary air. Furthermore, pulmonary ventilation can be considerably increased by the inhalation of a mixture of 93 per cent. of oxygen with 7 per cent. of carbon dioxide. The frequent sequelæ necessitate caution in forming a prognosis, even if the patient has survived the acute poisoning.

4. CURARINE

The most celebrated of the numerous arrow-poisons found among wild tribes is the South American curare, the properties of which became known through the accounts of explorers ; they describe how the Indians prepared their arrows with a poison that caused even the most lightly wounded animal after a few minutes to cease running, or to fall powerless from the branch of a tree, and quickly die. This poison was of special value to hunters, because the flesh of the animal killed could be eaten without danger. Curare consists of dry, brown masses, and is obtained from the bark of *Strychnos toxifera* and other species of *Strychnos* growing in the regions of the rivers Orinoco and Amazon. There seems to be a certain mystery about its preparation with which Europeans are not fully acquainted ; and reliable preparations are gradually becoming scarcer, probably because the production is neglected now that the bow and blow-tube are being superseded by modern firearms. Several kinds are still manufactured, however, all of them containing, according to Böhm's investigations, two series of alkaloids, namely, *curarines*, which exhibit the

typical action, and *curines*, weak heart-poisons, acting in a manner similar to that of digitalis, and of no significance.

Action. The curarines have an extremely characteristic action, as even in exceedingly small quantities (in a frog $\frac{1}{100}$ milligramme or less) they interfere with the normal transmission of motor impulses to the voluntary striated muscles. Paralysis therefore develops and affects first the muscles of the extremities, then those of the head and body, and lastly the respiratory muscles. Death ensues as soon as the movements of the chest and diaphragm cease, but may be warded off for a long time by artificial respiration, as the heart does not suffer, but rather beats more quickly because the inhibiting vagus-ends are paralysed. Notwithstanding the good heart action, however, the blood-pressure falls after large doses, because curarine paralyses the nerves of the vessels in the same way as those of the striated muscles. Muscular tissue itself is scarcely affected, the sensory nerves not at all, and the motor nerve-trunks only after prolonged action. Curarine is therefore a very valuable substance in physiological and pharmacological experiments, being employed for the purpose of eliminating the influence of the motor nerves when the direct muscular irritability is to be investigated.

The effects of curarine can be completely abolished by injecting physostigmine. This interesting observation has given rise to a great deal of research and further reference is made to the subject on p. 126.

A similar, but far slighter, effect upon the motor nerves, "*curarine action*," is possessed also by numerous other bodies, especially quaternary ammonium bases, more particularly methyl compounds of alkaloids (methyl strychnine, methyl veratrine, methyl quinine, etc., according to Brown and Fraser), various alkaloids, *e.g.* coniine and lobeline, the more simple ammonium compounds such as pyridine, quinoline and trimethylamine (Santesson), camphor, etc. Curarine-like substances may even be found in living animals. Thus the edible mussel, *Mytilus edulis*—from eating which many cases of poisoning have been known—when in stagnant, polluted water, may contain a poison acting like curarine, which disappears when the animals are removed to purer water. Certain fish, species of the Japanese tetrodon, appear, according to the investigations of Takahashi and Inoko, to contain normally in their ovaries a poison that possesses, among other effects, this curarine action.

When circumstances are favourable, curarine may show *strychnine action*. If, after the brain has been destroyed and the heart ligatured off in order to prevent the poison from reaching the peripheral nerves, a few drops of a very dilute solution of curarine are dropped upon the exposed spinal cord, a violent *reflex tetanus* quickly makes it appearance. In ordinary circumstances these spasms cannot be developed, because the paralysis of the motor nerve-endings, acting as a break in the connection, prevents all movement-impulses from reaching the muscles. Conversely, as will be mentioned in the next chapter, strychnine, besides producing

spasms, may also paralyse the motor nerves—yet another point of resemblance between these two apparently so different, but in reality allied, alkaloids occurring in the same plant-family.

Curarine is absorbed very slowly through the gastro-intestinal mucous membrane, and is excreted so rapidly in the urine that comparatively large internal doses occasion no poisoning. For this reason, as already mentioned, the flesh of animals killed with curare can be eaten without danger. It was therefore originally believed that curare was not at all poisonous when taken internally, until Claude Bernard showed, by ligature of the renal artery in animals, that the well-known action did not fail to appear when the excretion through the kidneys was stopped.

Therapeutic Uses. Curare has been tried in spasms (tetanus, strychnine poisoning), but has now been given up, as the activities of the preparations vary far too much.

5. STRYCHNINE

Strychnine is the most prominent representative of a group of poisons which are remarkable for their production of strong reflex convulsions. The best known among the remaining members of the group are *brucine*, which accompanies strychnine in *Strychnos nux vomica*, *gelsemine* in *Gelsemium sempervirens*, which also contains the coniine-like alkaloid gelseminine, and the opium alkaloid *thebaine*. Among the bacteria, the *tetanus bacillus* forms a poison, of which the action strongly resembles that of strychnine.

Action. The Central Nervous System. Strychnine produces tetanus by increasing to an extreme degree the reflex excitability of the spinal cord. Other sections of the central nervous system are also similarly affected; even small doses by acting on the medulla oblongata, and independently of the spinal effect, occasion constriction of the arteries and high blood-pressure (see Fig. 4). From the same cause the respiration becomes quicker and deeper, while the action of the heart continues unaltered, or, in consequence of the irritation of the vagus centre, becomes a little slower than in its normal condition.

In addition to these stimulant effects (convulsions, increased blood-pressure, etc.), various symptoms of *central paralysis* are very soon evident. After the administration of enormous quantities of strychnine the tetanus is limited to slight twitchings, and paralysis rapidly supervenes; this is complete, however, only in the lower animals (frog): the higher animals and man succumb during the convulsions, which conceal the incipient paralysis. Thus, although the nature of the action is the same,

its expression may vary somewhat in the various classes of animals (this being also the case, as will be seen, with morphine).

The **terminal organs of the motor nerves** are paralysed by very large doses of strychnine. The action is not so typically developed, however, as in the alkaloid curarine, which also occurs in the *Strychnos* species, and has been mentioned in the preceding chapter ; and it does not show itself distinctly in higher animals,

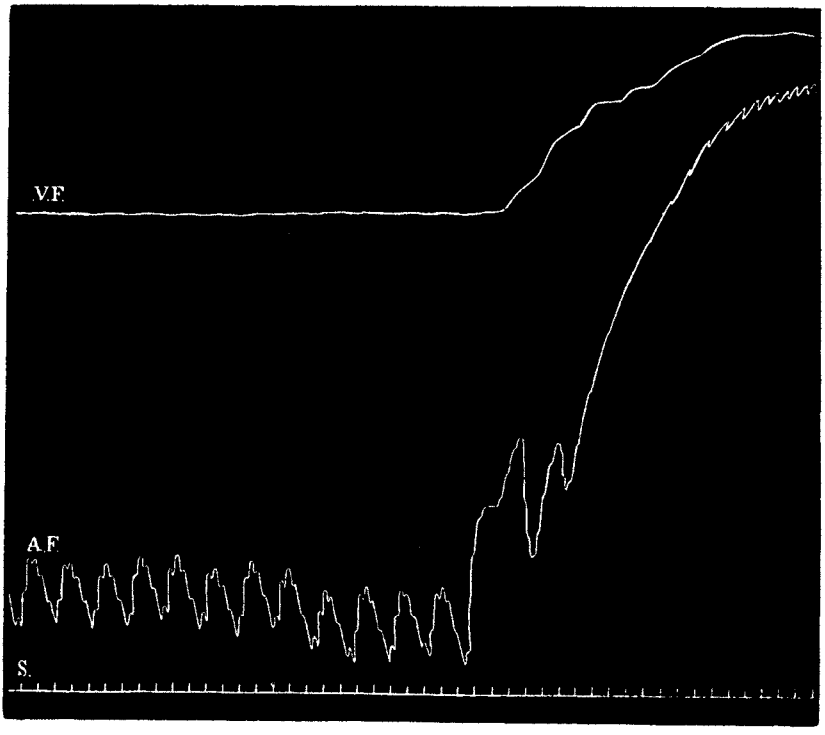


FIG. 4.—Dog that has been curarised and in which convulsions have thus been prevented. The blood-pressure nevertheless, after a strychnine injection, rises considerably, first in the arteries, a little later, and less, in the veins also. *A.F.* Femoral artery. *V.F.* Femoral vein. *S.* Time in seconds. (Delezenne.)

which die at an early stage of the poisoning. In frogs (*Rana esculenta*) the curarine action may be so fully developed that electric stimulation of the nerve does not elicit muscular contraction.

The frog's behaviour to strychnine is of interest, because of its sensitiveness even to minimal quantities, and it acts in so typical a manner that it can be employed to demonstrate the presence of the alkaloid. Even doses of $\frac{1}{100}$ milligramme produce symptoms of increased reflex excitability, and $\frac{1}{200}$ of a milligramme is sufficient

to bring on the poisoning in all its violence. Fifteen to thirty minutes after the subcutaneous injection of such a dose a gentle touch or a slight shaking of the surface on which the animal is lying causes it to start as if in alarm. A little later it reacts with exceedingly rapid extension of the lower extremities, and soon the very slightest stimulus elicits a typical convulsion. All skeletal muscles pass momentarily into tonic contraction; the light reflected by the damp skin reveals a flickering play of muscle, which shows that the attack consists of a number of contractions following one another with extreme rapidity, and together giving the impression of one long contraction. The entire animal becomes as stiff as a board, and is fixed—as the name "tetanus" (from τεινω = I stretch) implies—in the position of extension, not because the extensor muscles are subjected to a stronger influence, but because in most places they are more powerful than the flexors. Where the flexors are the stronger, they determine the position. Thus in the female the weak fore extremities are held extended along the body, while in the male the strong arm-flexors, which during pairing-time clasp the female for days together, cause the arms to be folded across the chest. When the action is fully developed there follows a succession of convulsions, with short intervals of rest, during which the animal lies exhausted; each attack, though apparently spontaneous, is in reality always elicited by some external stimulus. If stimuli to the spinal cord are interrupted by the division of the posterior roots of the spinal nerves (Claude Bernard) or if they are prevented by anæsthetising the entire surface of the animal with cocaine, the tetanus ceases. If the cervical region of the spinal cord is severed, or the brain destroyed, the effect is unchanged or becomes stronger, which is a proof of its origin in the spinal cord. Large doses produce no convulsions in the frog, or only brief spasms that are immediately superseded by paralysis that may last for many days. It is only when the greater amount of the alkaloid has been excreted that the action of the small doses, violent tetanus, makes its appearance; and, notwithstanding the prolonged paralytic state, life is preserved in the frog, as the heart continues to beat, and the cessation of the

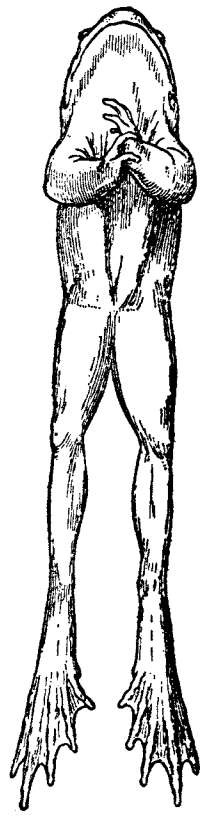


FIG. 5.—Rana temporaria. Strychnine position. (Führer.)

respiratory movements is counterbalanced by the active cutaneous respiration.

In man, 1—2 milligrammes of strychnine appear to a casual observer to have no effect, but a closer investigation reveals a distinct influence on the acuteness of **the senses**. The perimeter shows an enlargement of the field of vision (see Fig. 6), the field for the perception of blue is also enlarged, and the power of distinguishing delicate degrees in the strength of light is increased. After a single dose this effect is maintained for several days; after larger doses the augmented perceptive faculty may increase to photophobia. Corresponding changes also take place in the other senses; both hearing and touch become more acute, and the civilised being's dulled sense of smell may for a time acquire greater delicacy. This is due to an increased sensitiveness of the brain, corresponding to the greater irritability of the spinal cord. As regards the eye, the point of attack appears, partly in any case, to lie in the retina, which must, however, be regarded as an isolated part of the brain.

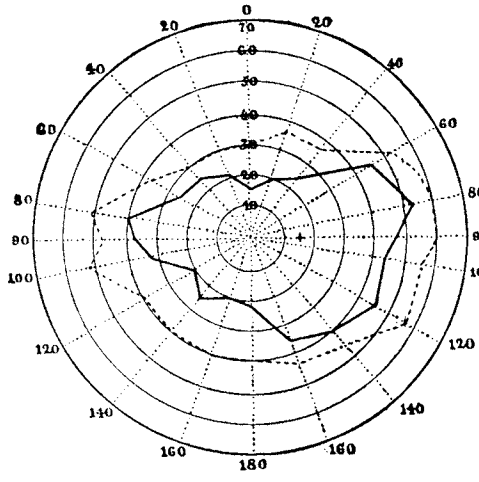


FIG. 6.—Enlargement of the field of vision by strychnine. Left eye. Two black spots, 5 mm. in diameter and 5 mm. apart, twenty-four hours after injection of 3 mg. strychnine. The continuous line shows the normal field, and the interrupted the effect after strychnine. (v. Hippel.)

In *man*, the first distinct signs of the increased reflex irritability of the spinal cord appear after the hypodermic injection of 5—10 milligrammes of strychnine. In the muscles the first warning of the commencement of tonic contraction is a painful stiffness and tension that make the movements slow and troublesome. There is difficulty in swallowing, a weight is felt upon the chest, breathing is laboured, the masseters are hard, the face acquires a stiffened, distorted appearance, and the head is drawn a little back by the muscles at the back of the neck. Yet clearer warning of the near approach of tetanus is given by fibrillary twitchings in the various groups of muscles. There may also be painful erections, which has led to the employment of strychnine as an aphrodisiac. Very large doses, *e.g.* a few centigrammes (0·03

gramme is quoted as the smallest lethal dose), quickly produce the violent symptoms of acute strychnine poisoning. After a short prodromal stage, in which there is uneasiness, anxiety, and sometimes vomiting, tetanus suddenly breaks out. All the striated skeletal muscles contract at once, the spinal column is hyperextended so that the stiffened body is raised on head and heels in a backward concave bow, the jaws are tightly closed, and respiration ceases, the chest being fixed in the inspiratory position. For some seconds, or a couple of minutes, the body remains as stiff as a board and motionless, while cyanosis increases, then the spasm begins to abate, the cyanosis disappears, and the muscles are relaxed until the next attack. Death generally occurs after a long attack, sometimes even in the first, as a consequence of asphyxia during the attack, or on account of the paralysing action of strychnine on the central nervous system, especially the medulla oblongata. Consciousness is maintained throughout, and the condition is extremely painful.

Strychnine, in accordance with the general rule that the more highly-developed the central nervous system, the more effectual are nerve-poisons, is most poisonous, calculated according to body-weight, to man. Other mammals are affected in more or less the same way as man, except that sometimes the convulsions are most prominent, sometimes the paralysis. Thus in the rabbit even small quantities occasion only a brief tetanus, which is soon superseded by complete paralysis and cessation of respiration. The companion alkaloid, brucine, is about thirty times less poisonous, but acts with comparatively greater paralysing power upon the motor nerve-endings, and thus forms a transition from strychnine to curarine.

Local Action. Strychnine has an exceedingly bitter taste, noticeable even in a dilution of 1 in 50,000, and for this reason promotes salivation. Small doses seem to sharpen the appetite and act upon the digestion, probably in the same way as other bitter substances.

Strychnine has a **cumulative action,** that is to say that many small doses administered during a long period may suddenly produce poisoning, or act as if a large quantity had been given at one time. The reason of this property, which strychnine has in common with several other substances—*e.g.* digitoxin—is, presumably, that it is rapidly absorbed, is retained for some time in the nervous system, and is *excreted slowly* and, to some extent at any rate, unchanged (even 8 days after acute poisoning it can be demonstrated in the urine), so that accumulation in the body may take place—*chemical accumulation.* Another explanation of this peculiarity has been that the action of each dose is prolonged, and each fresh dose that is administered finds the central nervous system already in a condition of increased reflex irritability, and

thus by degrees the numerous separate actions are aggregated—*dynamic accumulation*. In controlled medicinal employment, the cumulative action expresses itself only as a slight stiffness of the masticatory or cervical muscles, or an abnormal sensitiveness to sense impressions, symptoms which soon disappear when the use of the drug ceases.

Therapeutic Uses. Strychnine was formerly much employed for *paralysis*, but has now been superseded by the modern methods, mechanical and electric treatment. In peripheral paralysis (diphtheria, lead), strychnine has been recommended until quite recently in daringly large doses. The action on paralysis seems on the whole, however, of necessity to be problematical. It is difficult to understand how the strychnine can do anything more than simulate improvement by increasing the irritability in the cord. If the paralysis in the meantime has spontaneously improved, the change will easily be wrongly ascribed to the remedy employed. In *amblyopia*, with or without atrophy of the optic nerve, strychnine is not infrequently employed by the oculist, and is said sometimes to cause lasting improvement. That, in any case, it may have a temporary favourable influence upon the strength of vision may be readily understood from what has been said above of its effect upon the eye. Strychnine is often applied—upon the supposition that the affected eye is thus best acted upon—as a hypodermic injection in the corresponding temple.

Strychnine is given for *enuresis* in children, with greatly varying success. Sometimes, probably in cases where the incontinence is due to flaccidity or deficient reaction in the sphincter of the bladder, it does much good ; sometimes no action can be traced.

As a stimulant, superior to caffeine or camphor, strychnine in very large doses—as much as 5—10 milligrammes, subcutaneously—several times in the course of 24 hours has lately been recommended for *collapse of all kinds*.

In indefinite *conditions of weakness and languor*, as also in *sexual asthenia*, strychnine is employed as an invigorating and " strengthening " remedy ; the increased irritability of the central nervous system in such conditions may perhaps be useful. Strychnine is frequently prescribed for *dyspepsia* and *atony of the intestinal canal*, and seems often to be effectual ; it is given, as a rule, in the form of *Extractum nucis vomicæ*, because there the alkaloid, which is supposed to exert a local effect upon the mucous membranes, occurs together with substances that prevent a too rapid absorption. Finally, it may be mentioned that strychnine injections have been often recommended by Russian and French

physicians as an auxiliary remedy in the treatment of *chronic alcoholism ;* it is stated that the desire for alcohol is thereby diminished.

Treatment of Strychnine Poisoning. If the poisoning has just taken place, the stomach must be emptied as quickly as possible by the stomach-tube. Precipitation of the alkaloids with tannic acid (black coffee, tea) or tincture of iodine is of value, but the precipitate must be evacuated from the stomach. If convulsions have not begun, one of the barbiturates should be administered immediately, *e.g.* 2 grains of sodium phenobarbitone in hot water. When convulsions have already appeared, a general anæsthetic must be given to enable stomach lavage to be carried out. The dose of phenobarbitone should then be dissolved in about 5 mils of normal saline and injected slowly intravenously. When a more rapid sedative action is required, barbiturates such as sodium amytal, nembutal and evipan-sodium are preferable. Oral administration of the barbiturates should be continued for about a week or until the excess of strychnine has been excreted. Morphine is contra-indicated in strychnine poisoning as it tends to increase somewhat the excitability of the spinal reflexes.

Preparations and Doses

Nux Vomica Pulverata (B.P.), **Nux Vomica** (U.S.P.), the seeds of *Strychnos nux vomica* (*Loganiaceæ*), a tree indigenous to India and Further India, Ceylon, and perhaps North Australia. It must contain not less than 1·25 per cent. of strychnine, or 2·5 per cent. of total alkaloids. *Dose*, 6—25 centigrms., 1—4 grs. (B.P.) ; 0·1 grm., 1½ gr. (U.S.P.).

Strychnina, Strychnine, $C_{21}H_{22}N_2O_2$, colourless prismatic crystals, almost insoluble in water.

The remaining preparations are here given separately for the two pharmacopœias, as they differ in certain particulars, such as the alkaloid contents.

B.P.—Extractum Nucis Vomicæ Siccum, 5 per cent. strychnine. *Dose*, 16—60 milligrms., ¼—1 gr. Employed chiefly in the form of pills in digestive ailments.

Extractum Nucis Vomicæ Liquidum, 1·5 per cent. strychnine. *Dose*, 6—18 centimils, 1—3 mins.

Tinctura Nucis Vomicæ, 0.125 per cent. strychnine. *Dose*, 6—20 decimils, 10—30 mins.

Strychninæ Hydrochloridum, $C_{21}H_{22}N_2O_2HCl + 2H_2O$. Colourless prisms with an extremely bitter taste, soluble in 60 parts of water. *Dose*, 2—8 milligrms., $\frac{1}{32}$—$\frac{1}{8}$ gr. For dyspepsia often used together with dilute hydrochloric acid, *e.g.* solution of Strychn. Hydrochloride ($\frac{1}{10}$ per cent.), Dil. Hydrochlor. acid, āā *dose*, 30 mins. three times a day after meals. Maximal doses for children : 2 years, 0·4 milligrm. ; 4 years, 1 milligrm. ; 7 years, 2 milligrms. ; 10 years, 2·5 milligrms. (1 milligrm. = $\frac{1}{64}$ gr.).

Liquor Strychninæ Hydrochloridi, 1 per cent. of the hydrochloride. *Dose*, 2—8 decimils, 3—12 mins.

Syrupus Ferri Phosphatis cum Quinina et Strychnina, about 0·025 per cent. strychnine. *Dose*, 2—4 mils, ½—1 fl. dr.

U.S.P.—Extractum Nucis Vomicæ, 16 per cent. total alkaloids. *Dose*, 0·015 grm., ¼ gr.

Tinctura Nucis Vomicæ, 0·25 per cent. alkaloids. *Dose*, 1 mil, 15 mins.

Strychninæ Nitras, $C_{21}H_{22}N_2O_2.HNO_3$. Colourless needles or white powder with very bitter taste, soluble in 42 parts of water. *Dose*, 0·0015 grm., $\frac{1}{40}$ gr. *Strychninæ Sulphas* is also official in the same doses as the nitrate. [Regarding its use in dyspepsia, and the maximal doses for children, see above under *Strychninæ Hydrochloridum* (B.P.).]

6. HYDRASTIS ALKALOIDS (not official)

Hydrastine occupies an intermediate position between strychnine and the opium alkaloids, and is found in *Hydrastis canadensis* together with *canadine* and *berberine*, both unimportant, the latter also occurring in many other plants, *e.g.* the common berberis. By oxidation of hydrastine, opianic acid is formed, and another alkaloid, *hydrastinine* ; and in the same way opianic acid and the alkaloid *cotarnine*, which therapeutically belongs to the Hydrastis group, arise from *narcotine*, an opium alkaloid allied to hydrastine.

Action. With regard to its action, **hydrastine** resembles strychnine. In the frog it produces a typical tetanus, which gradually gives place to paralysis ; in higher animals, on the contrary, its behaviour is more that of morphine, as there are first symptoms of central paralysis and then increased reflex irritability, ending in tetanus. Even small doses that do not produce convulsions act upon the medulla oblongata and cause constriction of the vessels with increased blood-pressure, which, however, is not continuous, but is sometimes interrupted by pauses, during which the vessels are relaxed and the pressure falls. In the uterus, movements are aroused which may at one time be rhythmical, and at another have the character of a prolonged tonic contraction. This action also takes place in the excised organ, and is thus of peripheral nature. In toxic doses hydrastine shows itself to be a pronounced heart-poison ; it first strengthens the beat and later depresses cardiac muscle.

Hydrastinine has a somewhat different action from that of the parent alkaloid. It does not cause tetanus (only hyperæsthesia and slight muscular tremor), but still occasions constriction of the arterioles and increased blood-pressure. The most important action of hydrastinine is that of raising the tone of the uterus, and often producing strong rhythmical contractions. After very large doses the entire central nervous system becomes paralysed, and in the frog the terminations of the motor nerves.

According to experiments with pregnant rabbits **cotarnine** produces peristaltic uterine movements. Peristalsis of the

intestine is strengthened both by this alkaloid and by hydrastinine.

Therapeutic Uses. Various preparations of hydrastis have been employed in America for a long time, and in Europe for the last 30 to 40 years, for *uterine hæmorrhage* of all kinds. They have proved particularly effectual in menorrhagia in virgins, and in the irregular, often excessive hæmorrhage at the climacteric age. With profuse menstruation the treatment should begin about 1 week before the menses are expected, and be continued until the end of the period. The accompanying indisposition, vomiting and pain are frequently reduced simultaneously with the hæmorrhage. When any great change, *e.g.*, endometritis, oöphoritis, or abnormal position of the uterus, is the cause of the hæmorrhage, the action is uncertain, but is often satisfactory. In *other kinds of hæmorrhage*, such as from the lung, the effect is doubtful. The *night sweats of consumption* are checked. Hydrastis is not a suitable remedy for inducing labour, and as its action on the uterus is only weak, it cannot compare with ergot in serious post-partum hæmorrhage. Hydrastis preparations have a very bitter taste, and like other bitters are prescribed in *dyspeptic cases.*

The hydrochloride of **cotarnine,** which has been given the superfluous name stypticine, is employed with the same indications as hydrastis, frequently with good effect, especially in menorrhagia in which there is little morbid change, and in dysmenorrhœal trouble.

Preparations and Doses

Hydrastis Rhizoma (B.P.C.), Golden Seal. The rhizome and root of *Hydrastis canadensis* (*Ranunculaceæ*), a plant growing in the eastern part of North America.

Extractum Hydrastis Liquidum (B.P.C.) **Fluidextractum Hydrastis** (N.F.). *Dose,* 3—10 decimils, 5—15 mins. (B.P.C.); 2 mils, 30 mins. (N.F.).

7. OPIUM ALKALOIDS (MORPHINE GROUP)

The little family of the *Papaveraceæ* is remarkable from a chemical point of view for the number of active vegetable bases it contains. First among these plants is the sleep-inducing poppy, *Papaver somniferum*, whose dried, milky juice, opium, the most indispensable of all drugs, contains a great number of alkaloids, more than thirty of which are known. The most important is *morphine*, of which 10 per cent. occurs in the Asia Minor opium employed in medicine. Among the remaining alkaloids may be mentioned *narcotine* (5—7 per cent.), *codeine* (0·2 —0·4 per cent.), *papaverine* (0·5—1 per cent.), *narceine* (0·1—0·4 per cent.), and

thebaine (0·1—0·55 per cent.). The alkaloids occur partly free, partly in combination with sulphuric acid, lactic acid, and a peculiar dibasic acid, meconic acid, which gives a bright red colour with ferric chloride, a reaction which is utilised to demonstrate the presence of opium. The opium from other regions presents great irregularities, arising from the soil, the climate, and the manner of obtaining it. From various European countries where the cultivation of the poppy has been tried a very varied percentage of morphine, from 7 to 20 per cent., has been

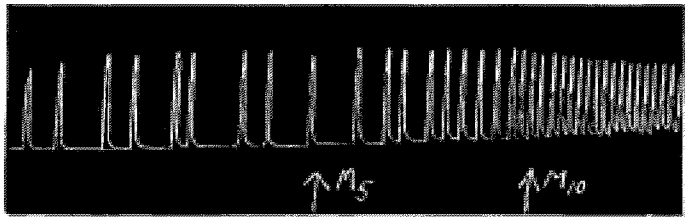


FIG. 7.—Pig's ureter in 50 c.c. of Locke solution. Five and 10 milligrammes of morphine sulphate increase the frequency of the contractions. (Macht.)

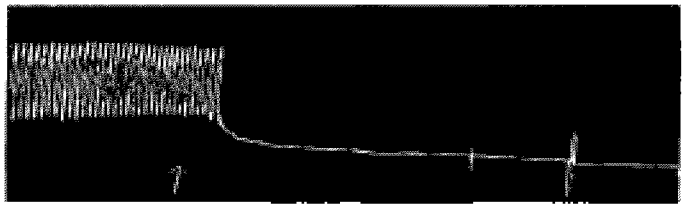


FIG. 8.—Pig's ureter in 50 c.c. of Locke solution. The movements cease after the addition of 10 milligrammes of papaverine hydrochloride. (Macht.)

obtained. Opium from poppies grown in Norway (Christiania) in 1914 contained 13·4 per cent. of morphine.

The chemistry of the opium alkaloids has not yet been fully explained. It is known for a certainty, however, that these alkaloids fall into two groups, namely, the pyridine-phenanthren group, of which the most important members are morphine and codeine, and the benzoyl-isoquinoline group, which is principally represented by papaverine and narcotine.

Recent investigations have shown that opium does not exclusively attack the central nervous system, but also has a peripheral action on numerous organs with unstriated muscles. The study of the physiology of such organs and their behaviour to poisons has of late years been much facilitated and simplified by the discovery that even in the higher animals they are much more tenacious of life than was formerly supposed. If, immediately

after death, pieces of various organs, *e.g.* artery, bronchus, intestine, ureter, uterus, etc., are taken and placed in a saline solution at the temperature of the body, kept continually saturated with oxygen, it will be seen that the organs are never at rest, but are incessantly performing rhythmical movements, which differ, however, from the contractions of the striped muscles in that they take place very slowly. Even organs that one would suppose to be in complete repose and functionless, such as the uterus in new-born animals, are in ceaseless motion.

By investigations made in this manner it has been shown that the opium alkaloids are just as sharply divided pharmacologically as chemically. The alkaloids of the pyridine-phenanthren group raise the tone of the vegetative organs and strengthen the automatic contractions, while those of the benzoyl-isoquinoline group have a relaxing effect and hinder motion (see Figs. 7 and 8).

The actions of opium and morphine are therefore not identical. In the Asia Minor opium, however, the morphine so predominates that its central action in all main features determines the character of the action as a whole. The other alkaloids in part give support to the morphine, so that opium acts more powerfully than would correspond to the amount of morphine ; but, on the other hand, qualitative differences arise from the antagonistic attitude of the isoquinoline alkaloids to morphine in certain points. Straub has shown that narcotine, in itself almost inert, potentiates the morphine action, and Pal that the isoquinoline alkaloids have a share in the influence of opium upon the intestine.

A description will be here given of the action, first, of morphine (and opium), and then of certain of the other alkaloids, and of some morphine derivatives.

Action of Morphine. General Features and Acute Poisoning. If the action of morphine were known only from what is seen in man, our knowledge of this alkaloid would be very imperfect. It produces narcosis, and when this has reached a certain depth, the person dies of respiratory paralysis. It is only in the more hardy animals that the second action, increased reflex irritability, is fully manifest.

In the *frog* a large dose of morphine first produces narcosis ; but when this has lasted for some time—often several hours—the condition entirely changes. The animal lying in a heavy torpor, is attacked by slight reflex twitchings, which gradually increase in strength and frequency, and finally merge into prolonged attacks of tonic convulsions, which are due to the extremely augmented reflex irritability of the spinal cord, and as regards strength may be compared to violent strychnine tetanus. Later the morphine is excreted, and the animal passes through renewed

narcosis to recovery, or dies from exhaustion. The same two phases may be traced up through the animal series, but they are less marked in mammals, and the second stage is not obvious as it is in the frog, which can live independently of pulmonary respiration. On the whole, the higher the position in the scale of animal life, the greater is the narcotic action and the less are the exaggerated reflexes, until in man the former has almost undisputed sway. There is also an immense difference between man and animals with regard to the doses that can be tolerated. The full action is attained in a frog only after 0·05 gramme (corresponding with about 10 grammes for a man weighing 11 stone), and small dogs of 6 or 7 kilogrammes weight often survive a subcutaneous injection of 2 grammes of morphine sulphate.

In *man*, after a small dose of morphine, 0·01 gramme, the susceptibility to pain is first reduced, so that even violent pain may quite disappear, or in any case be deadened. Meanwhile consciousness is still unaffected, the apprehension of external impressions is even quickened, and mental work can be performed. The symptoms of motor excitation and the strong desire for movement which characterise alcohol intoxication are quite absent. Somewhat later a pleasant drowsiness comes on, often accompanied by a flow of ideas and waking dreams in which the imagination has free play, while connected thought cannot be maintained nor the attention concentrated upon any definite subject. Sooner or later these irregularities disappear, and there follows a slumber resembling natural sleep, which at first is quite light and can be prevented by strong sense-impressions, passive movements, by addressing the patient in loud tones, etc.

The initial action may vary greatly. Whereas in the cultured nations of the West the dreamy stage is generally not very marked, or only just indicated, among Eastern races it is usually—judging from descriptions of the ecstatic condition of opium-eaters and opium-smokers—more pronounced, and sometimes passes into wild delirium. The reason is perhaps to be looked for in the fact that the Indian and Chinese opium is richer in the other alkaloids, perhaps in a difference of temperament and mental development. Intoxication with Indian hemp, too, does not afford the European the same enjoyment as it does the Oriental.

Larger doses, *e.g.* 0·03 gramme, quickly produce, as a rule without any previous excitement stage, a deep sleep, in which the face is congested, and the mucous membranes of the mouth and throat are dry. After dangerous doses, which for an adult may be reckoned as beginning with 0·06 gramme (0·10 gramme is considered to be the average lethal dose), the unconsciousness soon passes into deep coma, from which all attempts to rouse the patient are fruitless. The pupils are greatly contracted, the

aperture being no bigger than a pin's head, and they do not dilate in the dark nor when the eye is shaded by the hand. The respirations begins to suffer ; the respiratory movements, after decreasing in frequency, become superficial and sometimes of the Cheyne-Stokes type. The blood in consequence assumes a venous character, and imparts a cyanotic hue to the face and the visible mucous membranes. Notwithstanding accumulation of carbonic acid and the presence of cyanosis, the pupils still remain contracted—an unusual combination, which is a valuable guide in making a diagnosis. Finally the heart-action diminishes. The pulse becomes weak and irregular, and death takes place very quietly, or a short time before the end there are slight convulsions, which, in deep narcosis, cannot be regarded as a symptom of asphyxia (*cf.* chloroform asphyxia, in which no spasms appear), but must be explained as the precursor of a spastic stage that would ensue in man as well as in animals, if death did not supervene. The cause of death is respiratory paralysis. Immediately before it the pupils dilate.

Action on Various Organs and Functions. The action of morphine on the **central nervous system** has been described in all essentials above. Its great difference from that of the narcotic remedies of the fatty series is that the anodyne action begins long before the consciousness is affected, and that morphine combines with the narcotic action on the brain, increased reflex irritability of the spinal cord. The details of its influence on the various psychic functions have not as yet been so carefully investigated as in the case of alcohol.

The **respiration,** both in man and animals, becomes slow. At first the separate inspirations and expirations are often longer, and in this way, as long as the diminution in frequency is slight, the total respiratory volume, *i.e.* the amount of air inhaled in a certain time, may increase or remain almost stationary. Large doses greatly reduce the irritability of the respiratory centre and make respiration slower and irregular. By the employment of opium the effect on the respiration is slighter, but, on the other hand, the general narcosis is stronger, chiefly owing to the presence of narcotine.

Circulation. It is a fact of great importance in the practical employment of morphine that the working-capacity of the heart is reduced only by very large doses. After the ordinary therapeutic doses the pulse-rate is at first rather increased, but later, during the sleep, is a little diminished, probably only because all factors that increase the frequency, such as muscular movement and psychic impressions, are absent just as during natural sleep. Even after 0·01 gramme of morphine the same vessels are dilated

in man as are first affected by alcohol and other narcotics of the fatty series, namely those of the head (feeling of congestion and heat in the face). This partial dilatation of blood-vessels, however, has no appreciable influence upon the blood-pressure, which is the same during the morphine sleep as in natural sleep.

Next in practical importance to the action on the brain is the influence of morphine on the **alimentary canal.** Both the normal peristalsis of the healthy person and the morbid, stronger intestinal movements are retarded by morphine, which, in sufficient doses, produces complete repose of the entire alimentary canal. The elucidation of the nature of this important action has encountered many difficulties. In a number of animals a reaction is found differing so greatly from that in man (*e.g.* morphine in dogs regularly induces strong evacuations) that it is only with the strictest reservation that conclusions can be drawn from animal experiments. By X-ray examination Magnus has found that the constipating effect (in cats), to a great extent in any case, is due to the fact that even the evacuation of the stomach is delayed, so that the food, instead of quickly reaching the pylorus, lies for many hours in the fundus of the stomach.

Numerous experiments that have since been made on man according to the same method do not quite agree. For the present all that can be said is that the results seem to indicate that also in man the period during which the food remains in the stomach is lengthened, that the small intestine is less affected, and that the constipating action is due mainly to the arrested action of the large intestine.

According to experiments on rabbits, the action is to some extent, at any rate, local, aimed directly at the wall of the intestine, for if opium or morphine be introduced into a ligatured loop of the intestine, this first ceases to move on stimulation of the vagus, while the other sections of the intestine still react vigorously. In accordance herewith, both animal experiments and clinical experience show that the internal application of opium has a more sedative action on the intestine than the hypodermic injection.

It has long been known that opium has a more constipating action than morphine. This may to some extent be due to the colloid constituents, which prevent a too rapid absorption, so that the alkaloids remain longer in contact with the ganglia and nerves of the intestine. According to Pal, the reason of the superiority of opium lies, above all, in the presence of papaverine and the other isoquinoline alkaloids, which have a relaxing effect upon the longitudinal muscles, for in normal conditions the contraction of the latter contributes very essentially to peristalsis.

Sensory Nerves. Wiki and Moukhtar have demonstrated a local anæsthetising action, which is too feeble, however, to be of any practical importance. The anodyne influence is due to the action on the brain.

Glands. Large doses of morphine frequently cause profuse perspiration, the reason of which is not known. Otherwise the secretion of most of the glands diminishes. This applies especially to that of the intestinal and bronchial glands, the secretion of milk, and probably also urine. Salivation may at first be increased, only to decrease so greatly subsequently that even doses of less than 1 centigramme may be followed for some time by a feeling of dryness in the mouth and throat.

No influence on the **metabolism** has been found. Only in serious cases of poisoning does sugar appear in the urine, just as after many other poisons acting on the nervous system.

The slight *fall of temperature* during morphine sleep is principally due to the repose of the muscles, and also partly to the loss of heat through dilated cutaneous vessels. The origin of the great *contraction of the pupil* which accompanies acute morphine poisoning is unknown ; it is not due to local action on the nerves or muscles in the iris, for the dropping of morphine solution into the eye occasions no such change in the size of the pupil.

Untoward Effects. As already mentioned, the *tolerance* to morphine is far greater in animals than in man. In the latter, the susceptibility varies, as some persons exhibit exceedingly great sensitiveness or actual *idiosyncrasy.* A frequent and troublesome secondary effect, to which women more especially seem to be liable, is vomiting. The intestinal canal may also react abnormally, thus causing diarrhœa to take the place of the ordinary action. The secretion of urine may become scanty, and its evacuation difficult and painful (tenesmus of the bladder). The ordinary action on the brain may be abnormally strong, or, on the other hand, there may be excitability. An itching eruption is not infrequently seen, such as erythema, urticaria, vesicular and pustular eczema. Weak and irregular heart-action may occur ; in exceptional cases the pulse, even after injections of only 0·01—0·02 gramme, may become alarmingly slow (30—40) and soft. Very seldom the respiration suffers in a similar manner. It is of the greatest practical importance to recollect that morphine is *exceedingly poisonous for infants*, so that the ordinary rules for the proportion between age and doses do not hold good as regards this alkaloid.

Morphine would be still more valuable in medicine than it is, were it not one of those poisons that are attended with very great danger of **habit.** By its constant use an ever-increasing

desire and tolerance is rapidly formed, and at last doses may be reached which are many times in excess of the lethal dose for normal persons. The smallest dose known to have been fatal to an adult is 6 centigrammes, and the largest quantity a morphinist has been known to consume in 24 hours amounts to as many grammes. The largest doses on record are as follows: about 7 grammes of morphine salt in 24 hours; 30—36 grammes of opium consumed daily for years by a woman opium-eater; and De Quincey's statement in his "Confessions" of having reached a daily dose of "8,000 drops" of tincture of opium. The question as to how such enormous tolerance can be acquired has gained added interest since we have obtained some knowledge of anti-body formation. In the case of protein poisons the organism may acquire an enormous degree of protective power. In accordance with the mode of procedure in rendering immune to bacterial poisons, animals have been gradually accustomed to constantly increasing doses of morphine (active immunisation), and trials made as to whether their serum was capable of protecting normal animals against large doses of morphine (passive immunisation). The result, however, was negative; morphine does not elicit any process answering to the formation of antitoxin. Another explanation of the tolerance has been sought in the fate of morphine in the organism. Concerning that it is known that the hypodermically injected morphine disappears from the blood within as little as 20 minutes, half or more of it being soon excreted in the alimentary canal, principally in the stomach. Only a small percentage is found again in the urine. According to Faust's experiments with dogs, these conditions are changed in a remarkable manner in chronic morphinism. In the first place, it appeared that dogs, like men, could soon become accustomed to very large doses, and sometimes received the injections with evident pleasure. In the next place, it appeared that the quantity that was excreted in the alimentary canal gradually decreased in spite of the increasing doses. At first up to 70 per cent. of the amount injected could be regained in unchanged condition, then continually less, and at last, in a few cases, only a very small percentage, or even none, of the morphine given was found again, although the doses were continually increased and at last were enormous (as much as 3·50 grammes daily in animals of 6—7 kilogrammes body-weight). Thus the power of the organism to destroy the morphine increases quickly while the habituation is proceeding (*cf.* alcohol), and this has probably some share in, though it can hardly in itself account for, the tolerance, for the destruction of the alkaloid can scarcely take place quickly enough to protect altogether from the acute

toxic action which ordinarily appears in the course of a few minutes after hypodermic injection. We must therefore still have recourse to the assumption that the brain-cells are in some way or other deadened to the action of morphine.

It is hardly known with certainty whether the regular use of small doses of opium or morphine throughout a long period is deleterious. In Iran moderate opium-eating (a few centigrammes daily) is said to be usual without apparently having any injurious effects, and the moderate opium-eaters of India are said to enjoy long life. The constant consumption of large quantities, on the other hand, conduces to a serious intoxication, **chronic morphinism.** A full description of its manifold symptoms must be left to toxicological text-books and monographs, only the principal features being mentioned here. The symptoms that generally appear early are exanthemata, loss of appetite, irregular evacuations, generally constipation, sometimes diarrhœa, sleeplessness, malnutrition, *inter alia*, of the teeth (caries), and loss of strength. In advanced cases most of both the bodily and mental functions suffer; dyspnœa and palpitations are frequent upon the slightest exertion; dulness, a weakening of the will and memory, and a host of nervous symptoms develop, neuralgic pains, tremors, paræsthesia, irritability and varying anomalies of mood, and in the most serious cases albuminuria, tenesmus and paresis of the bladder, amenorrhœa and impotence. The sudden giving up of the accustomed "stimulant" produces, in a far greater degree than in other chronic poisonings, *abstinence symptoms* in the form of obstinate vomiting and diarrhœa, deep mental and physical depression, very great morphine-hunger, to satisfy which no means are eschewed (forged prescriptions), somnolence, or a condition of excitement which resembles delirium tremens, and, finally, as the most dangerous consequences, weakening of the heart with small, irregular pulse and serious collapse. A single sufficiently large dose of morphine causes all this at once to give place to complete well-being, which, however, is quickly followed by the desire for a fresh dose.

Other Opium Alkaloids. **Codeine,** or methyl-morphine, which is found only in small quantities in opium, increases the reflex irritability much more, and is less narcotic in its action on animals, than morphine, and accordingly in man it is more like a weak morphine. It acts less upon the psychical functions (the danger of a habit is therefore less), and less on the intestine, while its power of soothing cough is sufficient to satisfy practical purposes. Codeine, unlike morphine, is excreted principally through the kidneys. With continued use, Bouma could not find any diminution of the excretion, and thus there was no destruction. This

difference in the fate of the two alkaloids exists even in fœtal life, for in the hen's egg morphine (and heroine) is destroyed, but not codeine. As regards their action, the allied, synthetically-produced alkaloids, **ethyl-morphine** (*dionine*) and **benzyl-morphine** (*peronine*), resemble codeine. **Diacetyl-morphine** (*heroine*) is also principally excreted through the kidneys, but with habituation is increasingly destroyed in the body, until at last no alkaloid can be found in the urine and fæces. In man it very easily leads to habituation ; but, although in single doses it is more poisonous than morphine, the chronic poisoning is said to be less dangerous, and the habit more easily broken. Heroine is misused in America in a peculiar manner, namely, as snuff. In small doses it is remarkable for its very quieting action on the breathing, thus increasing the volume of the separate respirations. The particulars concerning the other opium alkaloids seem to vary greatly. **Narcotine** was formerly considered to be the alkaloid most like morphine, but was probably mixed with that drug. The pure narcotine no longer answers to its name, as it has only a feebly hypnotic action. It possesses, however, as already mentioned, the property of increasing the action of morphine. **Papaverine** has a relaxing action, not only on the intestine, but also on other smooth muscular tissue, especially the arterioles, and therefore is used in the treatment of high blood-pressure. **Thebaine** is an almost pure spastic poison with only slight narcotic action.

Therapeutic Uses of Opium and Morphine

Pain. It is their anodyne action that above all makes opium and morphine the most important of all drugs. Every pain, whatever its cause or intensity, yields to a sufficient dose of morphine, most quickly and surely when given hypodermically. It is fallacious to suppose that the injection should be made near the painful spot, as the action is on the brain ; and there is just as little reason in the old custom of giving morphine in suppositories for pain in the pelvic organs, except perhaps when it is apt to cause nausea or vomiting. It is principally the consideration for habit that restricts its employment. As a general rule morphine is given without hesitation only for acute pain and in chronic diseases in which the possibility of morphinism is of little weight as compared with the torments of the disease (malignant tumours, intolerable neuralgia, etc.). The normal dose is 1 centigramme.

Sleeplessness, Mental Diseases. The discovery of the narcotics of the methane series has made the physician to some extent

independent of opium and morphine, which were formerly the sole remedies for these purposes. Morphine is still, however, the sovereign remedy where pain or any other sensory stimulus, such as cough, palpitations, etc., is the cause of the sleeplessness. In cases of nervous sleeplessness the greatest judgment must be used in prescribing morphine, and it must be looked upon as a last resource. One reason for this is that such patients are the very ones who most easily acquire a habit; another reason is that the ordinary doses not infrequently produce dozing, with uneasy dreams, a mingling of narcosis and excitement; and, finally, the methane derivatives are often more certain. The bromine preparations should first be tried, and the new antipyretics, phenacetine, antipyrine, etc. For sleeplessness small doses of morphine, *e.g.* 5 milligrammes, are given at first. In mental diseases opium is employed as a sedative in very large doses, *e.g.* rising from 5 to 40 centigrammes 2 or 3 times a day. These large doses are generally tolerated remarkably well. *Delirium tremens*, which was formerly supposed to require the energetic employment of opium or morphine, is now treated with other narcotics and hypnotics.

Spasms. Clinical experience has proved, as the reflex-increasing action of morphine had already made probable, that conditions of motor excitation (spasms) are less affected by morphine than sensory (pains), and that chloral hydrate and the barbiturates are more rational in general spasms, *e.g.* tetanus and epilepsy. On the other hand, morphine is by far the better remedy for *local spasms* produced by a painful stimulus, *e.g. blepharospasm* in eye-diseases, frequent *nisus* in *cystitis*, and especially in *renal* and *biliary colic*. In the last-named cases, morphine not only relieves but really cures by causing the convulsive constriction, which prevents the passage of the renal calculus or the gall-stone, to cease.

In *diseases* of the **alimentary canal,** in accordance with what has been already said regarding the action on stomach and intestine, it is better to prescribe opium than morphine. Generally speaking, opium is the principal remedy whenever the object is to *immobilise the intestine*. In *inflammation of the alimentary canal*, it thereby brings about one of the most important conditions for recovery; in *hæmorrhages*, it is the best hæmostatic; and in *peritonitis*, immobilisation is the most effectual means of confining the inflammation and preventing its spread over the entire peritoneum. Of its special indications only some of the most important can be mentioned. In *diarrhœa*, the principal rule is that the increased peristalsis produced by deleterious substances in the intestine (poisons, bacteria) is at first left undis-

turbed or even assisted by a laxative, after which follows treatment with opium. Diarrhœa that is a symptom of great inflammation, however, is treated at once with opium, which subdues the violent movements that keep up the irritation, relieves the pain, and checks the profuse secretion from the affected mucous membrane. In *Asiatic cholera*, opium is the right thing during the prodromal diarrhœa, of little effect during the developed attack, and contra-indicated during the reaction period. In *diarrhœa in infants* opium is employed in very small doses after other remedies have been tried. *Typhoid diarrhœa* is treated with opium when the evacuations are too frequent and abundant. In *intestinal hœmorrhage* in typhoid fever, opium is absolutely necessary. In *constipation*, too—apparently a paradoxical indication —opium may be given when the retention is due to spasm of the intestine (lead-colic). In the conservative treatment of *appendicitis*, consideration for the peritoneum dictates the immobilisation of the intestine ; opium is therefore administered at first in liberal, afterwards in smaller, doses, and the more marked the symptoms from the peritoneum are, the more decidedly is it indicated. The intestine may be kept in repose for a couple of weeks without any fear of the fæces becoming too hard, for the accumulated masses are at last dissolved by the secretion from the mucous membrane. In *pains in the stomach*, in accordance with the general rule given above, the employment should be limited as far as possible to acute pains of rare occurrence (*e.g.* infrequent attacks of violent cardialgia), or to incurable diseases in which there is no reason to be sparing of morphine (cancer). Its employment may also be indicated by many other painful conditions, such as gastric ulcer or gastric crises in tabes.

Organs of Respiration. In *hœmorrhage from the lungs*, morphine is the best hæmostatic ; it acts by suppressing the cough that keeps up the bleeding. *Cough.* When a large quantity of secretion has collected in the alveoli and bronchioles, the cough is a beneficial reflex action which must not be suppressed ; in such cases the cough-subduing doses of morphine may easily cause a deleterious accumulation of secretion, and cyanosis as a sign of insufficient ventilation. The dry, " hard " cough, on the contrary, which comes on when the mucous membrane is swollen and hyperæmic and only secretes a small quantity of tough mucus which adheres to the bronchial walls, indicates morphine. When the cough, which represents a mechanical stimulus, is subdued, the swelling and hyperæmia diminish, and morphine may even apparently act as an expectorant, as during the longer intervals between the fits of coughing the scanty mucus collects in larger quantities, and is thus more easily got rid of. As regards the

dyspnœa that is a consequence of the over-filling of the lungs with mucus, the same rule applies as for the analogous cough. If the difficulty in breathing arises from the restriction of the movements of the chest on account of pain, *e.g.* in *dry pleurisy*, morphine is indicated, as also in violent attacks of *nervous asthma*.

The indications in **heart diseases** are great pain and dyspnœa. The employment depends upon the condition of the heart. If very advanced heart-weakness, cyanosis and large œdemata are present, morphine should be avoided if possible ; but small doses may almost always be tried, and may often act very beneficially, without occasioning any further weakness. It must be remembered that the heart is very tolerant of morphine, and in acute poisoning is the last organ to fail.

Both in *diabetes mellitus* and in *diabetes insipidus*, the diuresis decreases by the employment of opium or morphine. In the first-named disease the amount of sugar also, as a rule, diminishes, and the great thirst and hunger are subdued. All these effects, however, are only temporary.

The *external employment* of opium or preparations of opium in poultices, etc., to relieve pain, is quite valueless.

Contra-indications. The most important contra-indication is infancy, as sensitiveness to morphine at this period of life is so great that a single drop of tincture of opium may be fatal to children under 12 months of age. Morphine and opium are further contra-indicated, or must be employed with special caution, in extreme old age, in advanced stages of weakness in general, in pulmonary œdema, and in great dilatation of the heart, especially the right half. Other contra-indications have been mentioned above with the indications. Fever is not considered a contra-indication of opium or morphine.

In comparison with morphine the other opium alkaloids are of secondary importance. **Codeine** is employed as a soothing remedy for cough, and has the advantage over morphine of being less constipating. It is prescribed, like morphine, for *dry cough*, *e.g.* of consumption, but not where there is much secretion. During the breaking-off of the morphine habit codeine serves as a less dangerous substitute. With children it must be employed with the same caution as morphine. *Ethyl-morphine*, or *dionine*, has the same indications as codeine. It is used principally for the dry, *tuberculous cough*, and, unlike morphine, is said to check sweating. If dionine, either in substance or solution, is brought into contact with the eye, there appears after a little burning and smarting, which soon vanishes, great injection and swelling of the conjunctiva, produced by the exudation of serum from the vessels. After some hours the fluid is again absorbed,

and with it often morbid products. Dionine is therefore employed, after the irritative symptoms in the main have passed away, as a means of *procuring absorption in diseases of the eye*, such as inflammatory thickening of the cornea, parenchymatous keratitis, hæmorrhage of the anterior chamber, iritis with deposits upon the posterior surface of the cornea, traumatic cataract. *Benzoyl-morphine* (*peronine*), which, as regards activity, comes between morphine and codeine, has a soothing action on cough. The danger of habituation is probably about as great with these remedies as with morphine. Concerning *diacetyl-morphine*, known commercially as *heroine*, opinions are varied. It is recommended by many as a cough-soothing remedy, and has undoubtedly great influence on respiration. Others have objected that, though it makes each separate inspiration deeper, it simultaneously diminishes the respiratory frequency so much that the respiratory volume during a certain time, " the minute volume," becomes less. *Papaverine*, on account of its vaso-dilator properties, is employed in *arterio-sclerosis*, in *hypertension* during *disease of the kidneys*, in *angina pectoris* and *arterial vascular crises* in tabes. *Bronchial asthma* may be arrested by intravenous injection.

Treatment of Morphine Poisoning. Acute poisoning is treated according to the general rules for alkaloid poisoning, first of all by washing out the stomach ; and, as morphine is eliminated into the stomach, this must also not be neglected when the poisoning has been caused by subcutaneous injection. Instead of water a dilute solution of potassium permanganate (1 in 1,000) may be used, which quickly oxidises morphine into non-poisonous products. Tannic acid does not throw down morphine like other alkaloids. Emetics take effect only in the earliest stage of the poisoning. Attempts to prevent the onset of narcosis by flagellation (flicking the patient with wet towels) and by compelling him to move about are likely to cause exhaustion, and are therefore of doubtful value. Injections of caffeine, camphor and coramine are employed as cardiac stimulants. If the narcosis has begun, and there is cyanosis, artificial respiration is the most important measure to be taken. The inhalation of a mixture of oxygen with 7 per cent. of carbon dioxide is of special value at this stage. Cold sponging in a hot bath is also employed. Hypodermic injections of permanganate of potash, which is recommended for the purpose of oxidising the absorbed morphine, are quite useless, as that salt in contact with the tissue is reduced immediately at the point of injection. There has been great difference of opinion on the subject of atropine as an antidote in morphine poisoning. It is certain that the pupil, even in very deep morphine narcosis, is

dilated, that the pulse frequency is increased by the paralysing of the inhibitory apparatus of the heart, and that the respiration is often improved ; but the disputed point is whether the ultimate result is to the benefit of the patient. While atropine is considered by many to be dangerous and to be used only in small doses (½—1—1½ milligrammes), a few designate enormous doses (3—6 centigrammes) as the permissible and only effectual treatment in desperate cases.

Cases of *chronic morphine poisoning* require to be placed in retreats where the patient is under constant supervision. Treatment at home is always a failure with decided morphinists, whose weakened will is unable to face the deprivation imposed by the treatment. Unlike alcohol, the withdrawal of morphine cannot be made suddenly, as dangerous abstinence symptoms (acute heart-weakness) may appear ; it must take place gradually. Dangerous collapse requires a morphine injection. It is very frequently observed that at first the diminution of the doses works comparatively well up to a certain point, at which abstinence symptoms and the torturing " morphine-hunger " appear. During the treatment the patient is aided by hypnotics (chloral hydrate, trional, etc.), baths, nourishing diet. To employ cocaine is to expose the patient to a new and even more dangerous poison. In pronounced morphinism the prospect of a cure is doubtful, and relapses are very frequent.

Preparations and Doses.

B.P. Preparations

Opium is the juice obtained from the unripe capsules of *Papaver somniferum*, inspissated by spontaneous evaporation. The official (Asia Minor) opium, in its commercial form, is in round, flattened cakes, each of a few hundred grammes weight, covered outside with poppy-leaves and strewn over with rumex fruit. Inside they are brown, rather soft when fresh, becoming hard later. They contain, besides the alkaloids, mucilage and gum, sugar, resin, wax, and inorganic salts. Opium is obtained by incision in the unripe capsules, when a white, milky juice flows out of the cut milk-ducts which form an anastomosing network immediately beneath the epidermis. This juice soon stiffens into reddish-brown " tears," which are carefully scraped off, and after further drying are kneaded up into opium cakes. Each capsule yields only a few centigrammes of opium. Opium must contain 9·5—10·5 per cent. of morphine. *Dose*, 3—20 centigrms., ½—3 grs. The doses vary greatly according to their object. For diarrhœa a small dose, *e.g.* 5 centigrms., 3 times a day, often with 1—2 grms. of bismuth oxynitrate ; as an anodyne and hypnotic, 10—15 centigrms. *Re* large doses in mental affections, see p. 85. For children under 1 year,

as many milligrammes daily as the age of the child in months up to 10 milligrms.

Opium Pulveratum. Powdered opium. Dried opium finely powdered and adjusted by the addition of lactose, if necessary, to contain 10 per cent. of anhydrous morphine.

Extractum Opii Siccum, 20 per cent. of morphine. *Dose*, 16—60 milligrms., $\frac{1}{4}$—1 gr.

Tinctura Opii, Laudanum, 1 per cent. of morphine. *Dose*, 3—10 decimils, 5—15 mins., for repeated administration; 12—18 decimils, 20—30 mins., for a single administration.

Tinctura Opii Camphorata, Tinctura Camphoræ Composita, Paregoric, Paregoric Elixir. A frequently employed cough-remedy, containing $\frac{1}{20}$ per cent. of morphine, as also benzoic acid, camphor, and oil of anise. *Dose*, 2—4 mils, $\frac{1}{2}$—1 fl. dr.

Pulvis Ipecacuanhæ et Opii, Dover's Powder. Opium 1, ipecacuanha 1, lactose 8. Much used for bronchitis, also as a sedative and diaphoretic. *Dose*, 3—6 decigrms., 5—10 grs.

Pulvis Cretæ Aromaticus cum Opio. Opium (2·5 per cent.) and aromatic chalk powder. *Dose*, 6—40 decigrms., 10—60 grs.

Pulvis Kino Compositus (B.P.C.). Opium (5 per cent.), kino and cinnamon. *Dose*, 3—12 decigrms., 5—20 grs.

Pilula Saponis Composita (B.P.C.). Opium (20 per cent.) and hard soap. *Dose*, 12—25 centigrms., 2—4 grs.

Suppositoria Plumbi cum Opio. Each suppository contains 2 decigrms. (3 grs.) of lead acetate and 60 milligrms. (1 gr.) of opium, unless otherwise prescribed.

Morphinæ Hydrochloridum, $C_{17}H_{19}NO_3.HCl+3H_2O$, acicular crystals with a bitter taste, soluble in 25 parts of water. *Dose*, 8—20 milligrms., $\frac{1}{8}$—$\frac{1}{3}$ gr.

Liquor Morphinæ Hydrochloridi contains 1 per cent. of morphine. *Dose*, 3—20 decimils, 5—30 mins. *Tinctura Chloroformi et Morphinæ Composita* (B.P.C.) has the same percentage of morphine, and further contains chloroform and dilute hydrocyanic acid and Indian hemp. The *dose* of this unnecessary preparation is 3—10 decimils, 5—15 mins.

Suppositoria Morphinæ. Each contains 15 milligrms. (about $\frac{1}{4}$ gr.) of morphine hydrochloride.

Trochiscus Morphinæ et Ipecacuanhæ. Each lozenge contains 2 milligrms., or approximately $\frac{1}{30}$ gr., of morphine hydrochloride and 6 milligrms. ($\frac{1}{10}$ gr.) of ipecacuanha.

Morphinæ Tartras, $(C_{17}H_{19}NO_3)_2.C_4H_6O_6+H_2O$, is more readily soluble in cold water (11 parts), and is therefore more useful than the hydrochloride when large doses are to be employed as injections, *e.g.* for morphinists. *Dose*, 8—20 milligrms., $\frac{1}{8}$—$\frac{1}{3}$ gr.

Codeinæ Phosphas, $C_{18}H_{21}NO_3.H_3PO_4+2H_2O$. White, efflorescent crystals with slightly bitter taste, soluble in 3·5 parts of water. *Dose*, 16—60 milligrms., $\frac{1}{4}$—1 gr. Prescribed as a soothing remedy for cough in the form of powders, pills, or as :

Syrupus Codeinæ Phosphatis (B.P.C.), strength 0·5 per cent. *Dose*, 2—8 mils, $\frac{1}{2}$—2 fl. drs.

Diamorphinæ Hydrochloridum, Diacetyl-morphine hydrochloride, Heroine, $C_{17}H_{12}NO(C_2H_3O_2)_2HCl+H_2O$. A white, bitter, crystalline powder, soluble in 3 parts of water. *Dose*, 2·5—8 milligrms., $\frac{1}{25}$—$\frac{1}{8}$ gr.

(For *Dionine* see "U.S.P. Preparations"; for *Papaverine*, *Pantopon* and *Narcophine*, see "Unofficial Preparations.")

U.S.P. Preparations

Opium, the air-dried, milky exudation obtained by incising the unripe capsules of *Papaver somniferum*, and yielding in its normal, moist condition not less than 9·5 per cent. of anhydrous morphine. *Dose*, 0·06 grm., 1 gr. (For description of the drug and doses for children see "B.P. Preparations.")

Opii Pulvis, dried and powdered opium, yielding 10—10·5 per cent. of morphine. *Dose*, as of opium. *Opium Deodoratum*, with the same percentage of morphine, is deodorised by extraction with petroleum benzine.

Tinctura Opii, Laudanum, 1 per cent. of morphine. *Dose*, 0·6 mil, 10 mins.

Tinctura Opii Camphorata, Paregoric, contains 0·4 per cent. of opium, benzoic acid, camphor, and oil of anise. Often prescribed for cough and cold. *Dose*, 4 mils, 1 fl. dr.

Mistura Glycyrrhizæ Composita, Brown Mixture, contains 12 per cent. of the preceding preparation, liquorice, tartar emetic, etc. In many countries (and many varieties of composition) a favourite household remedy for colds. *Dose*, 4 mils, 1 fl. dr.

Pulvis Ipecacuanhæ et Opii, Dover's Powder. Opium 1, ipecacuanha 1, sugar of milk 8. Much used in bronchitis. *Dose*, 0·3 grm., 5 grs. For children doses 10 times as large as of opium.

Morphinæ Sulphas, $(C_{17}H_{19}NO_3)_2H_2SO_4+5H_2O$. Acicular, silky crystals, soluble in 16—17 parts of water. *Dose* as the preceding preparation.

Codeina, $C_{17}H_{18}(CH_3)NO_3+H_2O$. A white crystalline powder or prisms, sparingly soluble in water. *Dose*, 0·03 grm., ½ gr.

Codeinæ Phosphas, $C_{17}H_{18}(CH_3)NO_3.H_3PO_4+2H_2O$. Fine, needle-shaped crystals, soluble in 2—3 parts of water. *Dose*, 0·03 grm., ½ gr. for soothing cough, in powders or pills, or dissolved in water to which sugar syrup or orange syrup is added.

Codeinæ Sulphas is less practical, as it is less soluble (in 30 parts of water).

Æthylmorphinæ Hydrochloridum, Dionine, $C_{17}H_{18}(C_2H_5)NO_3HCl+2H_2O$. A white or yellowish powder, soluble in 8 parts of water. *Dose*, 0·015 grm., ¼ gr. Externally, in the eye in 5 per cent. or stronger solution, or in substance.

Unofficial Preparations

Benzylmorphinæ Hydrochloridum, Peronine. A white, easily soluble powder. *Dose*, the same as of dionine.

Papaverinæ Hydrochloridum, $C_{20}H_{21}NO_4.HCl$. White needles, soluble in water. *Dose*, internally or subcutaneously up to 0·1 grm., 1½ gr.; intravenously 0·005—0·04 grm., $\frac{1}{12}$—⅔ gr.

Papaveratum (B.P.C.), *Pantopon*, *Omnopon*, a preparation introduced by Sahli, containing all the alkaloids (as hydrochlorides) in the same proportion as opium, but without that drug's ballast material (mucilage, resin, etc.). It thus exhibits the aggregate alkaloid action, and may be injected hypodermically. A grey or brownish powder, soluble in water, containing about 90 per cent. of alkaloids, rather more than half of which consists of morphine. *Dose*, internally or subcutaneously, twice as large as of morphine.

Narcophinum, salt of morphine and narcotine with meconic acid. The preparation is based upon the previously-mentioned potentiating of the morphine action by narcotine. A crystalline powder, easily soluble in water, containing about 32 per cent. of morphine. *Dose*, internally or subcutaneously, 2 or 3 times as large as of morphine.

Addenda

In several other Papaveraceæ there also occur alkaloids that are allied to morphine or other opium alkaloids. The yellow or orange-coloured milky juice of *Chelidonium majus* (celandine), a plant found in Europe and North America, contains a number of alkaloids, among them being the protopine also occurring in opium, and chelidonine, in which the outlines of the morphine action—first narcosis and then increase of the reflexes—may be seen. *Sanguinaria Canadensis*, blood-root, an old emetic and expectorant (preparation, *Tinctura Sanguinariæ*. *Dose*, 1 mil. 15 mins.), contains the alkaloid sanguinarine, which, in large doses, causes tetanus, and thus most resembles the opium alkaloid, thebaine.

Several of the Cactaceæ (Cereus and Anhalonium species) are used by the Indians as intoxicants at their religious festivals, under the names Pellote, Peyotl, Muscale or Mezcal Buttons. They produce an exaltation that is remarkable for its vivid hallucinations of sight, resembling those of the Cannabis intoxication (see next chapter). From these plants alkaloids have been isolated, some of which resemble morphine in their action, others strychnine.

8. CANNABINOL (*CANNABIS INDICA*)

A form of the ordinary hemp, *Cannabis sativa*, growing in Eastern India, differs from the plant cultivated in Europe in that the numerous glands of the female inflorescence secrete a viscous resin containing a narcotic substance. In the hemp growing in countries with a colder climate it is found, if at all, only in minute quantities.

Cannabis indica is one of the most important narcotic drugs of the Oriental world. It forms the ordinary intoxicant for perhaps 200—300 million persons in Turkey, and all over Asia and Africa wherever Mohammedanism, which forbids wine, has entered, and is indulged in under various names, such as *bhang*, *ganja* and *haschisch*, and in various forms, being either smoked in pipes, or eaten, or drunk with the addition of sweets or spices. The active constituent is the semi-liquid, yellowish cannabinol, $C_{21}H_{30}O_2$, an unstable phenol-aldehyde.

Action. Indian hemp acts upon the cerebrum, and produces an intoxication that is remarkable in two ways. In the first place, the imagination is more untrammelled than in any other form of intoxication, and, in the next, the intoxicated person, even in the wildest flight of ideas and the most exuberant hallucinations, retains a remnant of reality ; he has a dim idea that he is only in

a pleasant dream-state, and can give more or less sensible answers when addressed. According to numerous accounts of travellers in the East and personal experiments made, among others, by von Schroff and his pupils, the action generally begins with a feeling of warmth and heaviness in the head, sounds as of rushing water, and a motley of colour hallucinations of incomparable beauty. Later on the ground seems to disappear beneath the feet; there is a feeling of being snatched away from this world; the body, freed from all weight, floats through space in a condition of the greatest physical and psychical well-being, and in alluring dreams, which for a short time transport Orientals to a paradise endowed with Mohammedan ideals. Sometimes the dreams are of a rapidly changing nature in which tears alternate with laughter, occasionally only of a sad or terrifying character, thus engendering deep depression or giving rise to a desire for destruction and fits of mania. The feeling of pain is lessened, and the sense of touch is blunted. The intoxication gradually deepens, there are periods of unconsciousness, and, in conclusion, a deep sleep ensues, from which the subject awakes feeling perfectly well. Moderate indulgence in *haschisch* is said to have no injurious effects, and does not induce constipation. Exaggerated misuse causes general debility and often permanent insanity. The various preparations are unequal in their action. After the extracts employed in Europe sleep has often been seen to ensue without any, or with only slight, excitement, and sometimes no effect has been attained except palpitations and rapid pulse, with neither narcosis nor excitement.

The pure cannabinol produces in dogs an intoxication of the same kind as hemp-extract in man, a mingling of sleep and waking dreams. Small doses cause the animals to fall into a visionary condition, in which, evidently under the influence of visual hallucinations, they now snap at, now follow with attentive eyes, imaginary objects that appear to be floating past. After large doses there is developed, as sometimes in man, a cataleptic condition, in which the most uncomfortable positions in which the limbs can be placed are long retained; later the narcosis becomes deeper, and the behaviour of the animal resembles that of a man when he is struggling against sleep; and at last it sinks into a heavy torpor. Even very large doses (2 grammes), however, do not cause really dangerous symptoms, and the abundant *haschisch* literature cannot show a single case of fatal poisoning in man.

Uses. Cannabis indica has been employed as a ***hypnotic*** and *anodyne* for *neuralgia*, *migraine* and *cardialgia ;* but as the action is uncertain, and the preparations—various extracts—have

proved very unreliable, it has been omitted from several pharmacopœias.

Preparations and Doses

Cannabis (U.S.P.), Indian hemp, the flowering or fruiting tops of *Cannabis sativa*.

Extractum Cannabis (U.S.P.). *Dose*, 0·015 grm., ¼ gr.

Fluidextractum Cannabis (U.S.P.). *Dose*, 0·1 mil, 1½ min.

9. THE COCAINE SERIES

Erythroxylon coca is a bush indigenous to Peru and Bolivia, and, like many other plants that have been long in cultivation, it is not now found wild, but is grown in many hot countries. It was a common intoxicant among the South American Indians even when the Spaniards came to the kingdom of the Incas for the first time. Chewing of the leaves produced a feeling of well-being, and, according to the accounts of many travellers, enabled the natives to endure the greatest exertion unhampered by weariness, hunger, or thirst.

The active ingredient of the coca-leaves is the alkaloid *cocaine*, $C_{17}H_{21}NO_4$, which, like the alkaloids of the atropine group, behaves like an ester that can be easily decomposed. As soon as it is boiled with water it gives off *methyl alcohol ;* with continued decomposition *benzoic acid* is liberated, and there is left a base called *ecgonine*, which closely resembles the base tropine (see next chapter) in atropine, with which the alkaloid cocaine is thus allied. From the above-mentioned constituents cocaine can be once more built up, and the substitution of certain of the original constituents by others leads to new cocaine-like bodies, concerning which more will be said. Even in coca-leaves variants are found in which the ecgonine is combined with aromatic acids other than benzoic acid.

Action. Cocaine is one of the few vegetable alkaloids that have a very pronounced **local action.** Even in a very dilute solution it paralyses the **terminations of the sensory nerves,** thus producing analgesia and local anæsthesia. The action lasts only as long as the nerve-ends are in contact with the solution—on an average, 10 to 20 minutes. It is briefest in places where an active circulation quickly carries the alkaloid away, and can be prolonged by arresting the flow of blood, *e.g.* by ligature above the seat of application, or by the aid of adrenaline. The paralysis especially affects those nerve-endings that feel pain and touch, whilst heat and cold may still be distinguished. In the *nasal and oral cavities*, the nerves of the respective senses are also partially paralysed, the sense of smell being entirely abolished, as also the

taste of anything bitter, while sweet and acid liquids can be more or less distinguished. The *mucous membranes*, besides being anæsthetised, become pale, as a consequence of *contraction of the vessels*, and also dry and shrivelled, as the *glandular secretion* is diminished. When taken *internally* the sensitiveness of the intestinal mucous membrane is dulled, and feeling of hunger suppressed. As cocaine in an aqueous solution does not penetrate the epidermis, it is unable to anæsthetise through the unbroken skin.

In a stronger solution, cocaine also destroys the conductivity of the *motor*, and still more of the **sensory, nerve-fibres** ; and the region supplied by the nerve becomes anæsthetised (regional anæsthesia). In this way it differs in a very important practical direction from most of the other nerve-poisons, which, as a rule, act only upon the ganglion-cells and nerve-endings, while the transmission through the connecting fibres is not interrupted.

Upon dropping a 2—3 per cent. solution into the eye a slight burning sensation is first noticed, then coolness, and in the course of 3 or 4 minutes the conjunctiva and cornea are quite anæsthetised, and subsequently, but less completely, the iris too. The anæsthesia of the cornea lasts for a long time, favoured by the slow flow of humour, which permits of prolonged contact between the nerve-ends and the alkaloid. From 15 to 20 minutes after the dropping in of the cocaine the pupil dilates to a moderate extent. It still reacts a little to light, contracts once more with physostigmine or muscarine, and is dilated still further by atropine. The accommodation is also paralysed, but imperfectly. The intra-ocular pressure is lowered in the normal eye, and the vessels visible to the naked eye are contracted, while the blood-supply of the retina is not distinctly changed.

The Central Nervous System. The absorbed cocaine does not exert any anæsthetising action upon nerve-ends, as it circulates in far too dilute a solution, but it exerts a central action which is of a very composite nature. A dose of a few centigrammes produces in most people high spirits and a feeling of well-being, sometimes a liveliness and happy exaltation that resemble the cerebral action of atropine. It is this influence and the removal of the feeling of hunger by the local anæsthesia of the stomach that has made the coca-leaves a highly-prized intoxicant in the countries of which the plant is a native. It has been shown by U. Mosso that cocaine, in internal doses of 0·1 gramme, also has a very favourable influence on muscular work, though only on individuals who were previously exhausted. It was, however, only the voluntary muscular work that was improved, while the contractions produced by electrical stimulation were scarcely affected.

The influence is thus of central nature, and it is doubtful whether there is any direct effect on the muscles. Large quantities of cocaine act upon the medulla oblongata, and frequent respiration and vascular contraction appear. As a consequence of stimulation of the accelerator nerve, the pulse-rate is also increased. Later, symptoms both of excitation and of paralysis of the brain and the medulla oblongata may develop side by side, or rapidly alternate.

Fate in the Organism. Cocaine has the property, so valuable in practice, of losing much of its toxicity when it is kept for some time at the seat of application. If, for instance, in the hind leg of a rabbit there be injected a dose of 0·10 gramme, which would ordinarily cause death in a few minutes, and immediately afterwards an indiarubber tube be wound round the leg, only slight toxic symptoms appear when the tube is removed after half an hour, and none when it is allowed to remain from 1 to 1½ hours. The explanation of this is that the cocaine is firmly absorbed by the tissues, and, after the loosening of the ligature, passes so slowly into the circulation that it is not present in the blood in active concentration. This is all the more marked the greater the dilution of the solutions. A similar activity-weakening absorption by colloid substances or bodies with large surface, *e.g.* animal charcoal, is also found in many other poisons. It has been supposed, too, that the cocaine would be rapidly decomposed by the ferments of the living tissue. How this may be with regard to man is not known, but in animals (rabbits) the greater part (42—85 per cent.) of the subcutaneously injected alkaloid is excreted in the urine.

In consequence of the composite action, **acute cocaine poisoning** may exhibit a very varied character. The slightest cases, which are frequently seen after the painting of mucous membranes, injections, dropping into the ear, etc., are limited to a feeling of languor and giddiness, anxiety, pallor, and inclination to faintness. Another form of slight poisoning expresses itself in cerebral excitement—gaiety of spirits, garrulousness, hallucinations and delirium. In more serious cases there are a great number of additional symptoms, such as dilatation of the pupils, dryness of the mucous membranes, vomiting, clouded mental faculties. The heart always suffers ; the pulse is very irregular, now slow, now rapid and small, the face pale, and the tip of the nose cyanosed. Sometimes there is a great rise in temperature. In conclusion, there is collapse with failing circulation and weakening of the respiration, as also clonic convulsions or tetanus, in the course of which death takes place from respiratory and heart failure. After the injection of very large quantities, *e.g.* 1 gramme, death may

ensue almost instantaneously. It is difficult to state exactly the lethal dose. Very serious cases have been seen after a few centigrammes, and little or no ill effects from several times the amount; and it is therefore supposed that the individual disposition has varied. It is more probable that the explanation is to be found in the fact, only recently sufficiently realised, that cocaine is far more dangerous in concentrated than in dilute solutions, for in the former case a considerable part can be absorbed, while in the latter, as already mentioned, more of the alkaloid is held at the seat of application and rendered harmless.

Chronic poisoning occurs in South America in habitual coca-chewers, and in recent times in Europe and in North America. The consequences are a rapidly increasing consumption of cocaine and serious intoxication, accompanied by digestive disorders, emaciation, loss of appetite alternating with voracity, œdemata, marasmus, hydrops, apathy, insanity and delirium. The dilatation of the pupil and the paræsthesia which gives rise to the idea that the skin is inhabited by innumerable little animals ("cocaine bugs") are important guides in diagnosis. The abstinence symptoms are far slighter than those of chronic morphinism. The cocainist's consumption may increase to several grammes a day. In the ordinary laboratory-animals, on the contrary, continued cocaine injections cause, if anything, increased sensitiveness. Man would thus seem to occupy a peculiar position with regard to cocaine. It is not known whether, while the habit is being acquired, an increased destruction of the alkaloid takes place.

Therapeutic Uses. Among the many new remedies with which therapeutics have been enriched in recent times, cocaine is one of the most important, partly on account of its own value and partly from the development it has occasioned of local anæsthesia in general, which permits of the performance of a multitude of minor operations which formerly required ether or chloroform; these are performed without pain, without danger, and without loss of consciousness. Quite recently its use, or that of allied remedies, has been still more extended by several new methods of employment, namely, *in combination with adrenaline*, *regional anæsthesia*, and *spinal* or *subarachnoid anæsthesia*. These methods, of which the principles will now be explained here, represent a new advance of local anæsthetics into fields that have hitherto been reserved for general anæsthesia.

Cocaine and other similar remedies have acquired their greatest increase in value by *combination with adrenaline* (*epinephrine*). Endeavours had previously been made by the local application of cold, or by ligature above the site of operation (on

the extremities), to counteract the absorption that raised the greatest barrier to its employment; but it was not until the co-operation between cocaine and adrenaline came to be known (Braun, 1902) that this method acquired its great practical value. By its vaso-constrictor properties adrenaline causes the cocaine to remain for a long period at the seat of application. From this it follows, not only that *the anæsthesia is prolonged*, but also that weaker cocaine-solutions can be used, because *the anæsthetising effect is increased* when none of the alkaloid is carried away, and, finally, the *toxicity of the cocaine is diminished* by the time given it to be fixed in the tissues and rendered harmless. All these advantages unite in making the combination of adrenaline and cocaine a decided advance in the production of local anæsthesia, all the more valuable from the fact that this method requires no special skill, whereas the two following belong rather to the specialist.

Regional anæsthesia is a blocking of the conduction. The feeling of pain is abolished by the injection of the remedy, alone or with adrenaline, close to the nerve-trunks within whose ramifications the operation is to take place. This method requires somewhat strong solutions, and is principally adapted to the extremities.

In 1898, Corning found that even small quantities of cocaine when introduced, in lumbar puncture, within the membranes of the spinal cord were able to produce anæsthesia throughout large portions of the body. Applied in this way, the alkaloid comes in contact not only with the spinal cord, but also with the axis-cylinders passing within the membranes, where they are not insulated by any medullary sheath, and produces a regional anæsthesia on a large scale. In 1899, Bier made the daring experiment of trying *spinal anæsthesia* also on man. It appeared that in from 6 to 8 minutes after lumbar puncture and injection of 1—1½ centigrammes of cocaine hydrochloride, complete analgesia was developed in the lower extremities and soon spread up the body as far as the epigastrium, or even farther. Operations could be performed painlessly, while sensibility to touch and difference of temperature were still noticed. Serious cases of poisoning were of far too frequent occurrence, however, and the method was therefore discarded. Since the discovery of the newer, less toxic, substitutes, its use has been revived; but it has so many dark sides—motor paralysis, *e.g.* of the bladder, collapse, etc.—that it is seldom used. (Regarding the newest method, sacral anæsthesia, see below under "Novocaine.")

It has long been known that it is not necessary, in order to abolish the feeling of pain, to employ any specific nerve-poison

which paralyses the nerve-ends or the axis-cylinders. Anæsthesia can also be obtained with water or indifferent saline solutions when the tissue, under a certain pressure, is thoroughly saturated or infiltrated with them. Upon these observations is based the *infiltration anæsthesia* (Schleich, 1894), which consists in the injection of common salt solution containing a very small quantity of cocaine. The liquid is first injected into the skin itself, not subcutaneously; a skin-œdema of about the size of a shilling is formed, which is completely without sensation. At the edge of this, new "anæsthetic papulæ" are made in the direction required; and when an insensitive incision-line has thus been formed, the infiltration is continued deeper. It is, as has been said, the actual infiltration that here operates; the cocaine should, properly speaking, be unnecessary, but the inflow of the liquid into the tissue causes slight pain before the anæsthesia commences, and it is this that the cocaine addition is to abolish.

The *indications for cocaine* are easily deduced from its action. It has acquired very great significance in *operations on the eye*, especially the conjunctiva, cornea and sclerotica, which are completely anæsthetised. One operation that in particular has been facilitated is the removal of foreign bodies from the eye. Operations on the eye muscles, and even enucleations, may also be performed without pain by the aid of sub-conjunctival injections, while the inner parts of the eyeball, *e.g.* the iris, are not completely anæsthetised. After the dropping in of cocaine the eye should be moistened or, by closing of the eyelids, be protected against evaporation, as the cessation of secretion (tears, lymph) may otherwise lead to drying up and superficial loss of substance.

Cocaine is further most extensively employed as an anæsthetic for the *mucous membranes of the nose, mouth, throat and larynx.* The accompanying vaso-constriction has a share in prolonging the action, as the absorption is delayed, and it, moreover, checks the bleeding during the operation itself, though the liability to secondary hæmorrhages is, if anything, increased, because after the constriction of the vessels there comes dilatation. Vascular constriction and the absence of secretion cause diminution of swelling in the inflamed mucous membranes, so that the examination of narrow cavities, such as the interior of the nose, is facilitated. In sensitive persons, who react with vomiting-movements, painting with cocaine is valuable for laryngoscopical examination.

For the rest, cocaine may be employed in practically all *minor operations. Painful sores* (*e.g.* herpes zoster and burns) and *itching* (*pruritus vulvæ et ani*) may also be treated with

cocaine. On the whole, however, *the frequency of cases of poisoning should act as a warning in the external employment of cocaine*, which is now, to an increasing extent, being replaced by less dangerous remedies.

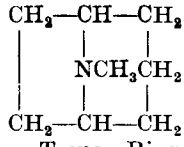
The *internal uses* of cocaine are few. It sometimes gives good results in *obstinate vomiting*, in *sea-sickness*, and even in the *vomiting of pregnancy*, and may relieve the pain of ulcer and cancer in the stomach. To let morphinists exchange morphine for cocaine is merely letting them change the form of intoxication.

Treatment of Cocaine Poisoning. Slight attacks of syncope yield to the assumption of a horizontal position and, if there is great pallor, inhalation of amyl nitrite. No antidote is known. For the rest the treatment is purely symptomatic. Convulsions call for the intravenous injection of 1 or 2 grains of sodium phenobarbitone or other soluble barbiturate. Morphine is contra-indicated as it increases the respiratory depression. If shallow breathing and cyanosis appear, artificial respiration should be instituted immediately with inhalation of oxygen and carbon dioxide. For heart failure intravenous injections of Coramine may be tried, but treatment is rarely of any avail as the circulatory collapse is due to paralysis of the vasomotor centre. Chronic poisoning requires treatment in an institution.

Recent Local Anæsthetics. Anæsthetising Studies

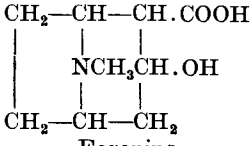
Cocaine was produced from coca-leaves as early as 1860, and its local anæsthetic properties were discovered soon after, but did not then arouse the attention they deserved. It was only when, in 1884 (Koller), they were discovered for the second time and employed in diseases of the eye, that cocaine all at once became one of the most frequently employed drugs. Valuable though it is, there is always a drawback to its employment, namely, its toxicity, which greatly restricts its use. Investigators were therefore soon occupied in trying, by new syntheses and transformations, to find bodies which, while retaining the local action, should be less poisonous ; and, after many unsuccessful attempts, the result has been the production of several new combinations which possess the required properties.

The foundation for these new synthetic products was determined by the investigation of the chemical constitution of cocaine, which in 1898 was fixed by Willstätter. The nucleus for cocaine, as also for the nearly-allied atropine, is the tropan ring, a ring with 7 carbons, formed by the combination of a pyrrolidine ring and a piperidine ring, which have 2 carbon atoms and 1 nitrogen atom in common.

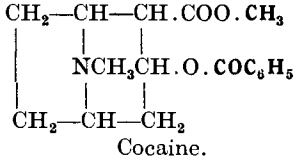


Tropan Ring.

In ecgonine, 2 hydrogen atoms of the tropan group are replaced by carboxyl and hydroxyl, and cocaine is derived from ecgonine by the esterising of carboxyl by methyl and the substitution of benzoyl for the hydrogen of the hydroxyl group.



Ecgonine.



Cocaine.

For the sake of a better general view, the formula may also be written in the following manner, which makes the three larger constituents more prominent :—

$$\underbrace{C_9H_{13}NO_3}_{\text{Ecgonine}}\text{—}\underbrace{COC_6H_5}_{\text{benzoyl}}\text{—}\underbrace{CH_3}_{\text{methyl.}}$$

In order to determine the *rôle* of each of these groups in the anæsthetic action, a number of compounds were made, in which now one, now another, member was missing or replaced by other groups of atoms. The investigations led to the result that in cocaine no single group that paralysed sensation can be pointed out as the sole supporter of the action. The paralysing influence on the sensory nerves is dependent on all the three main groups and on the chemical character that the molecule acquires through these groups being combined with one another in a special way. In the chemical configuration of ecgonine lies the foundation for the action on the nerves in the same way that its ally, tropine, is the basis for the action of atropine on other peripheral nerves ; but the action is first elicited in the two side groups. The benzoyl group is probably the staying member, which negotiates the reaction with the nerve-substance ; if it is replaced by other acid radicals, the anæsthetising properties suffer greatly or disappear. The methyl group plays a very important part. If it is omitted, the specific action on the sensory nerves is entirely lost, but the methyl can without detriment be exchanged for allied alcohol radicals, *e.g.* ethyl or propyl. Its only significance is that some alkyl group replaces the hydrogen of the carboxyl group, and gives to the whole molecule the character of an ester. That it is the place that methyl occupies in the atom that is the important thing is evident from the fact that the other CH_3, which has its place in the ecgonine, can very well be removed. The bodies that are thus obtained, the demethylised cocaines, are unchanged in their action, or stronger than the natural alkaloid. Upon the basis of these and similar results, a great number of local anæsthetics have been produced.

The most important of the new substitutes for cocaine are as follows :—

Eucaine (benzoyl-vinyl-diacetonalkamine) is superior to cocaine

through being a more stable compound, which is not decomposed by boiling. The solution can thus easily be sterilised. Eucaine has about the same local anæsthetic action, but does not cause ischæmia, but rather hyperæmia, no shrivelling of mucous membranes, and, finally, according to Vinci's animal experiments, is about 4 times less toxic than cocaine. It is inferior to cocaine in that it does not harmonise with adrenaline, the anæmia-producing action of which it to some extent counteracts. The anæsthetising action is therefore less increased.

Tropacocaine (benzoyl-pseudotropine), which is found in the coca plant cultivated in Java, and is also produced synthetically, has about $\frac{1}{3}$ the toxicity of ordinary cocaine. The anæsthesia begins quickly, and is not accompanied by local anæmia. It should be used alone (3—5 per cent. solution) as it completely abolishes the vaso-constrictor effect of adrenaline. The mydriatic action is also absent. When tried for spinal anæsthesia, it proved to be considerably less dangerous than cocaine, but the action was of shorter duration. It is *employed* with about the same indications as cocaine, but has only about one half the toxicity of the latter.

Amylocaine, Stovaine (dimethyl-amino-benzoyl-pentanol) is, as regards its anæsthetising power, about equal to cocaine, and has only half the latter's toxicity. It causes, however, dilatation of the vessels, and thus does not harmonise with adrenaline and greatly irritates the tissues. It cannot, therefore, be used for ordinary local anæsthesia, but was much employed for some years for spinal anæsthesia. According to Santesson's experiments with rabbit-nerves, it breaks the conduction in the sensory fibres just as much as, but affects the motor trunks more than, cocaine.

Alypine (tetramethyl-diamino-benzoyl-pentanol) is closely allied to stovaine ; it permits of being sterilised by boiling, and possesses about the same anæsthetising power as cocaine. It is little of a local irritant, causes no vascular contraction, but slight hyperæmia (goes fairly well, however, with adrenaline), and has no influence on the pupil or accommodation. To frogs, rabbits and guinea-pigs, alypine is more toxic than cocaine, but only half as toxic to carnivorous animals.

None of the above-mentioned cocaine substitutes, with the possible exception of amylocaine, are now employed to any great extent, as they are far surpassed by **Procaine** (p-amino-benzoyl-diethyl-amino-ethanol), which was introduced by Einhorn in 1905 as Novocaine, and is also a stable compound that can stand a short boiling. The two great advantages of procaine are that it does not irritate the tissues and that it has little toxicity. In personal experiments (Liebe), the subcutaneous

injection of 0·4 gramme produced no toxic symptoms, and those produced by 0·70 gramme were only slight. Combination with adrenaline reduces the toxicity still more, so that now 1—1·5 gramme is frequently injected.

The anæsthetising action is fleeting, and procaine would therefore not be able alone to compete with cocaine; but when adrenaline is added, a strong, prolonged anæsthesia is obtained which is at least equal to that produced by a corresponding cocaine-adrenaline solution. These drugs harmonise very well, for the adrenaline anæmia is greater when the solution also contains procaine. *Uses.* On mucous membranes the action of procaine is too weak, but otherwise procaine-adrenaline is the best means that is at present at our disposal for ordinary surgical local anæsthesia. On the whole, procaine, owing to its safety, has contributed largely to the development of local anæsthesia, and brought within its domain many major operations, *e.g.* every possible operative procedure on the extremities, operations for hernia, operations on the peritoneum, etc., which formerly required ether or chloroform anæsthesia. Procaine has also been tried for *spinal anæsthesia.* A newer variant of this now widely-used method is the *sacral anæsthesia,* introduced by Cathelin, in which procaine is injected through a sacral foramen into the spinal canal. As the solution does not penetrate within the spinal membrane (Fig. 9), dangerous secondary effects are practically precluded. The anæsthesia, commencing after about

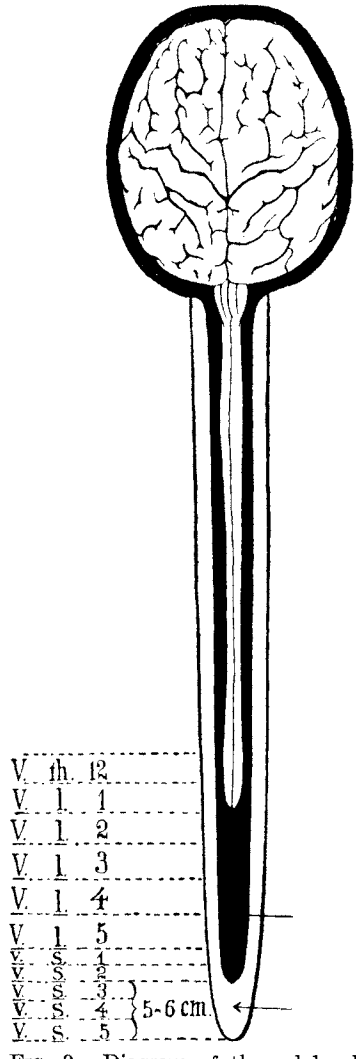


FIG. 9.—Diagram of the subdural and epidural spaces (Härtel). The subdural space is continued upwards into the brain. The liquid introduced by means of lumbar injection (upper arrow) can thence ascend to the centres of the medulla oblongata. The epidural space (lower arrow), on the contrary, is closed at the upper end.

a quarter of an hour, extends over the bladder, the anus and the lower part of the rectum, the external generative organs, and the inner surface of the thigh (" riding-breeches anæsthesia ").

Other attempts to produce local anæsthetics on the pattern of cocaine have resulted in a number of substances, which, owing to their insolubility in water, occupy a peculiar position. In accordance with what has already been said as to the significance of the benzoyl and methyl groups in cocaine, the first attempt was the simplest compound containing these two groups, namely, the well-known benzoic-acid methyl ester, which proved to possess anæsthetic action, although weak. In order to obtain a more cocaine-like compound, a basic group had to be added. For this an amino group was chosen, which could not be supposed to have toxic effects, like ecgonine. The result was a methyl ester of amino-oxybenzoic acid, or **orthocaine**. The same idea is found, in various disguises, in *benzocaine*, *propœsine* and *cycloform*, which are respectively ethyl, propyl and isobutyl esters of p-amino-benzoic acid. All these compounds have little toxicity and strong local-anæsthetic action, but are almost insoluble in water, which gives to the action a different character from that of cocaine. On the surface of a wound they are dissolved exceedingly slowly, are consequently not removed by absorption, and the action is therefore prolonged, so that the anodyne influence may extend over many hours, even as many as 24. In another direction their insolubility constitutes a weakness and limitation of the activity of these remedies, as they can only anæsthetise in places where they can be in immediate contact with nerve-ends, *e.g.* wounded surfaces, but cannot act through thick mucous membranes, and are not suitable for subcutaneous injection. The *employment of orthocaine*, as already mentioned, is confined to places in which the nerve-ends are exposed. It does not act, for instance, or hardly at all, upon cardialgia, but is an anodyne in *ulcer of the stomach* (proposed as a means of making a differential diagnosis between these diseases), *ulcerated cancer of the stomach* and *intestinal ulcerations*, *surface-wounds*, *burns*, *toothache* where the pulp is exposed, etc. The anæsthesia is said to commence in the course of a few minutes, and to last at least 2, as a rule several, hours, 24 or even longer. It is especially recommended as an anodyne for insufflation in *tuberculosis of the larynx*. Orthocaine may, although seldom, produce local irritation, erythema and eczema ; and an idiosyncrasy has been described expressing itself in urticaria and local œdema on every application. Benzocaine has the same indications, but seems also to be able to act through mucous membranes, and has been recommended, *inter alia*, for the *vomiting of pregnancy*, *sea-sickness*, and also for *irritation of the bladder*.

The fact that in cocaine and most nearly-allied compounds a connection can be demonstrated between chemical constitution and anæsthetising action does not preclude the possibility that also many other substances, which do not at all, or only very distantly, resemble cocaine, may paralyse the sensory nerves. *Acetone-chloroform*, for instance, which is classed among soporifics, is a local anæsthetic, and many aromatic compounds, *e.g.* concentrated carbolic acid, cause, like the benzoyl derivatives, a blunting of the sensibility. Phenacaine hydrochloride or holo-

caine (diethoxyethenyldiphenylamidine) is a compound of this kind, and is used in ophthalmology. Its action in animals is about 5 times as toxic as that of cocaine.

Preparations and Doses

Cocaina (B.P., U.S.P.), Methyl-benzoyl-ecgonine, $C_{17}H_{21}NO_4$. Colourless crystals with a bitter taste, almost insoluble in water. Cocaine is an alkaloid obtained from the leaves of *Erythroxylon coca* or synthesised from ecgonine.

Cocainæ Hydrochloridum (B.P., U.S.P.), $C_{17}H_{21}NO_4.HCl$. Colourless prisms, very soluble in water. *Dose*, 8—16 milligrms., $\frac{1}{8}$—$\frac{1}{4}$ gr. (B.P.); 0·015 grm., $\frac{1}{4}$ gr. (U.S.P.). Subcutaneously, $\frac{1}{4}$—1 per cent. solution; in the eye, 2 per cent.; for painting the mouth, throat, larynx or nose, 5—20 per cent. solution. In the anus, as a suppository, about 20 milligrms. The solutions must not be boiled, as the alkaloid is thereby decomposed. After being kept for some time, its activity diminishes without any change in the appearance of the solution.

Adrenaline admixture (*also applicable to the other remedies that are capable of combination with adrenaline*). To every 5 c.c. of solution, 1 drop of *Liquor Adrenalini* (1 : 1000), with a larger quantity of liquid comparatively less, so that altogether not more than 15 drops of adrenaline solution is injected.

Lamella Cocainæ (B.P.) contains 1·3 milligrms. or $\frac{1}{50}$ gr. of cocaine hydrochloride. *Trochiscus Krameriæ et Cocainæ* (B.P.) contains 3 milligrms. or about $\frac{1}{20}$ gr. of cocaine hydrochloride. *Oculentum Cocainæ* (B.P.), 0·25 per cent. cocaine hydrochloride.

Eucainæ Hydrochloridum (U.S.P.), Betaeucaine hydrochloride. A white, crystalline powder, soluble in 30 parts of water. Used as the previous preparation, with the limitations consequent on the smaller degree of solubility.

Tropacocainæ Hydrochloridum, $C_8H_{14}NO(C_6H_5CO).HCl$. Colourless needles, easily soluble. *Dose*, twice that of cocaine. Externally as cocaine. Normal dose for spinal anæsthesia, 50 milligrms. ($\frac{4}{5}$ gr.).

Alypinum, a white, crystalline, easily soluble powder. *Dose*, as cocaine. In the eye, 2—5 per cent.; on mucous membranes, 10 per cent. solution.

Amylocainæ Hydrochloridum (B.P.), *Stovaine*, colourless crystals, very soluble in water. Has been used especially for spinal anæsthesia. *Dose*, by mouth or subcutaneously, 2—5 centigrms., $\frac{1}{3}$—$\frac{3}{4}$ gr.; by intrathecal injection, 2—10 centigrms., $\frac{1}{3}$—$1\frac{1}{2}$ grs. For spinal anæsthesia 5—10 per cent. solution is used.

Procainæ Hydrochloridum (B.P., U.S.P.), Novocaine, Ethocaine. Colourless, very easily soluble crystals. (For doses, see p. 103.) For subcutaneous injection, 1—2 per cent.; for regional anæsthesia, 1—2 per cent.; on mucous membranes, 10 per cent. solution, with the addition of adrenaline as mentioned under Cocaine. For spinal anæsthesia about 1 decigrm. ($1\frac{1}{2}$ gr.). For sacral anæsthesia very large doses are now often employed, *e.g.*, 4 decigrms. (6 grs.) in 2 per cent. solution with 5 drops of adrenaline. The official *doses* (B.P.) are: 3—12 centigrms., $\frac{1}{2}$—2 grs.; by subcutaneous injection, up to 1 grm., 15 grs.; by intrathecal injection, up to 15 centigrms., $2\frac{1}{2}$ grs.

Orthocaina (B.P.), Orthoform-new, a white, voluminous powder, almost insoluble in water. Externally as a dusting powder, pure or mixed

with talc (1 : 4), or as a 10 per cent. ointment. *Dose*, 1—2 decigrms., 1½—3 grs.

Benzocaina (B.P.), Æthylis Aminobenzoas (U.S.P.). Benzocaine, Anæsthine. A white, crystalline powder, slightly bitter taste, very slightly soluble in water, freely soluble in alcohol. *Dose*, 0·3—0·6 grm., 5—10 grs. (B.P.); 0·3 grm., 5 grs. (U.S.P.).

Propæsine and *Cycloform* are white powders, insoluble in water. They are used in the same way as orthocaine. Internally, for gastric and intestinal diseases, 0·5 grm. (8 grs.), 3 times a day.

Phenacainæ Hydrochloridum (U.S.P.), Holocaine, colourless crystals, soluble in 40—50 parts of water. Used only in eye-operations; a few drops of a 1—2 per cent. solution produces an anæsthesia of about 20 minutes' duration, without affecting the pupil or accommodation. Toxic.

Percaine is an amido derivative of quinoline—the diethylethylenediamide of α-oxybutylcinchoninic acid. It is nearly ten times more powerful than cocaine but its toxicity is almost twice as great. To anæsthetise the conjunctiva a 0·05 per cent. solution suffices, and even for operations on the nose and throat a 1—2 per cent. solution of percaine is satisfactory. Up to 2 mils of 0·5 per cent. solution is employed as a spinal anæsthetic.

10. ATROPINE

In many plants belonging to the family *Solanaceæ*, two alkaloids occur, *hyoscyamine*, $C_{17}H_{23}NO_3$, which is found in the well-known official species, *Atropa Belladonna*, *Hyoscyamus Niger* and *Datura Stramonium*, and *scopolamine* or *hyoscine*, $C_{17}H_{21}NO_4$, which is principally obtained from species of *Hyoscyamus* and *Scopolia*. *Atropine*, the isomer of hyoscyamine, is found only in small quantities in the young leaves and shoots. The older plants and the roots contain no atropine, or almost none, but contain hyoscyamine, which very easily passes into the isomeric form, atropine, in the course of the chemical operations concerned in its production. Duboisine, which was used formerly for eye-diseases, has proved to be a mixture of hyoscyamine and hyoscine.

The occurrence of atropine-like poisons is not confined to the *Solanaceæ* *Ephedra vulgaris* (*Gnetaceæ*), among other plants, contains a mydriatic alkaloid, ephedrine, which has been suggested as a substitute for atropine. Bacteria, too, can form substances that have an allied action, and clinical observation of meat, sausage or fish poisoning sometimes reveals a striking resemblance to that of atropine; the so-called ptomatropine may be formed in dead bodies.

Chemically, atropine, hyoscyamine, and similar alkaloids, are characterised by the fact that they consist of an acid and a base, which are combined as esters. By treatment with alkalies, the alkaloids are split up into their components. Atropine and hyoscyamine give off *tropic acid* and the base *tropine*, scopolamine the same acid with another base, *scopoline* (oscine). Atropine and hyoscyamine are thus not only isomers, but also yield the

same decomposition-products. The investigations of the last few years have shown that they are stereochemical isomers. *Atropine is the optically inactive*, "racemic," *compound, which is composed of two optically active hyoscyamines*, "optical antipodes," of which the one, the lævo-rotatory, is the alkaloid occurring in the plants (l-hyoscyamine), while the other (d-hyoscyamine) is produced artificially. When isolated, neither tropic acid nor tropine has the action characteristic of atropine, this only appearing when they are combined. In 1879, Ladenburg formed atropine from tropic acid and tropine, a synthesis which has led to the production of several new compounds ("tropeines") of tropine with other aromatic acids. Of these, *homatropine* (a compound of tropine and oxytoluic acid) is employed therapeutically.

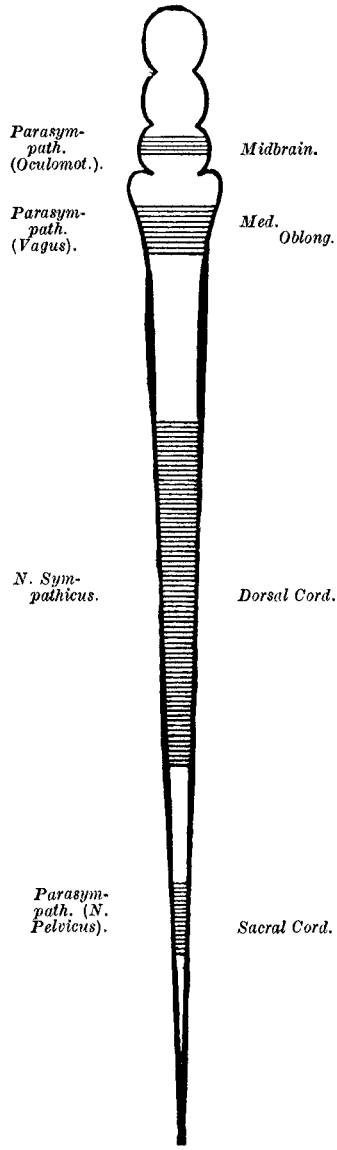


FIG. 10.—Diagram of the origin of the vegetative nerves in a cat. (Langley.)

Action. *Introductory Remarks on Vegetative Nerves.* The substances treated in the foregoing chapter act either on the central nervous system or on the sensory nerves (cocaine), or on the motor nerves that supply the voluntary striated muscles (curarine), thus on the so-called *animal nervous system.* With atropine begins a series of alkaloids, whose distinguishing feature is that they act on the nerves that supply the glands, vessels and all other organs with unstriated muscles, including the heart. This nervous system is called, as is well known, the *vegetative, involuntary*, or "*autonomic*," an expression that is meant to designate a certain, though by no means complete, independence of central nervous system control. A great number of the vegetative organs stand in a close mutual relationship to one another. When one organ works,

several others must often simultaneously co-operate; in other cases a mutual antagonism is found. The incessant regulation of the function of these organs is brought about by their being equipped with a double innervation. They are supplied by the *sympathetic* nerve originating in the dorsal region of the spinal cord, and also receive fibres that spring from the sections situated above and below, namely, from the mesencephalon (oculomotor) and the medulla oblongata (chorda tympani, vagus), and from the sacral region of the spinal cord (pelvic nerve, see Fig. 10). These cranial and sacral autonomous nerves Langley places together under the name of *parasympathetic*, because as a rule they are in an antagonistic relationship to the sympathetic system. In the eye, for instance, the pupil is contracted by the parasympathetic fibres running along the oculomotor, while it is dilated by the sympathetic nerves ending in the dilatator pupillæ; in the heart the parasympathetic vagus has an inhibitory action, while the sympathetic accelerans increases the frequency of the pulse; in the bronchioles and the intestinal canal, on the other hand, the vagus produces motion, the sympathetic rest, and so on.

The sympathetic and parasympathetic systems are not only anatomically and functionally different, but they differ from one another also in their behaviour towards many poisons. A very sensitive reaction that is common to all sympathetic nerves, whether they are motor or inhibitory, is that they are stimulated by adrenaline. The alkaloids that are mentioned in this and the following chapter are, on the contrary, remarkable from the fact that they affect, above all, the parasympathetic nerves. The selection is not absolute, however; the sweat glands, in spite of their sympathetic innervation, are not affected by adrenaline, but are very strongly affected by the parasympathetic poisons. Nicotine occupies a special position, as it paralyses in a peculiar manner certain ganglia all over the vegetative system; but of this more will be said in Chapter 14.

According to recent views it seems unlikely that the distinction between sympathetic and parasympathetic nerves will be retained in its original form. Numerous workers have adduced evidence which suggests that impulses arising in the autonomic nervous system bring about changes in the viscera by the liberation at the ganglia and nerve-endings of chemical transmitters or "neurocrine substances." Thus, it is suggested that adrenaline or a similar substance is set free at the endings of some of the nerve fibres which are accordingly said to be "adrenergic." If, on the other hand, acetylcholine is discharged, the fibres are described as being "cholinergic." On this basis some of the anomalies of the earlier classification are explained. (*cf.* p. 126).

The **action of atropine** is very characteristic. It affects parts

of the central nervous system, first stimulating and then paralysing, and also numerous parasympathetic nerve-endings (and sweat glands), which are only paralysed. These latter actions are the most important in practice, and will be mentioned first.

The effect on the **eye** is the most important. When a few drops of a weak atropine solution are dropped on to the conjunctiva, *the pupil dilates*, because the endings of the oculomotor in the sphincter of the iris are paralysed. This action is of a strictly local character, dependent on the direct contact of the alkaloid with the nerve-ends ; it occurs only in the atropine-treated eye, and can be elicited even in extirpated eyes. When the action has reached its height, the iris has shrunk into a narrow rim surrounding the large, black pupil. The entire eye seems to have become darker and more brilliant, whence the employment of the drug as a beauty remedy and the name of the plant—" belladonna." The paralysis of the oculomotor is complete, but the muscles are unaffected when dilute solutions are employed. The pupil enlarged by atropine does not react to light, nor contract with electrical stimulation of the nerve, or with substances that act upon the oculomotor nerve, *e.g.* muscarine ; but it is contracted by direct stimulation of the circular muscle-fibres themselves. Only highly concentrated solutions of atropine seem also to paralyse the unstriated muscle-substance. The mutual antagonism between atropine and physostigmine will be mentioned under the latter alkaloid. The atropine dilatation is not quite maximal ; a still greater, which reduces the iris to an almost invisible rim, is obtained by the simultaneous employment of substances that act upon the dilatator pupillæ (cocaine). The iris reacts with extreme delicacy to atropine (even $\frac{1}{200}$ milligramme elicits distinct dilatation of the pupil), and the effect is, moreover, greatly prolonged ; 10 to 15 minutes after the instillation of a few drops of a 1 per cent. solution the dilatation begins, reaches its maximum in the course of 20 to 30 minutes, remains at this height for 1 or 2 days, then subsides very slowly, and has not entirely disappeared until 10 to 12 days have passed.

Atropine further abolishes *accommodation*, probably by paralysis of the oculomotor branches of the ciliary muscle. In the normal eye when at rest, the lens lies pressed between the two tightly-stretched laminæ of the zonula of Zinn, and focuses parallel rays emitted from distant objects upon the retina. If the ciliary muscle contracts, the zonula of Zinn is relaxed, the lens yields to its inclination to assume a more convex form, and becomes more refractive and able to focus divergent rays from near objects into a clear image upon the retina. To the eye under the influence of atropine, which is unable to make use of the ciliary

muscle, and thus cannot change the form of its lens, but is steadily fixed on distant objects, all near objects (to hypermetropic eyes which must accommodate even for parallel rays, distant objects too) appear indistinct and blurred, often abnormally small (micropsia), and the broad cone of light which strikes upon the retina through the large pupil also produces an unpleasant feeling of too strong light. It is therefore a disadvantage, when using atropine only for diagnostic purposes, that its action is so long in disappearing; but in treatment it is an advantage. The paralysis of the accommodation appears somewhat later than the dilatation of the pupil, and begins to decrease earlier.

The *intra-ocular tension* is raised by atropine, with special distinctness when there is already a tendency to increase of pressure, *e.g.* in glaucoma. The reason is probably the contraction of the spaces of Fontana (obstruction of the lymph outflow) through retraction of the iris, for most mydriatics seem to have this action, while, conversely, the contraction of the pupil is accompanied by low pressure.

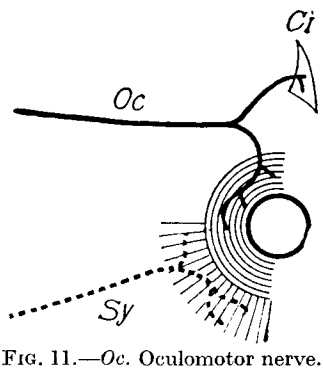


FIG. 11.—*Oc.* Oculomotor nerve. *Sy.* Sympathetic nerve. *Ci.* Ciliary muscle. Atropine paralyses, muscarine and physostigmine stimulate, the ends of the oculomotor; cocaine stimulates the ends of the sympathetic. (Diagram after Wood.)

In the **heart,** atropine paralyses the *endings of the vagus*, and thereby increases the pulse-frequency; electrical stimulation of the vagus does not as usual cause slow or arrested pulse, but, on the contrary, there is greater frequency, because the sympathetic accelerator nerves are not paralysed. This greater frequency varies considerably, however, both with animal species and age, as it depends upon whether the heart normally works against a strong or a weak vagus inhibition. In youth the action is inconsiderable, but in the full-grown man and the fully-developed carnivorous animal it is very pronounced, so that the frequency of the pulse in atropine poisoning, which is associated with a rise in blood-pressure, may increase to more than twice its normal number. Upon this factor, and the dilatation of the cutaneous vessels, depends also the great redness of the skin seen in cases of poisoning. In herbivorous animals the pulse-frequency changes but little. Rabbits, in particular, are refractory towards atropine in all directions. These animals can be fed for months on belladonna leaves and appear to thrive on the fare; and by subcutaneous injection they can stand doses twice as large as can

dogs. The rabbit's tolerance is probably conditioned by the fact that the liver and blood serum of these animals splits up the atropine into tropine and tropic acid, a process which is not, however, rapid enough to protect against the intravenously-injected poison.

The *vagus-ends* in the **lungs** are affected in the same manner as those in the heart, but the result is altogether different, as the vagus in the lung does not act as an inhibitory nerve. Electrical stimulation of the vagus produces normally contraction of the finer bronchioles, with consequent diminution of the respiratory volume ; if the animal has previously had atropine, vagus stimulation has not this effect. Atropine, or the hyoscyamine in *Stramonium* leaves, therefore, paralyses the vagus-endings in the bronchioles, a property to which its favourable effect in bronchial asthma is probably due. The frequent respiration that occurs after large doses is due to a stimulating action on the *respiratory centre*.

Notwithstanding numerous investigations, it is uncertain how the **intestinal movements** are affected by atropine. A general review of the conditions obtaining in the intestinal canal, with its complicated innervation, during peristalsis, is difficult, and exhaustive experiments cannot be made without complicated experiments on animals, which may elicit abnormal reactions. The fact that atropine acts upon different structures in an opposite direction makes it still more difficult to form an opinion regarding its action. According to investigations by Langley, Magnus, and others, by small doses of atropine Auerbach's plexus is stimulated (intestinal movement), but the vagus-endings are paralysed (intestinal rest). Thus atropine seems, in man, on the one hand, to promote the peristalsis, on the other, to control spasmodic constrictions of the intestine. In animals, too, it is seen that atropine annuls the action of those poisons which, by way of the nerves, produce violent intestinal colic (nicotine, pilocarpine, muscarine). Other organs, too, with *unstriated muscles*, *e.g.* uterus and bladder, are relaxed during spasmodic contraction after large doses of atropine.

Glands, whose work is governed by secretory nerves, cease or reduce their activity under the influence of atropine, because these nerves are paralysed. The skin and the buccal cavity react most sensitively, in man even after $\frac{1}{2}$ milligramme. The *secretion of sweat* ceases, although the vessels of the skin are dilated ; the *mouth*, *throat*, and *larynx* feel dry, as the secretion, both from the large salivary glands and from the small glands of the mucous membranes, is suppressed ; electrical stimulation of the chorda tympani no longer causes any secretion, while stimulation of the

glandular tissue does, a proof that it is only the nervous apparatus that is paralysed. The nasal cavity also becomes dry, and the *bronchial secretion* is greatly diminished. The same thing probably happens with the *pancreatic secretion;* possibly the amount of *bile* diminishes. The secretion of *gastric juice* is reduced most distinctly where previously there was hypersecretion. On the whole, it is very frequently seen, so frequently that it may be laid down as a general rule, that morbidly altered functions are much more easily affected than those functions that are proceeding normally. In nursing-women, the *secretion of milk* may cease after large doses of atropine; as a rule, however, it only seems to be somewhat reduced, while at the same time the milk

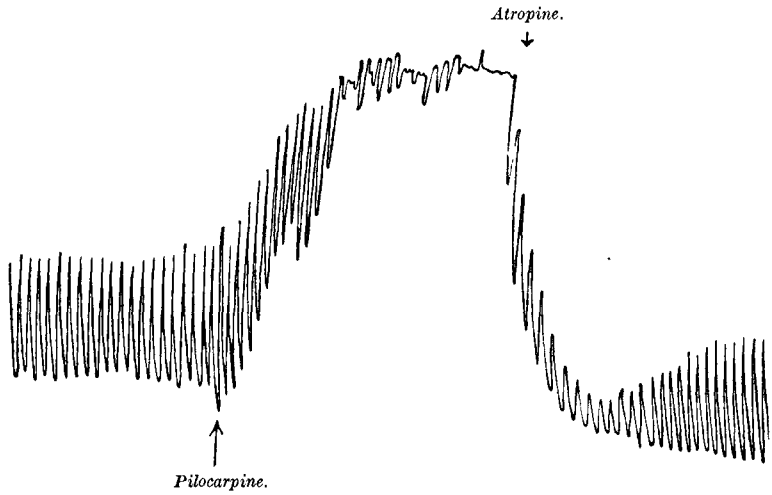


FIG. 12.—Intestine of a rabbit in Ringer solution. Pilocarpine causes violent contractions, which are immediately relaxed by atropine. (Kress and Magnus.)

becomes more concentrated, indicating that it is mainly the elimination of the water that is affected. The circumstances with regard to the *urine* vary; sometimes the amount is found to decrease, although, as far as is known, there are no secretory nerves in the kidneys.

On the **central nervous system** atropine acts, as already stated, first by stimulating, then by paralysing. In man the action after doses of 5—10 milligrammes appears first in the form of psychic excitement. A cheerful condition ensues, with a lively flow of ideas, garrulousness and desire for motion, hallucinations of sight and hearing, and delirium, which may sometimes be of a peaceful and happy nature, in other cases may express itself in violence and rage. Sooner or later the symptoms of excitement subside, and are followed by drowsiness and inclination to sleep. After very large doses coma finally occurs, the temperature

falls, the pulse becomes small, irregular, and extremely frequent, and death supervenes with asphyxial symptoms.

Hyoscyamine. The relationship between this alkaloid and its isomer, atropine, presents much that is of interest. That lower organisms may react differently to substances that are optically different (see p. 106) has been known since the famous investigations of Pasteur, who observed that an inactive solution of tartaric acid, in which the blue-mould fungus, *Penicillium glaucum*, grew, gradually became optically active and lævo-rotatory. The micro-organisms had thus, out of the racemic tartaric acid, which is supposed to consist of equal parts of dextro-rotatory and lævo-rotatory acids, used the former as a food, but had not succeeded in making use of the latter. The cells of higher animals, too, can distinguish between optical antipodes; the various tartaric acids have thus different toxicities, and the artificially-produced dextro-rotatory cocaine acts more quickly and strongly as a local anæsthetic than the ordinary cocaine, which is lævo-rotatory. As regards the sugars and albumin (*i.e.* the optically active amino acids), it is often seen, according to E. Fischer, that the one antipode is consumed far more readily in the organism than the other. Thorough comparative investigations have been made of atropine and hyoscyamine by Cushny and Laidlaw, and these show that the natural base, l-hyoscyamine, acts almost twice as strongly on iris, heart and glands as atropine, and 20 to 30 times more strongly than d-hyoscyamine. The probability is that atropine, like other racemic compounds, exists only in solid form, but when dissolved in water is divided into the two optical antipodes, and acts on the above-mentioned peripheral organs almost exclusively through its l-hyoscyamine, whereas the d-hyoscyamine has almost no share in the action. Thus, in ophthalmic practice, when an atropine solution is employed, it is only half of it that acts. All three alkaloids appear to act alike on the central nervous system of mammals, while in frogs d-hyoscyamine occasions a far greater increase of reflex irritability than the lævo-rotatory base.

Scopolamine, or **hyoscine,** which is the most toxic of all the alkaloids here described, possesses a few of the peripheral actions of atropine, and is deficient in others. It dilates the pupil and paralyses the accommodation even more rapidly and strongly than atropine, although not for so long a time, and it reduces the glandular secretion; but in man it seems to be deprived of its influence upon the heart's inhibitory apparatus, as generally it even makes the pulse slow. Further, its effect upon the brain is very different from that of atropine; even ½ milligramme produces, sometimes with a slight indication of an excitement-stage

sometimes without any, motor relaxation, a desire for rest, and a feeling of drowsiness followed by sleep. Scopolamine, too, occurs as lævo- and dextro-rotatory antipodes, of which the former acts by far the more strongly on the peripheral nerves, while, as regards the central nervous system, there is no difference (Cushny).

The synthetically produced **homatropine** acts like atropine, but is more feeble and transient. The dilatation of the pupil disappears in the course of 1 day, and the paralysis of the accommodation lasts only a few hours. Homatropine is therefore suitable for diagnostic purposes, for which also the synthetic alkaloids mentioned among " Preparations and Doses " may be used.

Acute **atropine poisoning** is not infrequent through mistaking " eye-drops " for medicines intended for internal use ; acute hyoscyamine poisoning is most frequent with children, who are tempted by the cherry-like fruit of the belladonna plant. The type of poisoning is the same in both cases, and very characteristic. The only difference is that after the berries and after Belladonna Extract the symptoms appear more slowly and are often accompanied by vomiting. After atropine vomiting is absent, and the specific action appears after a few minutes. All the symptoms described above occur simultaneously, and give a very alarming character to the condition. The patient complains of great giddiness, and headache with throbbing of the carotids, is restless, talks disconnectedly, has delirium and hallucinations, and suffers from all kinds of disturbed vision (indistinct sight, diplopia, micropsia, chromatopsia). The pulse becomes extremely frequent, *e.g.* 140—160, the skin burning and red, as in scarlet fever, the voice rough and hoarse until aphonia ensues (owing to the dryness of the vocal cords) ; the mouth and throat are dry, but the desire for water cannot be satisfied on account of the difficulty in swallowing. Repose gradually sets in with drowsiness, and, at last, narcosis, with the face still red and injected ; later there are cyanosis, irregularities of pulse and respiration, and occasionally slight convulsions. Sometimes it takes an intermittent course, and consciousness partially returns ; the patient once more replies when spoken to, but is still confused, and after a few hours sinks again into a state of lethargy. Notwithstanding the gravity of the symptoms, the prognosis is generally good ; but the recovery takes several days, and the dilatation of the pupil, with its consequences, may continue even for weeks. The smallest lethal dose known is 0·10 gramme of atropine sulphate. Cases of slight poisoning are frequently seen after too liberal an employment of atropine in eye-diseases.

Therapeutic Uses. Atropine is the **oculist's most important remedy,** above all in *diseases of the iris.* It is employed both in the fully-developed iritis, and prophylactically in *inflammation and lesions of the cornea.* Its antiphlogistic action is due to its immobilisation of the iris and the ciliary muscle, which are otherwise in constant movement. It is also a slight local anæsthetic. In iritis the atropine treatment is further indicated to prevent the formation of *adhesions,* or to break them up if they are already formed ; for the latter purpose it is sometimes employed alternately with the myotic physostigmine—a kind of iris-gymnastics. In diseases of the cornea, atropine is especially useful in superficial lesions, especially when there is much irritation. In deep ulcerations threatening perforation, the instillation of atropine may be followed by necrosis of the bottom of the wound ; if perforation is unavoidable, or has already taken place, the energetic employment of atropine may be successful in preventing prolapse of the iris, or cause the not as yet fixed iris to withdraw. A regular atropine treatment through a long period (atropine cure) is recommended in *extremely progressive myopia* in young persons, and is said to be able to check its rapid development for some time. Paralysis of accommodation, for eyes such as these, whose focal point lies very close to the eye, causes far less inconvenience than for normal or hypermetropic eyes. With high intra-ocular tension, especially in *glaucoma,* atropine is *strictly contra-indicated.* A single application to the eye may in such cases precipitate a glaucomatous attack.

For *diagnostic purposes* atropine is used when a very small pupil, or opacities within the eye, prevent the illumination of the back of the eye, and in incipient senile cataract to make the marginal parts of the lens that are normally hidden behind the iris visible. The paralysis of the ciliary muscle is also employed when it is wished to exclude all accommodation in determinations of refraction. If it is only a matter of securing dilatation of the pupil, exceedingly dilute solutions are sufficient, whereas complete paralysis of accommodation requires strong solutions. For diagnostic dilatation of the pupil, *homatropine* is also used, or the new *methyl-atropine,* whose action commences after a few minutes, and lasts only a few hours.

The great influence that atropine exerts upon the *inhibitory apparatus of the heart* has given rise to numerous attempts to employ it in *heart-weakness* of various kinds. It would seem very rational to assist a weakened heart by removing the impediment it has to overcome ; but in practice this indication is very limited, for, in the first place, a good vagus-action is only obtained by large doses, and, in the second place, it is brief. It can con-

sequently only be utilised with advantage when the cause of the heart-weakness is temporary, or can be removed, *e.g.* in poisoning (morphine, muscarine), while its value in diseases is doubtful.

Atropine is used in a number of diseases for spasm in unstriated muscles. *Nervous asthma* responds to atropine in a variety of ways. In some cases the attacks are relieved by atropine or *Stramonii Folia* (asthma cigarettes), presumably by relaxation of the bronchial spasm through paralysis of the vagus ; in other cases no favourable effect is seen.

Experience has shown that obstinate *constipation* which resists other remedies can often be removed by atropine or belladonna extract, especially when the constipation originates in spasmodic contraction of the intestine (lead poisoning), or is caused by hard fæcal masses, which, by mechanical irritation, elicit contractions that block peristalsis. In these cases atropine acts like morphine, which, as a rule, should be tried first. It is also supposed to produce peristalsis, and is therefore used as an aperient in atonia of the intestine. Of late, atropine has been strongly recommended for ileus ; and the treatment, when very large doses are used, is often effectual in fæcal stasis, reflex stricture, and atonia of the intestine, but of course useless in volvulus and intussusception. In *dysentery* atropine is recommended ($\frac{1}{2}$ milligramme subcutaneously 3—6 times a day). The treatment is said to abolish the pains and colic produced through irritation of the vagus. In *pyloric spasms* in children, atropine is also said to be useful. In painful affections of the *anus*, atropine or belladonna extract is employed in the form of suppositories in order to relax the spasm of the sphincter. In *enuresis nocturna* the effect may—especially in cases in which there is abnormal irritability of the bladder—be quite striking.

The action of atropine on *glands* is most frequently utilised in the exhausting *night sweats of phthisis*. The effect on other glands is less certain, but bad cold in the head and frontal headache (secretion in the frontal sinus), for which the use of iodide of potassium is almost precluded by idiosyncrasy for that drug, are often suppressed by atropine, whereas *mercurial salivation* only partially yields. In *gastric ulcer* atropine is recommended in order to counteract the injurious hyperacidity. Hyoscyamus preparations have long been employed in *bronchitis ;* they reduce the secretion, and are credited with a soothing action.

The uses mentioned above may be derived from the action of atropine found by experiment. Atropine and belladonna extract have been employed quite empirically in a great many diseases of all kinds, although the mode of action cannot be definitely

formulated, such as *chorea, whooping-cough, cardialgia, chronic urticaria,* and many other conditions.

Scopolamine acts as a sedative and soporific. It is employed in *mental diseases* associated with restlessness and insomnia, where it surpasses most, perhaps all, other sedatives, but often exhibits unpleasant secondary effects, such as dryness of the throat, nausea and anorexia. Its constant use for a long period (*i.e.* several weeks) must be avoided, as it is apt to produce chronic poisoning, as shown by weakness, emaciation, loss of appetite and small pulse (" hyoscine cachexia "). Scopolamine is often useful in various kinds of *tremor*, and particularly in *paralysis agitans*. In *multiple cerebro-spinal sclerosis*, too, tremor can be diminished. The action of scopolamine is strengthened when another narcotic (*e.g.* morphine) is given at the same time. The combination of these alkaloids, when the doses are sufficiently large, causes complete anæsthesia, during which operations may be performed painlessly ; but it is not free from danger, and this method of anæsthesia has been given up. Repeated smaller doses produce a semi-anæsthesia, the much discussed " twilight sleep," which is employed for the purpose of " depriving labour of its terrors." The pains are felt, but in a weakened form, and do not quite reach the consciousness of the patient, and after the birth there is only a vague recollection of suffering gone through. The value of the method is much questioned, and it may do harm in various ways to mother and child ; in any case its complicated technique must be accurately understood beforehand. Scopolamine-morphine is also employed in combination with ether or chloroform, of which only a small quantity is needed, as the patient, after the injection of the alkaloids, is already half asleep (see p. 18). In recent years basal narcotics such as Nembutal have been employed fairly extensively for this purpose (p. 41).

Treatment of Poisoning. If the poisoning has been occasioned by vegetable substances or extracts that continue to give off alkaloids in the intestine, the stomach-tube should be used first ; if this is not obtainable, emetics and laxatives. Of chemical antidotes, tannin or strong black coffee is the best. Morphine and pilocarpine are injected after absorption—pilocarpine with caution. The prolonged dilatation of the pupil may be treated with physostigmine. Cold compress on the head may be useful, and in case of collapse the usual stimulant treatment.

Preparations and Doses

Belladonna Pulverata (B.P.), *Belladonnæ Folium* (U.S.P.), the leaves and tops of *Atropa Belladonna*, a native of Central and Southern Europe and of Western Asia. Broadly ovate, acute, entire leaves, recognisable by

small, white dots, which are cells filled with minute crystals of calcium oxalate. Must contain not less than 0·30 per cent. of alkaloids. *Dose*, 3—20 centigrms., ½—3 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.).

Belladonna Radix (B.P., U.S.P.), contains more alkaloid (0·45 per cent.). *Dose*, 0·03—0·12 grm., ½—2 grs. (B.P.); 0·045 grm., ¾ gr. (U.S.P.).

Extractum Belladonnæ Siccum (B.P.), **Extractum Belladonnæ Foliorum** (U.S.P.). Internally as a laxative in pills, together with other aperients; also used for cardialgia. *Dose*, 16—60 milligrms., ¼—1 gr. (B.P.); 0·015 grm., ¼ gr. (U.S.P.).

Tinctura Belladonnæ (B.P., U.S.P.). *Dose*, 3—20 decimils, 5—30 mins. (B.P.); 0·6 mil, 10 mins. (U.S.P.).

Extractum Belladonnæ Liquidum (B.P.) and *Fluidextractum Belladonnæ Radicis* (U.S.P.) are both prepared from the root, but differ considerably as regards the amount of alkaloid they contain. This is respectively 0·75 and 0·45 per cent. *Dose*, 0·015—0·06 mil, ¼—1 min. (B.P.); 0·06 mil, 1 min. (U.S.P.).

Suppositoria Belladonnæ (B.P.), each containing approximately 1 milligrm. or about $\frac{1}{60}$ gr. of the alkaloids.

In some pharmacopœias are, moreover, included *Emplastrum*, *Linimentum*, and *Unguentum Belladonnæ*. These preparations were formerly much used, but are now, very rightly, used less, to relieve pain. The local action is insignificant, and cases of poisoning have been met with as a consequence of the absorption of the alkaloid.

Hyoscyamus (B.P., U.S.P.), from *Hyoscyamus niger*, henbane, a herb distributed all over the world, with the exception of the coldest and hottest regions. Its large, pale green leaves, when fresh, have a heavy characteristic odour, and in the dried state are easily recognisable from their broad, almost white mid-rib. They contain about 0·65 per cent. of alkaloids. *Dose*, 0·2—0·4 grm., 3—6 grs. (B.P.); 0.2 grm., 3 grs. (U.S.P.).

Extractum Hyoscyami (U.S.P.), *Extractum Hyoscyami Siccum* (B.P.). Sometimes employed in bronchitis to diminish secretion and soothe the cough. *Dose*, 2—6 centigrms., ¼—1 grs. (B.P.); 0·02 grm., ⅓ gr. (U.S.P.).

Pilula Colocynthidis et Hyoscyami (B.P.). The purpose of the combination is that the hyoscyamus shall support the aperient action of the colocynth. *Dose*, 25—50 centigrms., 4—8 grs.

Extractum Hyoscyami Liquidum (B.P.), used almost exclusively for the preparation of the tincture. *Dose*, 2—4 decimils, 3—6 mins.

Tinctura Hyoscyami (B.P., U.S.P.). *Dose*, 2—4 mils, ½—1 fl. dr. (B.P.); 2 mils, 30 mins. (U.S.P.).

Stramonium (B.P., U.S.P.). Large oval or triangular leaves of *Datura Stramonium*, a herb indigenous to the regions surrounding the Aral and Caspian Seas, commonly cultivated in gardens. Contains about 0·25 per cent. of alkaloids. *Dose*, 3—20 centigrms., ½—3 grs. (B.P.); 0·075 grm., 1¼ grs. (U.S.P.). Is employed for nervous asthma in the form of cigarettes and smoking-powder (the powder is ignited and the smoke inhaled), which often also contain belladonna and hyoscyamus leaves, as well as saltpetre and camphor. Is the principal ingredient in most of the "asthma powders" on the market.

Extractum Stramonii (U.S.P.). A pilular form and a powdered extract are available. *Dose*, 0·01 grm., ⅙ gr. *Extractum Stramonii Siccum* (B.P.). *Dose*, 0·015—0·06 grm., ¼—1 gr.; for post-encephalitic conditions, 0·06—0·5 grm., 1—8 grs.

Tinctura Stramonii (B.P., U.S.P.). *Dose*, 3—10 decimils, 5—15 mins. (B.P.); 0·5 mil, 8 mins. (U.S.P.).

Atropina (B.P., U.S.P.), $C_{17}H_{23}NO_3$. White, acicular crystals, sparingly soluble in water. *Dose*, 0·25—1 milligrm., $\frac{1}{240}$—$\frac{1}{60}$ gr. (B.P.); 0.4 milligrm., $\frac{1}{150}$ gr. (U.S.P.).

Atropinæ Sulphas (B.P., U.S.P.). White, crystalline powder, readily soluble in water. *Dose*, 0·25—1 milligrm., $\frac{1}{240}$—$\frac{1}{60}$ gr. (B.P.); 0·0004 grm., $\frac{1}{120}$ gr. (U.S.P.). In eye-diseases usually 1 per cent. solution; for diagnostic dilatation of the pupil, the smallest possible quantity, *e.g.* 1 drop of $\frac{1}{10}$ per cent. solution. Only comparatively fresh solutions must be employed. Old solutions are often turbid with fungi and algæ. Instead of the solution, *Lamellæ Atropinæ* (B.P.) may also be used, each of which contains 0·013 milligrm. or $\frac{1}{6000}$ gr. of atropine sulphate. In morphine poisoning, large doses hypodermically, first 1 milligrm. ($\frac{1}{60}$ gr.), later, if necessary, more; in ileus, too, very large doses are recommended, *e.g.*, first 3 milligrms. hypodermically, then several times 2—4 mins. of 1 per cent. solution every 2—4 hours; if the patient has previously been treated with opium, 5 milligrms. is injected. Maximal doses for children: 2 years, 0·04 milligrm.; 4 years, 0·1 milligrm.; 7 years, 0·2 milligrm. (0·1 milligrm. = $\frac{1}{600}$ gr.).

Liquor Atropinæ Sulphatis (B.P.C.), 1 per cent. solution. *Dose*, 3—6 centimils, $\frac{1}{2}$—1 min.

Oculentum Atropinæ (B.P.), atropine sulphate, 0·25 per cent.

Oculentum Atropinæ cum Hydrargyri Oxido (B.P.), atropine sulphate 0·125 per cent., yellow mercuric oxide 1 per cent.

Hyoscyamine salts were also official, but cannot be recommended, as they are not procurable in even approximately pure form (Cushny).

Hyoscinæ Hydrobromidum (B.P.), **Scopolaminæ Hydrobromidum** (U.S.P.), $C_{12}H_{21}NO_4.HBr + 3H_2O$. *Dose*, 0·3—0·6 milligrm., $\frac{1}{200}$—$\frac{1}{100}$ gr. (B.P.); 0·0005 grm., $\frac{1}{120}$ gr. (U.S.P.). Given internally or hypodermically as a sedative or to quiet convulsions. Twilight sleep for childbirth, hypodermically, 0·02—0·04 grm. ($\frac{1}{3}$—$\frac{2}{3}$ gr.) of pantopone, or corresponding doses of narcophine + 0·0004—0·0006 grm. ($\frac{1}{150}$—$\frac{1}{100}$ gr.) of scopolamine. The dividing of the doses has recently been recommended with injection, *e.g.*, every 1½ hours, and giving, in 6 injections, 0·06 grm. (1 gr.) of narcophine + 0·0015 grm. ($\frac{1}{40}$ gr.) of scopolamine. Pre-existent atony of the uterus constitutes a contra-indication.

Oculentum Hyoscinæ (B.P.), hyoscine hydrobromide 0·125 per cent.

Homatropinæ Hydrobromidum (B.P., U.S.P.), $C_{16}H_{21}NO_3.HBr$. Colourless, easily soluble crystals. Employed in 1 per cent. solution for diagnostic dilatation of the pupil. *Dose*, 1—2 milligrms., $\frac{1}{64}$—$\frac{1}{32}$ gr. (B.P.); 0·0005 grm., $\frac{1}{120}$ gr. (U.S.P.).

Lamellæ Homatropinæ (B.P.), each containing 0·65 milligrm., $\frac{1}{100}$ gr.

The following synthetical alkaloids are not official:—

Eumydrine, Methylatropine Nitrate. Easily soluble crystals. In the eye for dilatation of the pupil, ½ per cent. solution. Internally for night sweats, 1—2 milligrms., $\frac{1}{64}$—$\frac{1}{32}$ gr.

Euphthalmine Hydrochloride. Closely related to beta-eucaine in its composition. Easily soluble crystals. For the eye, 2—3 per cent. solution. The accommodation is but little affected.

11. AGARICINE (not official)

The once official *Polyporus officinalis*, a boletus growing on the larch (*Larix Europæa*), contains (i.) a strongly aperient resin, which was the cause of the former employment of the fungus as

a cathartic, and (ii.) an acid belonging to the malic acid series, agaric acid, $C_{16}H_{30}O_5$, which, under the name of *agaricine*, has been employed as an anhidrotic.

Action. Agaric acid, according to Hofmeister's investigations, has a local and specific action. On wound-surfaces and mucous membranes it produces irritation. Hypodermic injection of 3—5 per cent. solution causes violent pain, which is as a rule followed by extensive inflammation resulting in suppuration. Employed internally, its local action after large doses is seen in vomiting and diarrhœa. After intravenous injection, symptoms of medullary stimulation are first seen, and then paralysis, and death ensues from respiratory paralysis.

As absorption takes place extremely slowly, very large doses can be tolerated internally by mammals, *e.g.* ½—1 gramme of the pure acid, with no other ill-effects than such as are consequent on the irritation of the mucous membranes. The only specific action, and it is prominent even with small doses, consists in the *complete cessation of the secretion of sweat.* All that is known of this action is that it must be of peripheral nature, for it still continues after the nerves to the glands have been severed; but whether its seat is in the epithelium of the glands or in their nerve-terminals has not been determined. Agaric acid differs from atropine in influencing only the sweat glands and not the salivary and lachrymal glands; it does not, moreover, dilate the pupil, nor paralyse the cardio-inhibitory nerves. Agaric acid also has the same remarkable effect upon the cutaneous secretion in lower animals such as the frog. The wet, slimy skin becomes first sticky, then perfectly dry and quite smooth to the touch, as the numerous large mucus-glands, which in normal conditions impart a roughness to the surface of the skin, shrink up.

Uses. Agaricine is used for the *sweats of phthisis and other diseases.* The action, which, on account of the slow absorption, does not commence until after 5 or 6 hours, is more or less certain, and is preferable to that of atropine in that the unpleasant dryness of the throat which anhidrotic doses of the latter often occasion, is avoided. After the drug has been in use for some time, however, tolerance ensues, and it must therefore be used alternately with other remedies, such as atropine and camphoric acid.

Preparation

Agaricina, agaricine, a white powder with scarcely any taste or smell, almost insoluble in cold water, slowly soluble in hot. *Dose*, 2—10 centigrms., ⅓—1½ grs., in powders or pills, 5 or 6 hours before the action is required. If these doses cause diarrhœa (adulteration with the drastic Polyporous resin), a little opium should be added.

12. MUSCARINE AND PILOCARPINE

Muscarine (not official)

In countries in which the population lives to some extent upon fungi, cases of poisoning are not infrequent, owing to the gathering of poisonous fungi together with the edible. One of the most serious mistakes is that of taking the very poisonous fly-fungus, *Agaricus muscarius* (*Amanita muscaria*), for the common mushroom, which, when young, it resembles, though when fully developed it is easily recognisable by its orange or bright red cap covered with white warts.

The most important constituent of the fly-fungus is the alkaloid *muscarine*, discovered by Schmiedeberg. Having already described the action of atropine, that of muscarine can be given in a few words, for on all peripheral points its action is directly antagonistic and diametrically opposite to that of atropine, as it stimulates the nerve-endings that atropine paralyses.

Muscarine retards the *heart-beat*, and in sufficient doses occasions diastolic arrest by stimulation of the inhibitory nerves ; it produces *salivation* and *flow of tears*, an *increased secretion of gall and pancreatic juice*, *secretion* from *sweat and mucus glands* by its effect on the secretory nerves ; it causes *contraction of the pupil* and *paralysis of the accommodation*, and, finally, violent *contractions of stomach and intestine* (see Fig. 12, p. 112).

Its influence on the heart, which is the most characteristic of all these actions, can only be followed in its entire development in lower animals (frog), which are able to survive for some time the arrest of circulation. In these animals the contractions are seen to become steadily slower and weaker, and at last the heart comes to a standstill in diastole, while the animal, outwardly quite normal in appearance, still moves, and is able to make powerful leaps. The muscles of the heart are not paralysed, for mechanical or electrical stimulation of the muscle itself elicits contractions in the muscarine condition ; and if the inhibitory apparatus is paralysed by the aid of atropine, the heart, after a short time, once more beats as before. On a previously atropinised heart, muscarine has no influence. Atropine is therefore the rational antidote in muscarine poisoning, but not *vice versâ*.

The fly-fungus growing in northern countries further contains another unknown poison which acts somewhat like atropine, and produces psychical exaltation with a feeling of physical strength and a desire to exhibit it. The fly-fungus was therefore highly prized by the east Siberian tribes as an intoxicant before they had made acquaintance with spirits. The poisonous action

of the fungus on flies is due, not to the muscarine, but to an unknown volatile substance that disappears in drying.

In *poisoning with fly-fungus* the prevailing symptoms often resemble those of atropine. After large quantities violent convulsions are frequently seen, with subsequent coma and death. The treatment consists principally in evacuating the stomach and intestine by emetics or the stomach-tube and the administration of castor oil. On the other hand, should the greater number of symptoms point in the direction of muscarine, a hypodermic injection of atropine is indicated.

As a medicine muscarine will never acquire any importance, as the action that might perhaps be utilised, namely, that of increasing secretion, only makes its appearance with dangerous doses; but it possesses great theoretical interest, as its action is found to some extent in several of the alkaloids that will be mentioned in the next few Chapters, and also in certain other poisons of which the mode of action was formerly very obscure.

Muscarine is a trimethyl ammonium base $-(CH_3)_3{\equiv}N{<}^{R}_{OH}$, where R is $CH(CHO)CHOH.C_2H_5$. As the formula shows, it stands very near to *neurine*, $(CH_3)_3{\equiv}N{<}^{CH=CH_2}_{OH}$, which acts very much like muscarine, and is one of the numerous poisons that arise from the putrefaction of meat. It probably comes from choline, $(CH_3)_3{\equiv}N{<}^{CH_2-CH_3OH}_{OH}$, a substance widely distributed in the animal and vegetable kingdoms, and in which the muscarine action has already been indicated. By treating choline with nitric acid, a base may be produced (according to Dale, the nitrous acid ester of choline), which possesses most of the action of muscarine.

Pilocarpine

Action. A hypodermic injection of 1—2 centigrms. of pilocarpine nitrate immediately produces a feeling of warmth in the head, the carotids throb and the face is flushed; after a few minutes the secretion from all the salivary glands, large and small, begins to flow, and increases in quantity until there is profuse *salivation*. In the course of the 2 or 3 hours that this continues, about 1½ pints of saliva is secreted. Two or three minutes after the salivary secretion has begun, the first beads of sweat appear at the border of the hair, and soon after the entire body from head to foot is bathed in perspiration. Its amount has been calculated to be about a pint or more. Thus the *secretion of sweat* begins after the salivation, and also ceases first—generally after 1 to 2 hours. This order is rarely reversed, and still more rarely does salivation occur alone, or sweating alone.

The secretion from the *lachrymal glands*, from the *nasal* and *bronchial mucous membranes*, from the stomach, intestine and pancreas, is also increased, but less constantly. It is probable that the *renal secretion* is at first increased; but in a short time the diuresis diminishes in consequence of the great loss of liquid in other ways, and the ultimate result is a smaller amount of urine.

Simultaneously with the commencement of more active secretions, the *pulse-frequency* is somewhat increased, and the *temperature* rises ½—1° C., but falls to the normal or below it as soon as the sweating has begun.

In the *eye*, pilocarpine, like muscarine, causes a several hours' contraction of the pupil and accommodation paralysis, as consequences of stimulation of the oculomotor nerve; atropine removes the effect. The intra-ocular tension is first increased, and subsequently reduced.

Pilocarpine thus greatly resembles muscarine, but in opposition to it may be used medicinally, because the glandular action can be obtained with quantities that involve no danger. It is only in large doses that pilocarpine shows the other actions that make muscarine so toxic—diarrhœa, paralysis of the central nervous system. In enfeebled persons, however, even the therapeutic doses of pilocarpine may produce very serious secondary effects, such as clouded brain, disturbance of vision, heart-weakness, and profuse bronchial secretion.

Therapeutic Uses. Pilocarpine is employed in cases in which a hasty relief from accumulated liquid seems to be indicated. Its special use is in dangerous *retention of fluid in renal diseases*, and in perhaps expelling, together with the sweat, deleterious products of metabolism. In *uræmia* the effect may be beneficial, but its value in eliminating the hypothetical toxins of this condition is probably negligible. Caution is always necessary as the drug may cause acute œdema of the lungs and a state of collapse may supervene.

Pilocarpine is also recommended, but little used, as a diaphoretic in *diseases arising from cold* in the head or lungs, *e.g.* acute laryngitis and bronchitis, and in rheumatic affections, such as muscular rheumatism. In otology it is employed in *diseases of the labyrinth*, and to procure the absorption of *exudates in the tympanum;* the oculist employs it for similar purposes in *iritis*, *choroiditis*, and *detachment of the retina*. Exudations from larger serous membranes, such as the pleura, are but little affected.

The employment of slightly diaphoretic doses—for adults hypodermically, for children by the mouth—is worth, and sometimes well repays, a trial for *itching of the skin* without any

demonstrable cause or anatomical alteration of the skin. As pilocarpine in animals elicits contractions of the uterus, it has often been tried for the induction of premature labour and abortion, and as an *oxytocic*. The action does not seem to be very reliable, but justifies the view that in ordinary circumstances pilocarpine is contra-indicated in pregnancy. As a means for contracting the pupil it is inferior to physostigmine.

Slight *toxic symptoms* are not infrequent and disappear without special treatment. In more serious cases, atropine is employed (hypodermically), and in sufficient doses it annuls the peripheral effects of the pilocarpine.

Preparations and Doses

Pilocarpinæ Nitras (B.P., U.S.P.), $C_{11}H_{16}N_2O_2.HNO_3$. Easily soluble white powder and shining crystals, permanent in the air. *Dose*, 3—12 milligrms., $\frac{1}{20}$—$\frac{1}{5}$ gr. (B.P.). Hypodermically, 0·005 grm., $\frac{1}{12}$ gr. (U.S.P.). For children of the age of 2, the maximal dose may be put at 1 milligrm. ($\frac{1}{60}$ gr.). The doses begin (in prurigo) with $\frac{1}{2}$ milligrm. ($\frac{1}{120}$ gr.), *e.g. Sol. Pilocarpinæ Nitratis* 0·01—10·00 grms. 8—10 mins. once a day, and increase gradually to such doses as cause perspiration. Externally, in the eye, 1—2 per cent. solution.

13. PHYSOSTIGMINE

Three alkaloids are produced from the seed of *Physostigma venenosum*, a climbing plant of the family *Papilionaceæ*, growing in tropical West Africa. The seed is known as the "Calabar bean," and is large and of a dark brown colour, in shape a long reniform, and with a furrow along its convex margin. The most important of the three alkaloids is *physostigmine*, also often called *eserine*, although the first name has the priority.

Action. Physostigmine is also one of the parasympathetic poisons. It acts upon numerous peripheral nerves in the same way as muscarine and pilocarpine, and also on the central nervous system.

The central nervous system is paralysed, and death ensues from respiratory failure. In certain species of animals the paralysis is preceded by great excitement, with anxiety and desire for movement, symptoms that may partly be due to the great dyspnœa and changes in circulation. That there is cerebral stimulation appears, however, to be the case from the fact that guinea-pigs, which by operative procedure have become epileptic, after small doses of physostigmine exhibit very frequent attacks for some time, an experiment that has its analogy in the following observation in man. An epileptic, on 3 days in succession, received $\frac{1}{2}$ milligramme of physostigmine. His attacks increased

enormously in frequency, and in one night occurred almost uninterruptedly at intervals of only $\frac{1}{4}$ of an hour (Nothnagel and Rossbach).

Among the peripheral organs that are especially affected by physostigmine, the **eye** must be mentioned first. From 5 to 15 minutes after dropping a solution of the alkaloid into the eye the pupil begins to contract, and in the course of $\frac{1}{2}$ an hour has diminished to the size of a large pin's head ; it remains small for 12 to 14 hours, and has not completely regained its normal size and mobility until several days have passed. Shortly after the appearance of the myosis, the ciliary muscle contracts, but relaxes more quickly than the iris, so that the accommodation paralysis lasts only a couple of hours. The intra-ocular tension at first increases a little, but then falls below the normal, no doubt on account of the vaso-constriction in the eye, which reduces the secretion of fluid. The pupil that is contracted by physostigmine is dilated by atropine. In experiments with accurately measured solutions, it can be seen how now one, now the other, of the antagonists holds the supremacy. The slightly atropinised iris, in which the endings of the oculomotor are not completely paralysed, still reacts to physostigmine. If a strong atropine solution is employed, the contracted pupil dilates once more, and further doses of physostigmine have then no influence.

Many other organs, both with smooth and with striated muscles, are affected by physostigmine. In warm-blooded animals widespread **fibrillary twitchings in the skeletal muscles** are seen during poisoning. They are independent of all central impulse, for they continue during the deepest chloroform anæsthesia, and in groups of muscles whose connection with the centre is severed by dividing the motor nerve-trunks. They are probably elicited, like the contraction of the pupil, by an action on the motor nerve-endings (*cf.* p. 126).

The entire **gastro-intestinal canal** is thrown into contraction; vomiting and diarrhœa, at first fæcal, later watery mucoid, occur. During the intestinal colic the blood is pressed out of the mesenteric veins and arteries, and as at the same time the small muscular arteries in the rest of the vascular system are contracted, the river-bed of the blood is narrowed, and the pressure rises very high.

Like muscarine and its ally pilocarpine, physostigmine causes increased secretion from several **glands**, especially the salivary, which, on the whole, are the glands which most readily react to various poisons. The secretions are stopped by large doses of atropine.

Therapeutic Uses. Physostigmine is employed principally in

ophthalmic practice, in incipient and in developed *glaucoma* to reduce the intra-ocular pressure ; in peripherally situated, perforating *corneal ulcerations* to counteract the falling forward of the iris ; and in established peripheral *prolapse of the iris*. In posterior *synechia* physostigmine is employed, sometimes alternating with atropine, in order that the alternate contraction and dilatation of the pupil may break down the attachment between the capsule of the lens and the iris. When dilute atropine solutions are employed only for diagnostic purposes, the prolonged dilatation of the pupil and paralysis of the accommodation may be shortened by physostigmine. It is also prescribed for accommodation-paralysis from other causes, *e.g.* after diphtheria.

Attacks of *tachycardia*, which so frequently defy all other treatment, may often be made to cease, according to R. Kaufmann, by large doses of physostigmine (up to 3 milligrammes daily internally), especially when digitalis is used at the same time—a combination of two drugs, both acting on the cardio-inhibitory centres.

Physostigmine was formerly used as a *laxative* in atony of the intestine (chronic constipation) ; hypodermic injections are now recommended as effectual in cases of paralysis of the intestine after laparotomy. Many years ago physostigmine was believed to reduce the excretion of sugar in diabetes. It has also often been tried internally as a sedative in tetanus and in spastic neuroses ; but the results have not been encouraging (*cf.* the above-mentioned case of epilepsy).

The effects of *curare poisoning* in animals may be completely abolished by the injection of physostigmine or its analogue, Prostigmin. This remarkable action has not yet been fully explained. Acetylcholine is regarded as a chemical transmitter between motor nerve-endings and muscle fibres (p. 108). Excess of this substance is normally destroyed by an esterase in the body tissues. Recent work by Lady Briscoe suggests that in curare poisoning the threshold for stimulation of skeletal muscle is raised. In other words, a greater amount of acetylcholine is required at the nerve-endings to elicit normal contraction. It is further suggested that physostigmine and Prostigmin are capable of inhibiting the action of the esterase and therefore acetylcholine is allowed to accumulate. With appropriate doses of eserine, etc., the resulting quantum of chemical transmitter again becomes sufficient to excite muscular contraction. The similarity between curare poisoning and *myasthenia gravis* led to the use of physostigmine and prostigmin in this disease. Dramatic improvement is seen within half an hour of administering $\frac{1}{60}$ grain of Prostigmin subcutaneously or

a similar dose of physostigmine salicylate. Unpleasant "side-effects" are rarely seen with Prostigmin, but excessive sweating and salivation may occur when physostigmine is used. With this treatment, a patient severely incapacitated by myasthenia gravis may be restored to normal health. The injections must, however, be continued indefinitely. The pharmacological action of Prostigmin, etc., in these cases is probably similar to that described in curare poisoning.

Preparations and Doses

Physostigminæ Salicylas (B.P., U.S.P.), $C_{15}H_{21}N_3O_2.C_7H_6O_3$. *Dose*, 0·0006—0·0012 grm., $\frac{1}{100}$—$\frac{1}{50}$ gr. (B.P.); 0·002 grm., $\frac{1}{30}$ gr. (U.S.P.). Does not keep very well. Forms white, or yellowish white crystals, of which the aqueous solution, after only a few hours, assumes a reddish or brown colour, though without any appreciable loss of activity. The addition of 2 per cent. of boric acid has a certain preservative effect. For dropping into the eye, ½ per cent. solution, 2 or 3 drops. Hypodermically, for post-operative paralysis of the intestine, ½ milligrm. ($\frac{1}{120}$ gr.) thrice daily.

Oculentum Physostigminæ (B.P.), physostigmine salicylate 0·125 per cent. is a basis of wool-fat and yellow soft paraffin.

Lamella Physostigminæ (B.P.), each contains 0·065 milligrm., $\frac{1}{1000}$ gr. of physostigmine salicylate.

Prostigmin is the dimethyl carbamic ester of 3-oxymethyltrimethyl ammonium methyl sulphate. It is used in the treatment of myasthenia gravis. Usually two or three doses of 1 milligrm. are required per diem to abolish symptoms. Administered by hypodermic injection.

14. NICOTINE AND LOBELINE

Nicotine, $C_{10}H_{14}N_2$

The vegetative system (see p. 107) differs from the central system in that the nerves do not go direct to the respective organs, but pass through ganglia on the way. Through one or more ganglia the nerve-fibres may pass without forming connections (Fig. 13, *a*); but in one and one only, the path of the nerve is interrupted by a ganglion-cell (Fig. 13, *b*). Langley has shown that the liquid alkaloid of the tobacco plant, nicotine, after a brief period of stimulation, paralyses all these ganglion cells throughout the vegetative system, both the sympathetic and the parasympathetic. The symptoms arising from this are very similar to those described under muscarine, but the seat of action is quite different.

Nicotine produces only a brief period of arrest of the heart, which is succeeded by normal or rapid beat, for the stimulating action on the *cardiac inhibitory apparatus* is of a very transitory nature, and soon passes into complete paralysis, so that

stimulation of the vagus no longer has any influence upon the heart. The *oculomotor nerve* is affected in the same way, the pupil being first contracted and then dilated. Nicotine further causes hypersecretion from most of the *glands*, especially the sweat and salivary glands.

The *movements of the intestines* are very strongly affected. When a minimal quantity of nicotine is injected into the jugular vein of an animal, the entire alimentary canal is thrown into active peristalsis with colicky contractions from the stomach to the rectum (the small intestine especially) so powerful that the lumen altogether disappears. All the contents are forced with great rapidity down towards the rectum, and local colic occurs, during which the intestine becomes pale in colour, as the vessels are compressed. After a brief period of rest, during which the

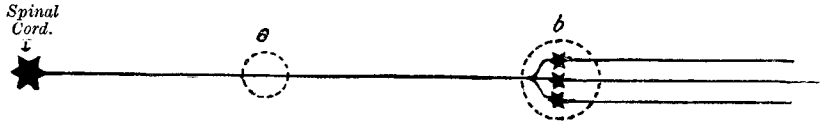


FIG. 13.—Diagram of the course of a vegetative nerve-fibre. *b*. Point of attack of the nicotine. After the application stimulation of the pre-ganglionic nerve between the centre and the ganglion (black) is without effect, while, on the other hand, stimulation of the post-ganglionic fibre (red) produces a normal effect, as it is only the cells, or the synapses, that are paralysed, not the nerve-fibres, nor their peripheral terminations. (After Langley.)

vessels once more fill, a strong, prolonged peristalsis commences, with renewed evacuations.

Nicotine cannot be employed as a medicine, for almost simultaneously with the commencement of the action on glands and intestine, the *central nervous system* is also affected. The former employment of tobacco infusion for intestinal obstruction has repeatedly occasioned fatal poisoning, and has therefore been abandoned as a far too dangerous treatment.

Acute Poisoning. The pure alkaloid equals prussic acid in toxicity. Small birds die almost instantaneously when a glass rod moistened with nicotine is held in front of their beak ; and for man the lethal dose is probably only a few centigrammes. Two medical students in von Schroff's laboratory, who experimented on themselves with 1 and 4½ milligrammes of nicotine respectively, both suffered serious poisoning, of which the most prominent symptoms were salivation and vomiting, intense headache, frequent and laboured respiration, drowsiness and clouded mental faculties, and, in the one who had taken the larger dose, also diarrhœa, great dyspnœa, fainting, and, finally, collapse with pale face, cold extremities, and repeated attacks of clonic convul-

sions. The poisoning lasted three entire days. In the few cases in which pure nicotine has been used for murder, death has taken place within a few minutes. Nicotine *is absorbed* very rapidly from all mucous membranes and also through unbroken skin (poisoning after the use of an infusion of tobacco for skin parasites, and in the case of smugglers who have concealed tobacco upon their body).

Notwithstanding the toxicity, the organism succeeds in attaining a certain degree of tolerance. Daily experience shows that the well-known inconveniences that the novice has to endure when smoking soon disappear and are replaced by a feeling of well-being, a calm, contented mood, and a keener pleasure in work, effects that combine to make tobacco the most indispensable of all articles of luxury. Moderate smoking has scarcely any deleterious effect apart from a slight throat catarrh, but prolonged excess may bring about a *chronic poisoning*, of which the most important symptoms are a depressed state of mind, "nervousness," anomalies of digestion (small appetite, now diarrhœa, now constipation), palpitations and irregular pulse, and, finally, the so-called tobacco amblyopia, an affection of vision characterised by two-sided central scotoma. Chewing tobacco and taking snuff give less frequent poisoning than smoking, as the leaves for this purpose often undergo processes which reduce the amount of nicotine in them. The prognosis of the poisoning is good, provided the cause is removed by the complete denial of tobacco for a long time. It has not been decided whether arterio-sclerosis can have any connection with a large consumption of tobacco. Arterio-sclerosis is very frequent, and is common in women who have never touched tobacco.

What little nicotine is excreted is mainly in the urine, with traces also in the saliva and sweat. It is partly destroyed in the liver, and this destruction is increased by habituation (Dixon).

Tobacco for smoking contains varying amounts of nicotine (0.6—4.8 per cent.), a considerable portion of which passes into the smoke. A sample of tobacco grown in Norway contained 1·5 per cent. of nicotine. Like a few other alkaloids, nicotine is known in two optical forms (see under "Hyoscyamine"); the natural alkaloid occurring in the plant is lævo-rotatory and, according to Mayor's investigation twice as poisonous as the dextro-rotatory, which is produced artificially.

Cytisine

The beautiful ornamental tree so frequently seen in gardens, *Cytisus Laburnum* (laburnum), and which is often the occasion of poisoning in children, contains *cytisine*, an alkaloid which also occurs in other species of *Cytisus*. This alkaloid, according to Dale and Laidlaw, closely resembles

nicotine. The toxic symptoms begin with pallor and cold sweat, vomiting, abdominal pains, frequently also diarrhœa, salivation and great thirst. In more serious cases there are also confusion of mind, unconsciousness, dilatation of the pupil, and muscular twitchings. The pulse is at first slow, later frequent, small and irregular. Death ensues as a consequence of respiratory paralysis, sometimes preceded by clonic convulsions. The treatment consists in evacuation of the stomach and intestine, hot fomentations on the abdomen, caffeine, camphor and artificial respiration.

Lobeline

Lobelia inflata, Indian tobacco, which contains the liquid alkaloid *lobeline*, $C_{16}H_{21}NO$, is a native of North America, where it grows by the roadside and at the edges of woods. In its native country it has long been employed as a remedy for ordinary bronchitis, and still more for asthma. According to the investigations of Dreser and Edmunds, lobeline has a two-fold action upon the respiration. It paralyses the terminations of the vagus in such a way that electrical stimulation of that nerve, which in normal animals causes contraction of the finer bronchial tubes and reduction of the respiratory volume, has no such influence after the animal has had a small dose of lobeline. In the next place it acts upon the respiratory centre of the medulla oblongata, respiration becomes more frequent, and its absolute force, measured by the height of the column of water that the expiratory pressure can overcome, increases. The action of toxic doses of lobeline is similar to that of nicotine.

Preparations and Doses

Lobelia (B.P.), consists of the dried leaves and flowering tops of the plant, and is often seen in commerce pressed into brick-like cakes. Is sometimes found in "asthma powders." *Dose*, 0·06—0·2 grm., 1—3 grs.

Tinctura Lobeliæ Ætherea (B.P.), 20 per cent. *Dose*, 3—10 decimils, 5—15 mins.

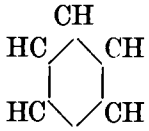
15. CONIINE AND SPARTEINE (not official)

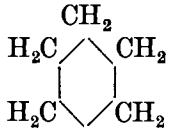
Coniine

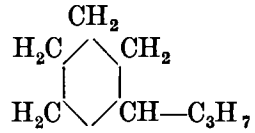
In all parts of the hemlock, *Conium maculatum*, and most abundantly in its unripe fruit, the volatile liquid, *coniine*, occurs together with the two allied alkaloids, *methylconiine* and *conhydrine*.

Coniine is closely allied to piperidine, and through the latter

to pyridine, and was the first vegetable alkaloid to be produced successfully by synthesis.


Pyridine.


Piperidine.


Coniine.

Coniine is absorbed easily, both through the unbroken skin and through mucous membranes, and is excreted, to some extent at any rate, in the urine. Like nicotine, it acts upon certain secretions, principally the saliva, and upon the intestinal canal, but, in addition, possesses, like curarine, the power of paralysing the motor nerve-endings of the striated muscles. In man this latter action and paralysis of the spinal cord are generally most prominent, and are the distinguishing features of a type of poisoning that is well known from of old, when the fresh hemlock juice was used for the execution of death-sentences; in recent times there have been many chance cases of poisoning. The paralysis takes an ascending course. First, the lower extremities become partially paralysed and refuse to bear the weight of the body, then the arms are affected and the muscles of the face and throat, and the voice becomes hoarse owing to the relaxed condition of the vocal cords. Finally, paralysis of the diaphragm and the muscles of the chest cause death, as a rule, in full consciousness (*cf.* Plato's account of the death of Socrates). Immediately before death there are asphyxial convulsions, but they are only slight, as the paralysis of the motor nerves prevents any very strong muscular contractions. Locally, coniine, like veratrine, acts upon the ends of the sensory nerves by first causing a burning, smarting sensation, and then a deadening of the feeling of pain. Various preparations, such as *Emplastrum Conii*, were formerly much used as anodynes, but have now been discarded.

Sparteine

Sparteine, $C_{15}H_{26}N_2$, is also a liquid and volatile alkaloid, and is found in *Spartium scoparium* or *Sarothamnus scoparius* (*Papilionaceæ*) of Central Europe. In toxic quantities it acts in the main like coniine, while small doses only produce vascular contraction and consequent increase in the arterial tension; it has, further, an *effect upon the heart*, the exact nature of which,

however, has not as yet been explained. Various preparations of *Sarothamnus* have long enjoyed a reputation as diuretics, and the sulphate of sparteine has of late been largely employed in France for *heart-diseases*. Germain Sée and others consider that in asystole it improves the pulse and also has a regulating action like digitalis. Clinical experiments have shown very varied results, sometimes good action even in cases that were not affected by digitalis, sometimes none at all. No definite indications for the employment of sparteine can thus at present be given, but it is worth a trial where digitalis and strophanthus fail. Huchard recommends it for arterio-sclerosis, together with iodide of potassium.

Gelseminine

The North American climbing plant, *Gelsemium sempervirens*, yellow or Carolina jasmine (*Loganiaceæ*), contains 2 alkaloids, the strychnine-like gelsemine (p. 67) and *gelseminine*, whose action is closely allied to that of coniine; it moreover dilates the pupil and paralyses the accommodation like atropine. A fluid extract and a tincture are employed in America, more rarely in Europe, for neuralgia. There are no official preparations of Gelsemium in the B.P. or U.S.P.

With regard to *Æthusa Cynapium*, fool's parsley, an umbellifer and a common weed in kitchen-gardens in Europe and North America, and feared of old as a poisonous plant, various views have more recently been advanced, some maintaining it to be harmless and, in the absence of anything better, even serviceable as a salad. Fresh reports of poisoning cases, and fresh confirmation (Power and Tutin, 1905) of the old statement that fool's parsley contains an alkaloid like coniine, make it imperative that it should once more be regarded as a poisonous plant.

Preparations and Doses

Tinctura Gelsemii (B.P.C.). *Dose*, 3—10 decimils, 5—15 mins.
Fluidextractum Gelsemii (N.F.). *Dose*, 0·03 mil, ½ min.

16. COLCHICINE

Colchicum autumnale is well known in Southern and Central Europe from its unusual time for blooming; in the late autumn months it covers the damp pastures with a rosy-hued carpet of flowers. It contains *colchiceine* and its methyl compound, *colchicine*.

Action. The most prominent action of colchicine is its effect on the lower section of the intestinal canal, and is obtained, whether the drug is given internally or hypodermically, with a characteristic slowness. After large doses in man, several hours generally elapse before the introductory symptoms appear in the form of general indisposition, nausea, and frequent vomiting,

and not until 12 to 24 hours a characteristic profuse diarrhœa. The evacuations, at first frequent and exhausting, but almost painless, consist of the ordinary contents of the intestine, but afterwards become watery and sometimes mixed with blood. This is very similar to the cholera-like diarrhœa in acute arsenic poisoning, for there, too, many hours pass before the intestinal symptoms commence, and the reason in the two cases is probably the same, namely, paralysis of the capillaries of the intestine. Clinically, there is the great difference that the colchicine diarrhœa is not dangerous when the treatment is suspended in time.

In toxic quantities colchicine paralyses the **central nervous system.** In animals the hind extremities are first weakened, and the paralysis then moves upwards until death, in convulsions, takes place owing to respiratory failure, while the heart is still working. The **striated muscles** behave as in veratrine poisoning ; the contraction-curve is changed by the lengthening of relaxation and by the muscle showing fatigue earlier than in the normal condition.

Regarding the urine, and more especially the **excretion of uric acid,** which is of interest on account of the employment of colchicine for gout, there are many observations recorded, but there is little harmony among them. The latest investigator (Denis, 1915) found no change in the excretion in 5 experiment-subjects who were placed on purine-free diet.

Jacobj has made the interesting observation that the frog is almost immune to colchicine, but that if the animal is warmed up to the temperature of a warm-blooded animal, poisoning takes place. Colchiceine is much less poisonous than colchicine (Führer).

Therapeutic Uses. Near the beginning of last century (1814), colchicum was very warmly recommended by English doctors for *gout*, and has since then been the principal remedy for that disease. Latterly, however, it has lost much of its former prestige ; but there is no doubt that it is an excellent remedy for acute attacks if it is allowed its full action by being administered at the beginning of the attack in somewhat large doses. The pharmacopœial preparations, *e.g.* Tinctura Colchici Seminis have been most commonly employed ; these are assayed chemically in terms of colchicine content. Precise dosage is possible by prescribing the now easily obtainable pure alkaloid. About 1 milligramme is given 3 times a day for at most 2 days. The first doses produce, as a rule, only anorexia and nausea. After the third and fourth doses the diarrhœa begins, the medicine is then discontinued, but the diarrhœa lasts for about 24 hours, with altogether from 12 to 15 loose, and later watery, evacuations.

In some cases, however, these intestinal symptoms may be almost absent. Pain and inflammatory symptoms in the affected joints usually diminish the first day; the following night the non-treated patient would once more suffer intense pain, but the treated is generally comfortable (if the diarrhœa has not begun). Very frequently patients who, judging from the course run by previous attacks, would be liable to be laid up for weeks, when treated with colchicine can again put their foot to the ground after 2 or 3 days. The attacks are thus aborted. It is useless to speculate regarding the nature of the action, so long as the pathology of gout is obscure; in the meantime we must be content with calling the action specific. The abundant evacuations may possibly have some share in the results, but they are not decisive, as slight attacks may frequently be arrested by giving the doses mentioned only two or three times, when the diarrhœa does not appear, or is only very slight. It is only the acute attacks that are affected by colchicine; the chronic condition remains unchanged, and the remedy is not useful in the intervals between acute attacks.

Preparations of colchicum are also employed for chronic rheumatism, but have no effect.

Preparations and Doses

Colchici Cormus (B.P.). *Dose*, 0·12—0·3 grm., 2—5 grs. From the corm or bulb are prepared:

Extractum Colchici Siccum (B.P.). *Dose*, 16—60 milligrms., $\frac{1}{4}$—1 gr.

Colchici Semen (B.P., U.S.P.). *Dose*, 0·12—0·3 grm., 2—5 grs. (B.P.); 0·2 grm., 3 grs. (U.S.P.). From the seed are prepared the following:—

Extractum Colchici Liquidum (B.P.), used for the preparation of the tincture. *Dose*, 12—30 centimils, 2—5 mins.

Tinctura Colchici (B.P.). *Dose*, 3—10 decimils, 5—15 mins.

Tinctura Colchici Seminis (U.S.P.), 0·04 per cent. of colchicine. *Dose*, 2 mils, 30 mins.

Colchicina (U.S.P.), $C_{22}H_{25}NO_6$, a pale yellow powder, soluble in about 20 parts of water, and freely in alcohol or chloroform. *Dose*, 0·0005 grm., $\frac{1}{120}$ gr. Two milligrms. ($\frac{1}{30}$ gr.) *per dosem*, and 4 milligrms. ($\frac{1}{15}$ gr.) *per diem* may be considered the maximum dose. Given in the form of pills, or dissolved in alcohol. The crystalline colchicine contains about 15 per cent. of crystal chloroform.

17. ACONITINE

Aconitine has been a collective name for a number of still not clearly defined alkaloids which occur in many species of the genus *Aconitum* (*Ranunculaceæ*). These are remarkable in being, like cocaine and atropine, esters of bases (*aconine*, *pseudaconine*), with organic acids (acetic, benzoic, and others). Many different aconitines have been described, but the number is being gradually

reduced, as the variations have proved to be only a consequence of decomposition that is apt to occur during the process of production. In Europe, *aconitine* is extracted from *A. Napellus*, a native of the mountain pastures of the Alps; the East Asiatic *A. Japonicum* contains *japaconitine*, and the East Indian *A. ferox* the exceedingly poisonous *pseudaconitine*. Several other alkaloids resembling the aconitines are found in the old medicinal plant *Delphinium Staphisagria*, which also belongs to the order *Ranunculaceæ*.

Action. Considered qualitatively, all the aconitines behave more or less uniformly. Although their action is very complex, only brief mention will be made here, as at present they are of little therapeutic importance.

When rubbed into the skin as an ointment, applied to mucous membranes, or taken internally, aconitine has a characteristic action on all *sensory nerves*. First the nerve-endings are stimulated, so that there is a hot, burning sensation, prickling and formication all over the body, pricking and roughness in the mouth and throat (salivation and vomiting), and tickling and itching in the nose. These symptoms in cases of aconitine poisoning are very valuable clues; only veratrine presents similar features. After a short time the action is reversed, the nerve-endings being paralysed, so that the hands feel as though covered with kid gloves, the perception of temperature is blunted, and the sense of taste is weakened. The *muscle-nerves* are affected in a similar manner—first stimulation with fibrillary twitchings, and then curarine action.

The *heart-action* is altered in a composite and, as yet, obscure manner. Small doses make the pulse in man slow and small; the diastole is lengthened and the systole is weakened. Judging from animal experiments, the cause of this is central vagus stimulation, for it does not occur when the vagi are divided. The investigations made by various observers of the action upon the heart of mammals show discordant results, *e.g.* auriculo-ventricular arrhythmia, extra-systoles, and pulsus alternans. In the isolated frog's heart there are, first, more frequent contractions, then irregularity, and, last, arrest in diastole. The stage of irregularity is especially characteristic for aconitine. The ventricle expels hardly any of its contents into the aorta and assumes a peculiar light and dark flecked appearance. These features appear even after $\frac{1}{100}$ milligramme of aconitine, and in cases of poisoning can be utilised to demonstrate the presence of the alkaloid. Large doses produce in man convulsions, and finally paralyse the heart and respiration. Aconitine is the most toxic of all the official alkaloids. A Dutch physician, who by

mistake took 3 or 3½ milligrammes of a crystallised French preparation, died in 4½ hours (1880).

Therapeutic Uses. Various preparations of *Aconitum Napellus* were formerly much employed, and are still used occasionally in England, North America, France and Italy, for *neuralgia* and in *febrile diseases*, when the pulse-frequency is very high without any very great heart-weakness; but in several other countries they have been given up and omitted from the pharmacopœias. Aconite is an ingredient in the well-known *A.B.C. Liniment*, the other constituents being belladonna and chloroform.

Preparations and Doses

Aconitum (B.P., U.S.P.), the dried tuberous root of *Aconitum Napellus*, wolf's-bane, monk's-hood, frequently cultivated in gardens. Contains 0·4—0·5 per cent. of alkaloids. *Dose*, 0·06 grm., 1 gr. (U.S.P.).

Tinctura Aconiti (U.S.P.), 0·05 per cent. *Dose*, 0·6 mil, 10 mins.

Linimentum Aconiti (B.P.), 2 per cent.

Aconitina, $C_{34}H_{45}NO_{11}$, colourless, transparent crystals, almost insoluble in water. The commercial product is often impure.

Staphisagriæ Semina, the seeds of *Delphinium Staphisagria*, stavesacre. An ointment (B.P.C.), or a fluid extract, the latter diluted with 10 parts of soap liniment, is sometimes used for pediculi capitis and pubis.

18. VERATRINE

In the genera *Veratrum* and *Schœnocaulon*, belonging to the *Melanthaceæ* or *Colchicaceæ* family, several alkaloids occur, which show a great resemblance in their action to the aconitines, and, like them, are esters of an acid and a base. The most important are *veratrine*, $C_{32}H_{49}NO_9$, which can be decomposed into angelic acid and a base, cevine, which is related to aconine, and *protoveratrine*, $C_{32}H_{51}NO_{11}$, which is probably a combination of isobutyric acid and a base resembling cevine. The first of these alkaloids is found in the seeds of *Schœnocaulon officinale*, which grows wild in Mexico and the north of South America; the second occurs in various species of the genus *Veratrum*, which is distributed over large portions of the Northern Hemisphere. Both veratrine and protoveratrine are very active substances, the latter even approaching aconitine in toxicity. They are accompanied in their respective plants by other alkaloids, some of which are poisonous, but of which little is known, as, owing to the decomposition that takes place, they are not easily obtainable in a pure state.

Action. Veratrine acts upon the **sensory nerves** in the same way as aconitine. The smallest quantity of the alkaloid itself, or of the powdered vegetable substances, produces in the nose great irritation and sneezing, in the eye hyperæmia, intense pain and a

flow of tears, in the mouth burning and salivation, and when inhaled violent coughing. Internally, they produce vomiting and profuse diarrhœa, which may be ascribed partly to local action on the mucous membrane of the stomach and intestine and partly to central action. When rubbed into the unbroken skin as ointment, veratrine quickly produces a burning, prickly sensation, followed by a feeling of cold and diminished sensibility. The skin becomes red, and a few vesicles may appear. In frogs, veratrine increases the cutaneous secretion so greatly that they have the appearance of being enveloped in soapsuds.

On the **striped muscles** veratrine has a most peculiar action, which was first studied by Koelliker. When a minimal dose of veratrine, *e.g.* $\frac{1}{20}$ milligramme, is injected subcutaneously into a *Rana esculenta* or *R. temporaria*, the movements of the animal are changed in a remarkable manner. Instead of moving with its customary quick leaps, the frog moves slowly forward with creeping, stiff gait, which gives to the formerly active animal the appearance of being transformed into its sluggish kinsman, the common toad. Upon closer observation it will be seen that the contraction of the muscles takes place rapidly, but the relaxation only very slowly. The ascending portion of the contraction-curve goes abruptly up to the summit, and the height of contraction is even greater than normal; but the relaxation, which represents the return to rest, occurs very slowly, taking 40 to 50 times as long as in normal muscle to reach the abscissa. This makes the characteristic quick leaps, which are the animal's usual form of movement, impossible. The work of the muscle does not suffer through this; it is even greatly increased after small doses, and the prolonged, forcible contraction is accompanied by a great development of heat. In mammals the same effect is seen after very small doses of veratrine; larger quantities paralyse the muscles.

In mammals the action on the circulation is very complex; veratrine acts on the cardiac muscles, the cardiac nerves, and the vaso-motor centre, sometimes stimulating, sometimes paralysing, according to the size of the dose. Medium doses cause a slow pulse, probably because the contraction is prolonged in the manner described. The blood-pressure therefore falls very considerably and the *temperature of the body* is lowered.

Therapeutic Uses. Veratrine is now employed only as an *antiparasiticide* and an *anodyne for neuralgia*, principally trigeminal neuralgia. The former employment of veratrine or Tinctura Veratri in febrile diseases, especially pneumonia, has now in most places been abandoned. The fall of temperature obtained is not brought about by any specific antipyretic action, but is an

outcome of the cardiac weakness and of the lowered arterial tension, and is really a symptom of collapse.

Preparations and Doses

Veratrina, a white or greyish white powder, almost insoluble in water, very readily soluble in alcohol, a mixture of the alkaloids occurring in the above-mentioned seeds. Has been given internally in doses of about 2 milligrms., externally in 5 per cent. ointment for neuralgia, a piece the size of a pea to be rubbed in. Veratrine is a component part of certain hair-washes, and it is not impossible that its stimulating and hyperæmic action on the skin may promote the growth of the hair. ℞. Veratrine 0·25—0·50, Spirit 80, Ol. Ricini 10—20. To be rubbed into the roots of the hair 3 times a week.

Veratrum Viride (U.S.P.), green hellebore, American hellebore. The rhizome and root. *Dose*, 0·1 grm., 1½ grs.

Tinctura Veratri Viridis (U.S.P.). *Dose*, 1 mil, 15 mins.

19. APOMORPHINE

Apomorphine does not occur in the natural state, but is produced from morphine by treatment with concentrated hydrochloric acid. The formula corresponds with that of morphine, minus H_2O. It is not only, however, that 1 molecule of water is split off, but greater changes have also taken place in the morphine molecule. Apocodeine is produced from codeine in the same manner.

Action. Notwithstanding its relationship to morphine, apomorphine has a very different action on the **central nervous system** from that of morphine. In moderate quantities it does not produce anæsthesia, but only excitement, its special point of attack being the so-called "vomiting centre," which is located in the medulla oblongata in the vicinity of the respiratory centre. This region reacts with extreme sensitiveness to apomorphine, so that very small doses, that otherwise have no demonstrable effect, very promptly elicit vomiting in man and carnivorous animals. That this is of central origin can be concluded with certainty from the fact that apomorphine acts more rapidly and in smaller doses by hypodermic injection than when given internally, and that the vomiting occurs also after section of both the vagi, which abolishes the effect of those emetics which act only peripherally, *i.e.* on the gastric mucous membrane.

The brain is also affected, but slight excitement is masked, in carnivorous animals, by the depressing influence of the vomiting. After large doses, dogs and cats exhibit great uneasiness, and an irresistible desire for movement, running about aimlessly regardless of obstacles, and often showing circus-movements. In herbivorous animals such as rabbits, which do not vomit, the usual

signs of stimulation of the cerebrum and the medulla oblongata appear with distinctness, even after small doses. The respiration is hurried and abnormally deep, the animals lose their usual apathy and become anxious and agile, make attempts at climbing, gnaw at everything within reach, and give vent to their excitement by their customary signal of alarm—quick taps of their hind feet upon the floor. Very large doses paralyse the central nervous system. Death occurs in dyspnœa, while the heart still beats. In lower animals apomorphine, like other emetics, paralyses the striated muscular tissue, including that of the heart, an action which does not appear in higher animals.

The **vomiting** is a very complex proceeding, which does not consist only in evacuation of the stomach. There are three separate phases. All emetics produce first certain prodromal symptoms which constitute the so-called *nausea stage*, which is characterised by a peculiar, exceedingly disagreeable, sensation along the œsophagus and in the epigastrium. Simultaneously with this there is an abundant secretion from numerous glands ; the mouth waters, sweating breaks out, and from the larynx and bronchi a thin mucus is secreted. Complete loss of power ensues, all the muscles are relaxed, the pulse is very frequent, the face is pale and the respiration rapid. After these unpleasant prodromata have lasted for some time, the actual *evacuation of the stomach* takes place. As X-ray examinations of dogs show, the relaxed fundus of the stomach is first filled from the pylorus ; deep inspirations with closed glottis produce a negative pressure in the chest, whereby the contents of the stomach are drawn up through the open cardiac orifice into the œsophagus. This is followed by separate, strong contractions of the abdominal muscles, the diaphragm and the stomach itself, which, in conjunction with forced expirations—the glottis being still closed—expel the contents of the stomach with considerable force, often through both nose and mouth. The final stage is that of *collapse*, a not unpleasant condition of languor, which is felt as a relief, although it not infrequently has the character of a really serious weakness ; but this is, as a rule, quickly followed by complete well-being and return to normal conditions, or by an inclination to sleep.

The three things required of a good emetic are that the nausea stage shall be brief, the vomiting certain, and the concluding stage of collapse without danger.

Therapeutic Uses. Emetics, and above all tartar emetic, played a very important part in the antiphlogistic therapeutics of former times. They were employed for the purpose of combating fever, of changing the course of the disease, and of expelling the

" materia peccans " both in internal diseases and in surgical cases, *e.g.* abscesses, inflammation, erysipelas. They were also employed, in the absence of ether and chloroform, in the treatment of dislocations ; the patient was given a powerful emetic, and as soon as the nausea was well developed the reduction operations, for which the relaxed state of the muscles was favourable, were commenced.

Emetics are now prescribed only with the following indications :—

1. For the *evacuation of the stomach* in cases of poisoning. When practicable, however, the washing out of the stomach is now preferably employed, this being a far less drastic process than vomiting, while it cleanses the stomach better and possesses the great advantage of fulfilling its purpose also in the case of patients who do not react to emetics (narcotic poisoning). When foreign bodies in the œsophagus cannot be removed with instruments, an apomorphine injection may be tried.

2. *False membranes* and *foreign bodies in the throat or windpipe* are not removed in the act of vomiting, as the glottis is closed, but may be so loosened by the violent movements and the increased secretion that the next fit of coughing brings them up.

3. It is supposed that most emetics, even in doses too small to act emetically, cause the secretion of a thin fluid in the air-passages, and they are therefore employed as *expectorants in dry catarrh* with scanty, viscid secretion adhering to the bronchial walls and difficult to cough up, although the current of air in violent fits of coughing has a great velocity. Clinical experience shows that in such cases emetics in repeated small doses may cause the viscid mucus to become more fluid and loosen, the dry râle to be changed to moist, and expectoration facilitated. When there is already abundant thin bronchial secretion, it would be a mistake to increase its amount still further ; the means resorted to in this case are such as are supposed to promote absorption or stimulate to more forcible coughing, *e.g.* benzoic acid, senega, and camphor (direct expectorants).

Emetics are contra-indicated in all conditions in which sudden and great changes of pressure in the chest and abdomen may act deleteriously, *e.g.* with *aneurisms*, *arterio-sclerosis*, *herniæ*, and far-advanced *pregnancy*, as also in phthisis with tendency to *lung hæmorrhage*. The collapse succeeding the vomiting necessitates caution in cases of cardiac weakness, in aged and feeble persons, and in young children.

Regarding apomorphine in particular, it should be added that it is the best emetic. It acts with great certainty, as a rule within 10 minutes, after comparatively slight prodromal symp-

toms, and the subsequent collapse is less pronounced than in most of the other emetics. It is employed hypodermically and can therefore be administered to patients who refuse to take medicine by mouth.

Apomorphine in small doses is said to have a mild hypnotic action, but this is of little importance.

The Quebracho Alkaloids

The bark of *Quebracho blanco* contains several alkaloids, of which quebrachine is the most important. Like apomorphine, it produces vomiting by direct central action; in small doses it induces only nausea and increased secretions. Quebracho sometimes proves to be a good soothing remedy in bronchitis with accompanying dyspnœa, in emphysema and in asthma.

Preparations and Doses

Apomorphinæ Hydrochloridum (B.P., U.S.P.), $(C_{17}H_{18}NO_2.HCl)_2.H_2O$. White or greyish white, easily soluble crystals, which, when exposed to damp, soon turn green in colour and lose some of their activity. *Doses*, expectorant, 1—2 milligrms., $\frac{1}{64}$—$\frac{1}{32}$ gr. (B.P.); 1 milligrm., $\frac{1}{60}$ gr. (U.S.P.); emetic, 2—8 milligrms., $\frac{1}{32}$—$\frac{1}{8}$ gr. (B.P.); 5 milligrms., $\frac{1}{12}$ gr. (U.S.P.). Apomorphine is also well adapted for administration to children. Emetic dose for children under 2 years, 1—2 milligrms., $\frac{1}{60}$—$\frac{1}{30}$ gr.

Apocodeinæ Hydrochloridum, $C_{18}H_{19}NO_2.HCl$, yellow or greenish yellow, easily soluble crystals, 10—30 milligrms., $\frac{1}{6}$—$\frac{1}{2}$ gr., a few times a day for bronchitis.

20. EMETINE (IPECACUANHA)

In ipecacuanha root there is a peculiar bitter acid of a glucoside character called *ipecacuanhic acid*, and the alkaloids *cephaëline*, $C_{14}H_{19}NO_2$, and its methyl compound *emetine*, $C_{14}H_{18}(CH_3)NO_2$, first isolated by Paul and Cownley in 1895.

Action. The ipecacuanha alkaloids, like preparations of the root, resemble tartar emetic in their action. On the *unbroken skin*, and still more on *mucous membranes*, they produce irritation and inflammation. After being applied for some time to the skin, itching vesicles and pustules make their appearance, but heal without leaving scars. When powdering the root, the operator must protect his face, as the fine powder is very irritating to the eyes, and when inhaled elicits a violent reaction from the mucous membranes of the respiratory passages, profuse nasal catarrh, hoarseness, coughing, and even, in very sensitive persons or those suffering from "ipecacuanha idiosyncrasy," bad attacks of asthma and temporary amblyopia.

Large internal doses of the powdered root, *e.g.* 1—2 grammes,

first cause nausea, often somewhat prolonged, with all its concomitant symptoms, among which is a thin bronchial secretion, and then one or more attacks of vomiting with attendant symptoms of collapse, which, as a rule, however, is slight. If the action fails, and the powder is not evacuated but passes down into the intestine, diarrhœa may result.

The vomiting is not, as with apomorphine, due to central action, but is the result of irritation of the gastric mucous membrane. This may be concluded from the fact that even doses of the root containing only a few centigrammes of the alkaloids are as a rule sufficient to cause vomiting, while intravenous injections of far larger quantities of emetine rarely act as an emetic. From investigations by Rogers and others on the treatment of dysentery, it appears that subcutaneous and intravenous doses of 6—15 centigrammes generally produce in man slight indisposition, languor and temporary congestion of the face, but seldom vomiting.

Subcutaneous or intravenous injections of large quantities of the alkaloids occasion in animals acute enteritis with all its signs and clinical symptoms—great inflammation of mucous membranes, swelling, injection, muco-purulent exudation, ulcerations, and evacuations mixed with blood. Similar changes in the bronchial tubes and alveoli may also occur with œdema of the lungs and red hepatisation. Finally death ensues from paralysis of the heart. According to the most recent investigations (Pick and Wasizky, 1916), emetine has a paralysing action on unstriped muscle, and the symptoms mentioned may be explained by the paralysis of the capillaries of the organs concerned (*cf.* the analogous intestinal action of colchicine and arsenic).

Ipecacuanha probably has also a mild *diaphoretic* action. Ipecacuanhic acid appears to be inert.

Uses. As an *emetic* ipecacuanha is now little employed. Its action is less certain than that of apomorphine, and, as the liberation of the alkaloids from the root requires some time in the stomach, the emesis does not always take place with the desired rapidity; it often makes its appearance in the course of 10 to 15 minutes, but may, on the other hand, be an hour in beginning. Apomorphine is therefore the greatly superior drug when a rapid evacuation is required (poisoning).

Where it is a question of expectoration, the case is reversed. Here it is an advantage for the action to be protracted, and ipecacuanha is still frequently employed as an *expectorant* in dry catarrh with deficient secretion. In acute bronchitis this drug is often combined with opium.

Ipecacuanha root has long been renowned as a remedy for

epidemic *dysentery* occurring in many tropical countries ("*Radix antidysenterica*"); but during the last few years the treatment has entered upon quite a new phase. Whereas formerly the alkaloids were regarded as superfluous, and a "*radix deëmetinisata*" was even used, emetine itself is now employed. One grain of the hydrochloride is injected hypodermically every day for 10 days. In this way the alkaloid, which is a specific poison to the dysenteric amœba, can, during excretion into the bowel, reach the parasites, which inhabit the deeper layers of the intestinal wall. If amœbæ are still present in the stools, the course is repeated after a fortnight. Overdose results in gastro-enteritis and fatal cases of peripheral neuritis have occurred. Bismuth emetine iodide is a compound which does not readily dissociate in the stomach, and this preparation can be administered by mouth without fear of causing vomiting. In practice, however, bismuth emetine iodide is given in capsules (1 grain twice daily for 10 days). The same precautions regarding dosage should be observed as in the case of emetine. In bacillary dysentery preparations of emetine are of no therapeutic value.

Emetine is sometimes used also in the treatment of schistosomiasis.

Chiniofon is an iodine-quinoline compound containing about 28 per cent. of iodine. Originally introduced under various trade-names as an antiseptic for wounds, it is now used almost exclusively in amœbic dysentery, ulcerative colitis and similar conditions. Chiniofon appears to be directly toxic to the amœbæ in the bowel and in the intestinal wall, but remote lesions are unaffected. The drug is administered in pilular form in doses of 0·3 grm. three or four times daily. In acute cases enemata of chiniofon may also be given (1—3 grms. in 2 per cent. solution).

Vioform, iodochlorhydroxyquinoline, is reported to be more effective than chiniofon. It is a greyish-yellow powder, almost insoluble in water. Vioform is given in doses of 4 gr. in capsules thrice daily for 10 days. After an interval of 2—3 weeks another course may be given if necessary. Gastro-intestinal and hepatic disturbances sometimes occur as toxic effects but untoward symptoms are uncommon.

Preparations and Doses

Ipecacuanha (B.P.), the dried root of *Psychotria* (*Cephaëlis*) *Ipecacuanha*, *Rubiaceæ*, a native of Brazil, known in commerce as Rio Ipecac. Cylindrical pieces, twisted and flexuous, externally dark brown, closely annulated, with thickened, incomplete rings, which give to the root the appearance of a string of beads. Must contain not less than 2 per cent. of the alkaloids. **Ipecacuanha Pulverata** (B.P.), adjusted to contain 2 per cent. of total alkaloids calculated as emetine. *Dose*, 3—12 centigrms., ½—2 grs.; *emetic*, 1—2 grms., 15—30 grs. **Ipecacuanha** (U.S.P.), the root of the above plant and of *Cephaëlis acuminata*, growing in the north of South America, and known as Cartagena Ipecac. Must contain not less than 1·75 per cent. of alkaloids. *Dose*, expectorant, 0·06 grm., 1 gr.; *emetic*, 1 grm., 15 grs.

Ipecacuanha is given as an emetic in doses of 1 grm. every 10 or 15 minutes until it takes effect, 2—4 grms. in all; for children half these doses. As an expectorant, 2—5 centigrms. in powders or troches, or as a ¼—½ per cent. infusion, 1 tablespoonful every 2 or 3 hours. In sensitive persons the first doses often produce nausea, rarely vomiting.

Pulvis Ipecacuanhæ et Opii (B.P., U.S.P.), Dover's powder. *Trochiscus Morphinæ et Ipecacuanhæ* (B.P.). (Regarding these preparations, see Chapter 7, "Opium," p. 90.) *Trochiscus Ipecacuanhæ* (B.P.C.), each containing 0·015 grm., ¼ gr., of the root.

Extractum Ipecacuanhæ Liquidum (B.P.), *Fluidextractum Ipecacuanhæ* (U.S.P.), 2 per cent. of alkaloids. *Dose*, 3—12 centimils, ½—2 mins. (B.P.); 0·05 mil, 1 min.; *emetic*, 1 mil, 15 mins. (U.S.P.).

Tinctura Ipecacuanhæ (B.P.). *Dose*, 6—20 decimils, 10—30 mins.; *emetic*, 16—24 mils, 4—6 fl. drs.

Syrupus Ipecacuanhæ (U.S.P.). *Dose*, expectorant, 0·75 mil, 12 mins.; *emetic*, 15 mils, 4 fl. drs. Suits children well.

Emetinæ Hydrochloridum (B.P., U.S.P.), $C_{30}H_{44}N_2O_4.2HCl$. White or yellowish white crystalline powder, freely soluble in water. Hypodermic *dose*, 0·03—0·06 grm., ½—1 gr. (B.P.); 0·06 grm., 1 gr. (U.S.P.). In amœbic dysentery this dose is given daily for 10—12 days. If necessary, in serious cases the doses may be increased to 0·12—0·18 grm., 2—3 grs., a day for a few days. The alkaloid cephaëline cannot be used, as it is a stronger emetic.

Emetinæ et Bismuthi Iodidum (B.P.), a complex iodide of emetine and bismuth, containing about 25 per cent. of emetine. Orange colour, bitter taste, insoluble in water. Dispensed in keratin-coated capsules. *Dose*, 0·06—0·2 grm., 1—3 grs.

Chiniofonum (B.P.), *Pulvis Chiniofoni* (U.S.P.). A mixture of 4 parts of 7-iodo-8-hydroxy-quinoline-5-sulphonic acid and 1 part of sodium bicarbonate. A light yellow powder, bitter taste with a sweetish after-taste. Soluble in 25 parts of water. Insoluble in alcohol. *Doses*, 0·06—0·5 grm., 1—8 grs. By rectal injection 1—5 grms., 15—75 grs. (B.P.); 1 grm., 15 grs. (U.S.P.).

21. SAPONINS

Saponin is the name given to a number of non-nitrogenous glucosides, of which a distinguishing feature is that their aqueous solutions froth like soapsuds. The greater number of saponins do not crystallise; it is believed that they are colloid bodies with large molecules; they dialyse with difficulty, can be salted out of solutions like albumin, and have the property of holding particles, insoluble in water, in suspension in it. They are therefore employed in the manufacture of permanent emulsions (cod-liver oil, castor oil), and are sometimes added to lemonade and ginger beer to produce a froth. According to Kobert's investigations, the saponins, both as regards their action and chemically, probably stand in close mutual relationship to one another. A few of them are acids and form salts with alkalies; others have a neutral reaction. By the action of acids, alkalies and ferments, they are decomposed into sugars and little-known,

inert products. The more poisonous saponins are often called *sapotoxins*.

Investigations of recent years have shown that the saponins have a far wider distribution in the vegetable kingdom than was formerly supposed, and their presence is continually being demonstrated in an increasing number of species. Schaer estimates the number of plants containing saponin to be about 400, a number which will certainly be augmented by further investigations.

The following are the most important :—

Saponaria officinalis (*Caryophyllaceæ*), soapwort, was formerly employed as a drug, but its use has now been abandoned. The root contains 4—5 per cent. of saponin. *Quillaia saponaria*, soap bark, contains quillaic sapotoxin and quillaic acid. Besides its employment in medicine, it is used for the washing of dyed materials (silks) which will not bear the ordinary alkaline fatty soaps. *Polygala senega* contains senegin and polygalic acid ; and the numerous species of *Smilax*, which yield sarsaparilla root, contain no less than 3 different saponins. *Agrostemma Githago* (*Caryophyllaceæ*), the well-known weed with its large purplish-pink flowers, contains githagin, which is considered to be one of the most poisonous of the saponins. Paridin in *Paris quadrifolia* (*Smilaceæ*), the familiar, four-leaved, spring-flowering plant, is also very poisonous, as is cyclamin in *Cyclamen Europeum* (*Primulaceæ*), various forms of which are cultivated as pot plants. The ophiotoxin found by Faust (1907) in the poison of the *East Indian cobra*, pharmacologically resembles the saponins.

Action. Almost all the saponins are very poisonous when introduced directly into the blood. Large quantities produce convulsions, followed, in the course of a few minutes, by paralysis of the respiration : small doses, which do not paralyse the *central nervous system* so quickly, cause *inflammation of the intestine* which both in its symptoms and post-mortem appearance resembles dysentery ; there is the same bloody evacuation, swelling, injection, extravasation of blood and necrosis of the intestinal wall. There is also extravasation in the swollen mesenteric glands and in the endocardium. Many of the saponins, moreover, have a destructive action on the *red blood-corpuscles*, so that the hæmoglobin is set free and is dissolved into serum. Dioscorin (in *Dioscorea alata*) acts most powerfully in this way ; two of the saponins of sarsaparilla root, even in solutions of 1 in 400,000 and 1 in 125,000, completely dissolve the blood-corpuscles.

Notwithstanding all these varieties of action, drugs containing saponin, *e.g.* sarsaparilla, can be given with impunity internally in large doses, for the saponins are not absorbed through uninjured mucous membranes, or they are split up by the alkalies and ferments of the intestine into inert compounds. The agrostemma sapotoxin, githagin, is easily absorbed, however, and may, therefore, cause poisoning when much of the seed of this plant is

mingled with grain. The other saponins are as a rule only *irritants of mucous membrane.* Introduced into the eye, they cause a flow of tears, pain and inflammation, and in the nose copious secretion and sneezing; they have an unpleasant biting taste, and in small doses (this applies especially to senega and quillaia) have on the whole the same action as ipecacuanha and other similar emetics, namely, salivation, increased bronchial secretion, and often nausea, and are therefore employed as expectorants. Large doses may occasion vomiting and diarrhœa. Many of the saponins are local anæsthetics, but cannot be employed in practice on account of their irritating and inflammatory action.

The cause of the hæmolytic and all other toxic actions of the saponins is probably that they combine with the lipoids cholesterin and lecithin, which are important constituents of the blood-corpuscles and other cells.

Therapeutic Uses. Senega root. Indian snake-root—so called because it is said to have been originally employed by the Indians to alleviate the difficulties of respiration that followed snake-bite—is supposed, in the doses ordinarily used, to produce a thin, mucous, bronchial secretion, and is, therefore, employed as an expectorant. As the acrid taste sets up coughing, senega, unlike other drugs for increasing secretion, is employed not only for *dry bronchitis*, but also, when moist râles show that there are already large quantities of mucus, *i.e.* in the second stage of acute bronchitis, in *chronic bronchitis*, and in *pneumonia in its resolution stage.*

Sarsaparilla, which was formerly employed for chronic skin diseases, rheumatism, and especially *syphilis*, contains several saponins, which, however, can scarcely be absorbed from the alimentary canal. In any case, even after large internal doses, no other symptoms have as yet been found either in man or animals but such as are due to the local action on the mucous membranes. It is very doubtful whether sarsaparilla has any influence upon the diseases mentioned. This root, like so many other so-called "blood-purifying" medicines, is prescribed in weak decoctions, which, in accordance with prescriptions that have been handed down from generation to generation, are to be taken hot and in considerable quantities. It is probable that the action of the hot water in increasing metabolism, and also its diaphoretic, diuretic and, on account of the saponins, laxative action, may promote the elimination of various morbid poisons, and thus contribute to the cure. Whether the water contains saponin or an indifferent salt, such as sodium chloride, is probably a matter of no great importance.

Guaiacum. This old-fashioned drug, which was once a highly esteemed remedy for syphilis, but has now been discarded, also contains several saponins ; in the inner, dark part of the wood, a green resin which mainly consists of guaiaconic acid is present. Alcoholic solutions of the resin are coloured deep blue by compounds which give off active oxygen, an oxidation product of guaiaconic acid being formed ; it is, therefore, employed as a sensitive re-agent to blood.

Solanine, an alkaloid that is found in several species of *Solanum*, among others the formerly official *S. dulcamara*, bittersweet, has, like the saponins, a hæmolytic action (hæmoglobinuria). It produces inflammation of the intestine and kidneys, paralysis of the central nervous system, and finally cardiac paralysis. Solanine is found in comparatively large quantities in improperly stored, half-rotten or mouldy potatoes, and in the bleached shoots that sprout from them in warm, damp cellars ; it has repeatedly occasioned wholesale poisoning (Schmiedeberg). The little white-flowered *Solanum nigrum*, a common weed in kitchen-gardens, whose black berries are sometimes eaten by children, is also poisonous. The most marked toxic symptoms are vomiting and diarrhœa with consequent indisposition and languor, confusion of mind which may pass into a narcotic condition, cardiac weakness, dyspnœa and convulsions.

Preparations and Doses

Senega (B.P.), from *Polygala Senega*, fam. *Polygalaceæ*, a North American herb. Its thin, yellow, or greyish yellow, twisted root, is easily recognisable by a keel on the concave side of the curve. *Dose*, 0·4—0·8 grm., 6—12 grs.

Infusum Senegæ Recens (B.P.), 5 per cent. *Dose*, 15—30 mils, ½—1 fl. oz.

Infusum Senegæ Concentrum (B.P.), 40 per cent. *Dose*, 2—4 mils, ½—1 fl. dr.

Extractum Senegæ Liquidum (B.P.). Used in the preparation of the tincture. *Dose*, 0·3—1 mil, 5—15 mins.

Tinctura Senegæ (B.P.), 20 per cent. *Dose*, 2—4 mils, ½—1 fl. dr.

Syrupus Senegæ (U.S.P.). *Dose*, 4 mils, 1 fl. dr.

Quillaia (B.P.), soap-bark, Panama bark, large, flat, yellowish white pieces of the inner part of the bark of *Quillaia Saponaria*, fam. *Rosaceæ*, a tree growing in Peru and Chili. Is employed in a decoction of 5 in 200, given by the tablespoonful, with the same indications as senega.

Sarsaparilla (U.S.P.), the thin, almost cylindrical roots, about ½ yard in length, of various species of Smilax (fam. *Smilaceæ*), climbing plants indigenous to Mexico, Central and South America. Was formerly often given in weak infusions or decoctions, *e.g.* 30 in 1,000, 1 pint to be drunk hot, morning and evening. A fluid extract (*dose*, 2 mils, 30 mins.) and a compound syrup (15 mils, 30 mins.) are official.

Guaiacum, the greenish brown heart-wood and resin of *G. officinale* and *sanctum*, fam. *Zygophyllaceæ*, trees growing in the West Indies and the Bahama Islands.

22. CAMPHOR

Camphor is the name given to some aromatic compounds which occur in many ethereal oils, and are deposited when the volatile constituents in which they are dissolved evaporate, or when the oil is greatly cooled. Most kinds of camphor are found only in small quantities, and they will be mentioned incidentally in the chapter on volatile oils. Only a few are produced in large quantities and used medicinally. The most important are the *ordinary camphor* ($C_{10}H_{16}O$) and *menthol* ($C_{10}H_{20}O$). *Borneo camphor* (Borneol, $C_{10}H_{18}O$), which occurs in a crystalline state in old trunks of *Dryobalanops camphora* (*Dipterocarpeæ*), and can be produced artificially from ordinary camphor, is a drug of high repute in Southern Asia.

Ordinary Camphor, Japan Camphor

The ordinary camphor, or Japan camphor, is produced by distillation with water of the wood and leaves of *Cinnamomum Camphoræ* (*Lauraceæ*), a tree growing in Eastern Asia, and now cultivated also in other hot countries.

Action. The action of camphor after absorption is principally on the central nervous system and the circulation.

Large doses of camphor act upon the **central nervous system,** in man especially on the brain, there being first symptoms of excitation, frequently with sweating and increased diuresis, afterwards drowsiness and sleep, and finally profound unconsciousness, which may be accompanied by violent epileptiform convulsions. Even after very large doses the poisoning ends, owing to the rapid transformation of the camphor into non-poisonous compounds (see below), almost always in recovery. The course of the poisoning is very much the same in other warm-blooded animals as in man. Convulsions are not seen in the frog, for in that animal camphor very soon paralyses both the spinal cord and, like curarine, the *motor nerve-ends* of the voluntary muscles.

Animal experiments show that camphor possesses a stimulating influence on the **circulation.** Even if the convulsions caused by large doses are excluded by curarising the animal, there are still periodical rises of the blood-pressure after the injection of camphor. These are due in part to vaso-constriction by stimulation of the medulla oblongata, but also to the improved contractions of the heart (probably action on the muscles); for camphor causes a considerable rise of blood-pressure, even in deep anæsthesia in which the vascular nerve-centres are paralysed. Experiments with the isolated mammalian heart led to the discovery that there

was no pronounced action to be traced in the heart that was working regularly and well. On the other hand, when the heart, as may sometimes be the case in such experiments, does not get into proper working order, but only shows feeble, fluttering movements, the introduction of fluid containing camphor almost always causes the abnormal condition to give place to regular, powerful contractions (Seligmann and Gottlieb). A frog's heart that is partially paralysed by some poison is made to pulsate once more by camphor vapour. These experiments accord well with clinical experience, which teaches that camphor under normal conditions has little effect, but is a valuable remedy in cardiac weakness.

The **respiration** becomes slower with camphor, but at the same time each breath drawn is so much deeper that the respiratory volume per minute is increased. In fever, large doses of camphor *reduce the temperature.*

Local Action. Externally camphor produces on the unbroken skin redness and an irritation that may, if the drug is continued for some time, increase to inflammation. In the mouth it produces a burning, spicy taste, followed by salivation and a feeling of cold ; in the stomach, with small doses, a pleasant feeling of warmth in experienced, and with larger doses more marked symptoms of irritation. Camphor is mildly antiseptic ; it arrests the amœboid movement of the white blood-corpuscles and counteracts putrefaction and fermentation.

Absorption and Excretion. Camphor is absorbed both from the unbroken skin, from mucous membranes, and from the subcutaneous tissue ; but, owing to its feeble solubility in water, the absorption is subject to great irregularities. If injected, dissolved in oil, into the subcutaneous tissue, it is more easily and quickly taken up than from the intestinal canal. After very large doses, some is excreted unchanged through the lungs (odour of camphor in the expired air) ; the greater part, according to Schmiedeberg's and Meyer's investigations, after first being changed into the oxidation product campherol ($C_{10}H_{15}(OH)O$), is excreted through the kidneys as campho-glycuronic acid, which reduces Fehling's solution. The rapid formation of these non-poisonous compounds explains the transient nature of the action.

Ordinary camphor is dextro-rotatory. In a few volatile oils there is a form that possesses a corresponding lævo-rotation, while *artificial camphor*, which, after many unsuccessful attempts, has now been produced from turpentine oil, is optically inactive. Pharmacologically, all three forms may be regarded as equivalent.

Therapeutic Uses. Camphor is used as a *cardiac and respiratory stimulant in febrile diseases* and in cases of *narcotic poisoning.* In

all conditions of collapse it should be given as early as possible, and not be regarded as the last resource ; for when the circulation has become very weak the drug will not be absorbed in effectual quantities.

Formerly camphor was extensively employed in *pneumonia*, not only as a stimulant, but also, on the assumption of a specific action on the disease (the growth of the pneumococci ceases in a camphor solution of 1 in 10,000), in large doses from the very beginning of the illness. It is very doubtful whether this is of therapeutic value (*cf.* Optochine, p. 219).

Camphor is sometimes employed in *bronchitis* to promote the expectoration of the secretion. Intraperitoneal injections of camphor have been tried as a prophylactic and curative remedy for *peritonitis* after abdominal operations.

Camphor was of old considered to be an anaphrodisiac (" *camphora per nares, castrat odore mares* "). It still occasionally finds employment in *irritation of the urinary and sexual organs, e.g.* for *frequent micturition in cystitis*, and *painful erections in gonorrhœa.*

Externally camphor is employed as an ingredient in various popular liniments for inunction, or in solution for poultices in a great variety of ailments—*neuralgia, rheumatic pains, inflammation, contusions*, etc. A *too abundant secretion of milk* is diminished by the application of powdered camphor to the mammæ ; it is not impossible that this volatile substance, making its way into the gland, may have a paralysing effect upon the secreting cells, as also upon the white blood-corpuscles.

Camphoric acid, $C_{10}H_{16}O_4$, which is produced by the oxidation of camphor, has a stimulating action, according to Fujitani's investigations, upon the respiration, and raises the blood-pressure, but has little toxicity, and, unlike camphor, does not occasion convulsions. Even after moderate doses, the secretion of sweat is diminished or arrested. The cause of this is not known. There does not seem to be any peripheral influence on the glandular nerves similar to that of atropine. The action often begins somewhat slowly, but lasts longer than that of other anhidrotics. In man, too, camphoric acid shows itself to have little toxicity (daily doses of 6 grammes are tolerated without inconvenience).

Menthol

Menthol, or mint camphor, occurs in the common peppermint oil of *Mentha piperita*, but in far greater quantities in the volatile oil of the Chinese and Japanese *Mentha arvensis*, and has been a highly-prized drug for centuries in Eastern Asia, while its employment in Europe goes back only about fifty years.

Action. If the *skin* is rubbed with menthol a refreshing sensation of cold is at once perceptible, giving place, after 10 to 15 minutes, to slight pricking and burning. Goldscheider's explanation of the action is that menthol stimulates the nerves that perceive cold. The nerves that are susceptible to heat are also affected, for in places where the sensitiveness to heat is physiologically greater than that to cold the feeling of heat is predominant. For instance, in certain spots, such as the forehead and temples, the feeling at first is only one of cold ; this is due to the fact that the " cold nerves " are here in the majority. The feeling of cold is accompanied by hyperæsthesia to cold, so that bodies of an ordinary temperature placed on the spot treated feel abnormally cool. The change in the perception of temperature is accompanied by an anæsthetising, analgesic action, which only affects, however, the nerves lying just beneath the skin.

In alcoholic solution, menthol is powerfully *antiseptic*. It is far less poisonous than ordinary camphor, and on absorption has a less irritating and more paralysing action upon the central nervous system, especially the medulla oblongata. On frogs it has a curarine action. Menthol, like camphor, also causes a rise of the blood-pressure, and is excreted in the urine in combination with glycuronic acid.

Therapeutic Uses. Menthol in the form of the so-called *migraine pencils* is a favourite remedy for *migraine* and *face-ache*, especially supra-orbital neuralgia, in which it may often bring temporary relief. It is also applied externally to *allay itching*, and diminishes the secretion in *nasal catarrh*. Internally menthol, like camphor, is recommended for *pulmonary tuberculosis*, and appears, in most cases at any rate, to have a favourable effect on the appetite, and to diminish night sweats ; it is often beneficial in *cardialgia* and *vomiting*. Menthol is employed as an intestinal antiseptic in *summer diarrhœa*. Large doses sometimes prove very useful in obstinate *itching of the skin*.

Preparations and Doses

Camphora (B.P., U.S.P.), colourless, translucent masses of a tough consistency, and also in rectangular tablets, or pulverised masses. Soluble in about 700 parts of water, but dissolves very readily in alcohol, chloroform, fixed and volatile oils. *Dose*, 12—30 centigrms., 2—5 grs., by subcutaneous injection 6—20 centigrms., 1—3 grs. (B.P.) ; 20 centigrms., 3 grs., hypodermically 0·1 grm., 1½ grs. (U.S.P.). Camphor is prescribed either in the form of pills or as an emulsion, *e.g.* Camphor 1, Mucilag. Acaciæ 40, Aqua ad 200, 1 tablespoonful every 2 hours. In cases of serious collapse, 1 mil of 20 per cent. filtered and sterilised solution of camphor in olive oil is injected subcutaneously every ½ hour, say 4 times. In pneumonia very large doses are recommended, *e.g.* 10 mils (about 2 grms.

or 30 grs.) twice a day during the first few days. Larger doses are also on record.

Aqua Camphoræ (B.P., U.S.P.). *Dose*, 10 mils, 2½ fl. drs. A preparation of little activity, as camphor is difficult to dissolve in water.

Spiritus Camphoræ (B.P., U.S.P.), 10 per cent. *Dose*, 3—20 decimils, 5—30 mins. (B.P.); 1 mil, 15 mins. (U.S.P.). A favourite stimulant, and frequently taken to prevent "chill."

Linimentum Camphoræ (B.P.), *Linimentum Camphoræ et Saponis* (U.S.P.), 20 per cent. solution of camphor in olive or cotton-seed oil (not intended for hypodermic use). *Lin. Saponis* (U.S.P.), *Lin. Camphoræ Ammoniatum* (B.P.), *Lin. Chloroformi* (B.P., U.S.P.), *Lin. Belladonnæ* (B.P., U.S.P.) and *Lin. Aconiti* (B.P.), contain camphor combined with skin-irritant and analgesic constituents, and are employed as household remedies for inunction for pains of various kinds.

Tinctura Opii Camphorata (B.P., U.S.P.).

Tinctura Camphoræ Composita (see under "Opium," pp. 90 and 91).

Acidum Camphoricum (non-official), colourless crystals, slightly soluble in water and readily in alcohol. *Dose*, 1—2 grms., 15—30 grs., in the evening, 1 or 2 hours before the time when the sweating usually begins.

Oxycamphora (non-official) is another oxidation product of camphor, and differs from it, among other properties, by diminishing the irritability of the respiratory centre. Has been tried as an antidyspnœic, and is said sometimes to give relief in laboured breathing occasioned by pulmonary disease or disturbance of the circulation. Colourless crystals, soluble in alcohol. *Dose*, 50 centigrms., or about 8 grs., 2 or 3 times a day. As it does not keep well, it appears in commerce in a 50 per cent. alcoholic solution.

Menthol (B.P., U.S.P.), $C_{10}H_{19}OH$, colourless acicular crystals with an odour of peppermint, almost insoluble in water, freely soluble in alcohol, ether and fixed oils. *Dose*, 3—12 centigrms., ½—2 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.); externally, for itching, 2—10 per cent. solution in alcohol or in oil. In nasal catarrh powdered menthol mixed with talc (1 in 50) is used as snuff. Migraine pencils are of melted menthol, often mixed with camphor and thymol, moulded into sticks or conical pencils.

Addendum

Musk is a secretion found in a pouch situated between the navel and the sexual organs of the male musk-deer, *Moschus moschiferus*, which inhabits the mountain regions of Central Asia. The secretion contains a substance with a very strong odour, the chemical nature of which is unknown. Several plants, such as *Adoxa moschatellina* and *Malva moschata*, have an odour of musk, as also the white acicular crystals of trinitrobutyltoluol, $C_6H.(NO_3)_3.CH_3.C_4H_7$, which is produced synthetically and employed in perfumery under the name of artificial musk.

Musk had formerly a great reputation as the most powerful of all stimulants, and was prescribed as the last resource in collapse; but experimental investigations give no ground for ascribing to it a specially stimulating action, and it is now only very rarely employed, chiefly in bronchitis and broncho-pneumonia in childhood. Like many other substances with a strong odour, it was formerly often prescribed for hysterical fits. *Moschus* forms a dark brown, unctuous or granular, crumbling, greasy mass, very frequently adulterated.

23. THE PICROTOXIN GROUP (not official)

Picrotoxin is the most prominent representative of a group of non-nitrogenous, exceedingly poisonous and chemically little-known vegetable substances, which both in man and in all animals produce violent convulsions. Picrotoxin occurs in the fruits of *Anamirta cocculus* (*Menispermaceæ*), a woody climber growing in the East Indies. The *phytolaccotoxin* contained in *Phytolacca decandra* resembles picrotoxin in its action. The most important of the other substances belonging to the same group are *coriamyrtin*, which is found in *Coriaria myrtifolia* (*Coriariaceæ*, the countries surrounding the Mediterranean), and *cicutoxin*, the poisonous constituent in the umbelliferous plant *Cicuta virosa*, or water hemlock, a native of Northern Europe. The well-known ornamental shrub *Buxus sempervirens* (box) also contains a similar convulsive poison. *Digitaliresin* and *toxiresin*, decomposition products of the digitalis glycosides, have also allied actions, and, lastly, *samandarin*, a nitrogenous base in the cutaneous secretion of the salamander (Faust).

Picrotoxin

Action. *Cocculi fructus*, the so-called Indian berry, has repeatedly been found in beer, probably added for the purpose of increasing the bitter taste, and has occasioned several fatal cases of poisoning. Its employment as a fish-poison has also caused poisoning ; for this purpose the fruit, either powdered or in pills, is scattered over the water. The swimming-bladder of fish becomes filled with air, and they rise to the surface. The symptoms characteristic of the poisoning consist in exceedingly violent convulsions of very irregular appearance, principally in the extremities, but also tonic rigidity in the masseter, and brief attacks of tetanus, now episthotonic, now emprosthotonic. Animal experiments show that these convulsions are partly due to increased reflex irritability of the *spinal cord*, but that they chiefly have their origin in the *medulla oblongata*. Other symptoms of irritation of the latter also appear with regularity ; the *respiration* becomes frequent through stimulation of the respiratory centre, the *pulse* slow as a consequent of central vagus stimulation, and the *blood-pressure* rises, as the vessels are contracted because of similar action on the vasomotor centre.

In man, *brain symptoms* may be the most prominent, consisting first in restlessness, afterwards in unconsciousness ; and the convulsions do not appear until a short time before death. The action in all species of animals is in the main the same. The frog shows strange and peculiar characters : it passes through all kinds of odd, convulsive movements, such as twisting round, rolling and going backwards.

Therapeutic Uses. Picrotoxin has been tried, sometimes with encouraging results, for *chorea* and for *convulsions in children*, and seems,

contrary to what one would expect from the action described, sometimes to be useful in *epilepsy*. It may, however, cause decided ill effects, and must therefore be tried with great caution.

Cicutoxin

Cicutoxin acts slowly, as it is sparingly soluble and slowly absorbed; but when the absorption has once taken place, its action is, if possible, even more violent than that of picrotoxin. The large, hollow root of *Cicuta virosa*, which is divided into several compartments by horizontal septa, resembles celeriac, and is sometimes eaten by children. The toxic symptoms consist in vomiting, prolonged unconsciousness, and very violent convulsions, often ending in death.

Preparation

Picrotoxinum, $C_{30}H_{34}O_{13}$, colourless, acicular crystals with very bitter taste, soluble in water and in alcohol. *Dose*, 1—3 milligrms., $\frac{1}{60}$—$\frac{1}{20}$ gr., as pills, 2 or 3 times daily after meals.

24. THE DIGITOXIN GROUP (DIGITALIS)

A great number of peculiar vegetable substances are comprised within the group to which has been given the name of the digitoxin group, the distinguishing feature common to them all being a characteristic action on the heart. They are nearly all glycosides, several of them often occurring in the same plant, and being frequently accompanied by substances that are nearly related to the saponins.

The most important members of the digitoxin series occur in *Digitalis purpurea* and species of the family *Strophanthus*.

Digitalis, which shares with the poppy and the cinchona tree the reputation of being the most important of all medicinal plants, first became known in 1785 through the English physician William Withering, and before long was esteemed as one of the most indispensable of drugs. When the knowledge of the alkaloids and other powerfully-acting vegetable substances during the years 1820—1830 had begun to increase, the attention of investigators was turned to this plant, the strength of which, as clinical experience soon showed, might vary very considerably. A number of investigators, among whom Homolle, Quevenne and Nativelle stand first, succeeded in isolating various active principles, but arrived at different results. Many " digitalins " were by degrees produced, and much conflicting opinion existed when the foundation of our present knowledge of these difficult bodies was laid by Schmiedeberg (1875). Important works of recent

years are from the pen of Kiliani and Kraft. According to these investigators, the active substances consist of a number of glycosides, which to some extent are different in the leaves and seeds. The characteristic constituent of the seeds is *digitalin*, which is not easily soluble in water, while the leaves contain *digitoxin*, which is insoluble in water, but soluble in alcohol, and can be easily isolated in a pure, crystalline condition, and possesses the strongest action of all digitalis glycosides. Both in the leaves and the seeds there are, moreover, a number of therapeutically important glycosides that are soluble in water (*digitalein*, *gitalin*), which we have not yet succeeded in producing in a pure state ; several saponins are also present which do not possess the characteristic action on the heart.

Similar substances also occur in many other plants belonging to all kinds of families. Several of them, on account of their rapid and powerful action, are used by native tribes as arrow poisons, while others are ancient, half-forgotten diuretics, some of which have been once more taken into use since their relationship to digitalis was discovered. The following are the best known : the glycosides accompanied by a saponin-like body in *Scilla maritima*, which is said to have been used by the ancient Egyptians ; *convallamarin* in the flowers of the lily-of-the-valley, a popular Russian drug ; the little-known glycosides that give toxicity to the favourite pot plant, the *oleander ; adonidin* in species of Adonis, and the readily soluble *helleborein* in species of hellebore, both old-fashioned diuretics ; *antiarin* in the upas antiar, the arrow poison of the Borneo natives prepared from the sap of Antiaris toxicaria. Similar cardiac poisons are further said to occur in several of the ornamental bulbous plants, *e.g.* amaryllis and narcissus. They are also represented in the animal kingdom. The cutaneous secretion of the common toad (*Bufo vulgaris*) contains the cholesterine-like substance *bufotalin*, and the parotid secretion of the large tropical toad, *Bufo agua*, the crystalline *bufagin*, both substances possessing the action of digitalis (toads are comparatively immune to digitalis).

Action. The digitalis substances act upon the heart, the peripheral vessels and the central nervous system, and most of them have a more or less marked local irritant action.

The peculiar action on the **heart**, which is common to all these substances, and places them in a class by themselves, is first and best studied in the frog's heart, as this is more accessible to direct observation, and can be more easily examined when isolated than that of warm-blooded animals.

If the isolated heart of a frog is perfused with blood containing digitalin, or the animal is given one of the digitalis substances subcutaneously, a definite series of characteristic changes takes place. The first departure from the normal manner of working is that the heart-action becomes slower, the diastolic dilatation slightly increased, and the systole longer and more complete. The muscle-fibres are shortened more than normally, and at every

contraction the ventricle is emptied to its last drop, whereas in the ordinary way it contains a small residue of blood after the contraction. The result is that each systole forces an increased amount of blood out from the heart. Soon, however, the extent of the diastolic dilatation diminishes ; the heart is no longer completely relaxed, but during diastole remains in a half-contracted condition, and now, not being sufficiently filled, there is a decrease in the amplitude of the pulse-waves. Sooner or later there is alteration in the normal relation between auricle and ventricle (conduction disturbances) ; often the ventricle performs only one contraction while the auricles perform two. It is only the degree of shortening that the digitalis substances affect in the frog's heart ; the actual force, expressed by the height of a column of liquid that the heart is able to raise, is not increased.

In the next stage the contraction of the ventricles is still more decided. The heart is more imperfectly relaxed after each contraction, while at the same time the movements become irregular and " peristaltic " ; some muscle-fibres are shortened earlier and more than others, certain parts of the walls are relaxed while others are in full work, and sometimes the right and left halves of the ventricle are contracted alternately, so that the blood is thrown backwards and forwards within the heart, and only a small portion expelled into the aorta. At last the diastole is quite effaced, the empty ventricle is arrested in maximal systole and dies in that position. The auricles still pulsate, but cannot empty themselves into the ventricle, and at last become exhausted and stop, dilated with blood. With all this the general condition of the animal does not suffer much ; when released it jumps about briskly, quite normal in appearance, a proof that the seat of action is not the nervous system. It is only after the lapse of some time that death of the entire organism takes place as a necessary consequence of the arrest of the circulation. Loewi, in experiments with the isolated heart, found that the presence of calcium is of fundamental importance ; in the absence of this element, the typical action of digitalis was not produced.

In the isolated heart of a mammal, the same muscular action is found as in the frog's heart. As soon as the digitalis blood circulates in the coronary arteries, the volume of the heart-beats begins to increase, mainly by reason of the more perfect systole, but partly, too, in consequence of the increased diastole. After some time the diastole gradually decreases, the systole becomes permanent, and the heart comes to a standstill in a firmly contracted condition. The initial stage of the digitalis action is very favourable to the work of the heart, as each contraction conveys more than the normal amount of blood. The experiments give a

good idea of the action on the heart directly, but the influence of the central vagus-stimulation (slow pulse) does not, of course, appear. In the living animal no systolic standstill occurs, as death takes place at an earlier stage.

The digitalis action is a consequence of a reaction taking place between cell-constituents and the glycosides. That a part of these —though only very little—is fixed is apparent from experiments which show that a strophanthin solution is weakened, *i.e.* that some of its active substance is kept back, when it passes through a number of frogs' hearts (Straub).

In *man* the *changes in circulation* brought about by digitalis may be divided into the *therapeutic stage*, during which the work of the heart is increased, and the *toxic stage*, during which it is reduced ; and between these two a *transition period* often occurs. These different stages will be more fully discussed below.

1. *The therapeutic digitalis stage* is one of the most valuable actions known in medicine. Its characteristic features are a *slow pulse* and an *increase in the amount of blood forced out of the heart*, two quite different actions, independent of one another, and mutually antagonistic, but together extremely advantageous. The *slowness of the pulse* arises from the stimulation by the digitalis of the cardio-inhibitory nerves. The *increased output* is due to the strengthened systole. The shortening of both the muscles in the walls and the papillary muscles is greater ; that is to say, the systole is more perfect. The cavities of the heart, especially the muscular ventricles, are emptied better at each contraction, each systole sends out an increased amount of blood from the heart, the entire arterial system is filled, and at the same time the pressure falls in the veins, which find an easy outlet in the emptied heart. The *slowness of the pulse* acts, within certain limitations, in the same direction, for during the prolonged diastole the heart gains time to be entirely filled. It is easy to see, however, that only a moderate diminution in the frequency of the pulse is profitable, for only that can be compensated for by the more perfect systole. If the pulse becomes too slow, the output of blood from the heart, which is the product of the output of each beat multiplied by the number of beats per minute, will diminish, and the blood-pressure fall, notwithstanding the complete emptying of the heart. *Thus the great essential of the first stage is the filling of the arterial system and unloading of the venous system, produced by a more complete systole combined with a moderately increased relaxation in, and lengthening of, the diastole.* Improvement in the circulation is dependent upon a suitable proportion between these two actions. Such a change in the distribution of blood can only take place, however, when the conditions

have previously become prejudicial to the arterial system. The normal circulation cannot be improved by digitalis.

2. *The transition stage.* If larger doses are given, or administration of the drug is continued longer than is necessary for obtaining the above-described action, the pulse-frequency decreases so greatly—in man, for instance, to 40—that the output of blood diminishes, and the pressure falls, even if each contraction still delivers a large quantity of blood ; and frequently the systole now begins to be less perfect. It is a characteristic sign that so-called extra-systoles occur. These beats originate in an ectopic focus more or less remote from the sino-auricular node. Moreover, following over-dosage with digitalis, they occur regularly, *i.e.* every other beat is an extra systole, and thus coupling of the pulse is produced. This is an important sign, because it is one of the earliest and most frequently occurring indications of poisoning. Of more serious significance is the so-called pulsus alternans : alternate strong and weak beats are to be felt at the radial pulse. As a rule the transition stage in man is clear, but sometimes it may be very brief, and the therapeutic stage then passes directly into the toxic stage.

3. *The toxic stage* begins with a rapid pulse. This cannot, as was formerly supposed, be due to paralysis of the vagus (for it also occurs when the heart has been previously atropinised), but is probably caused by an increase in the irritability of the heart-muscle, an increase so great that the muscle can no longer be held in check by the inhibitory mechanism. Soon a number of irregularities appear indicating injury to the conduction system ; high and low pulse-waves alternate : two, three, or more beats may follow so quickly one upon another that the heart is not filled in the intervals ; little blood is driven out of the heart, notwithstanding the rapidity of the pulse ; the pressure falls greatly, ventricles and auricles work out of time, and after a period of delirium cordis of varying length the heart comes to a standstill in diastole.

Peripheral Vessels. In the first stage of the digitalis action a rise of blood-pressure sometimes, but by no means invariably, occurs. Whether this rise, which is principally seen when the pressure has previously been low, is dependent on the work of the heart or on the contraction of the arterioles has been a much-debated question. As regards the higher animals, the decision is beset with great difficulties, because conclusions must be drawn, not from direct observation of the isolated heart, but from changes in the quality of the pulse and in the blood-pressure, conditions in which both the vessels and the heart play a part. In order to bring out the influence of the heart quite clearly, it

must be placed under conditions in which its work may be gauged independently of the changes in the vessels. This has now been done in various ways. Bock has succeeded in making the heart work against a constant resistance by ligaturing all the arteries from the aorta with the exception of the one carotid ; from this a system of glass tubes conveys the blood to the jugular vein ; the entire pulmonary circulation is left intact, as also the coronary circulation. The arterial portion of the systemic circulation is thus replaced by unyielding tubes, and every change occurring in pulse or blood-pressure can then only originate in changes in the work of the heart itself. When a soluble digitalis preparation was injected into an animal prepared in this way, the blood-pressure immediately rose. The rise in strongly working hearts was not considerable ; in weak, exhausted hearts it was very great, *e.g.* from 29 to 80 mm. of mercury. Certain types of heart-failure in the human subject respond remarkably well to digitalisation and the cardiac output is undoubtedly increased. Although in these circumstances there may be a tendency for the blood-pressure to rise, reflex adjustments occur rapidly and prevent important fluctuations.

More recent investigations show, however, that the digitalis action also affects the vessels. According to animal experiments by Gottlieb and Magnus, the intestinal arteries in particular are contracted, while the renal arteries expand (Loewi). The arterial contraction in the splanchnic region begins simultaneously with the action on the heart. *In heart patients, however, the improvement in the work of the heart itself is the decisive point.* The calibre of the coronary arteries is scarcely changed by therapeutic doses of the drug, nor, according to Mellin and Tigerstedt, is the pressure in the pulmonary arteries affected.

Diuretic Action. From the very first digitalis and many of the plants belonging to the same pharmacological group were employed as diuretics in diseases associated with dropsy, without any thought of the action on the heart. Their diuretic action, however (except that of scilla), is dependent on their influence on abnormal circulatory conditions. In the healthy person these drugs cause little or no increase in the secretion of urine, and are diuretics only when there is venous congestion in the kidneys ; they act by filling the renal arteries and removing the venous stasis. This last factor is of importance, not only as regards the renal veins, but also the other veins, for the lower the venous pressure the more easily do the veins take up the liquid from surrounding œdematous tissue.

The Central Nervous System. With the exception of the vaso-motor centre and the vagus centre, the central nervous

system does not seem to be affected by therapeutic doses of digitalis. The vomiting that occurs after continued use seems, however, to be of central origin. After large doses other cerebral symptoms also appear, such as noises in the ears, headache, giddiness, delirium, and, in fatal poisoning, convulsions. The dyspeptic troubles that even the first small doses may occasion in sensitive subjects must be ascribed to the local action mentioned below.

During the therapeutic stage the **temperature** rises a little (0·5° C.) on the surface of the body, and falls slightly within it, both changes being consequences of the diversion of the current of blood to the external parts of the body, which are exposed to the air. More considerable falls of temperature only follow large doses which threaten to poison the heart.

Local Action. The greater number of the bodies belonging to the digitalis series have a bitter, burning taste and local irritant action, which is sometimes followed by paralysis of the sensory nerve-endings. Among the constituents occurring in *Digitalis purpurea*, digitoxin is the most irritating, and produces large abscesses when injected subcutaneously.

Digitalis has a **cumulative action,** the cause of which is supposed to be that the glycosides become very firmly fixed in those elements of the heart that are receptive to the poison, and are slowly eliminated. To a certain extent the cumulation is an advantageous property which ensures a prolonged action. What the physician understands by cumulative action is, however, a toxic condition which reveals itself, after the employment of therapeutic doses for some time, by the sudden appearance of the previously described transition-stage (very slow, sometimes irregular, pulse) or the toxic stage (very rapid, irregular pulse), while at the same time there is generally also headache, obstinate nausea and vomiting. In practice, a cumulative action amounting to digitalis poisoning is seldom seen, and appears to be feared more than it deserves. A. Fränkel's animal experiments show that the doses that are just sufficient to elicit definite action (stronger heart-beats and slow pulse) may be given week after week without danger. It is only when these doses are exceeded that toxic symptoms make their appearance after a few days. In man, too (continuous digitalis treatment will be mentioned later), small doses may be given during an almost unlimited period without a trace of cumulative action.

In practice it is a circumstance of some importance that the various digitalis and allied glycosides behave in a variety of ways as regards cumulation. This is shown with special clearness in experiments by Hatcher, who gave cats first a certain fraction (pre-dose) of the minimal lethal dose

(M.L.D.), and then tried at various times what supplementary dose (final dose) was required to kill them. If pre-dose + supplementary dose = the minimal lethal dose, then none of the first dose had disappeared in the interval; but if the supplementary dose had to be increased, then a corresponding part of the pre-dose had disappeared. The results are shown in the following table :—

Substance.	Preliminary dose in percentage of M.L.D.	Percentage of preliminary dose still present after			
		24 hrs.	5 × 24 hrs.	10 × 24 hrs.	20 × 24 hrs.
g-Strophanthin .	76	24	0	—	—
Digitoxin . .	55	52	46	38	17
Digitalein . .	65	55	15	—	—
Digitalis leaves .	66	62	46	25	—

The table shows in the clearest manner possible, and in accordance with clinical experience, the great difference between digitalis on the one hand and strophanthus on the other, and also shows that it is above all digitoxin that gives to the digitalis leaves their prolonged action. The figures found in the case of the cat cannot, of course, be applied directly to the human heart, but it is probable that the relative times are very similar.

Therapeutic Uses. It has been explained that the therapeutic importance of the digitalis action lies in its filling of the arterial system and emptying of the veins. Hence it follows that *all disturbance of the circulation that causes diminished filling of the arteries and accumulation of blood in the venous part of the circulation is a general indication for its use.* An abnormal distribution of blood such as this occurs in the last stage with almost every condition in which there is an obstacle to the free course of the blood, whether the obstacle is within or outside the heart. Digitalis works best, however, in the purely cardiac disturbances of circulation, and less surely when the obstacle to the circulation is situated in other organs, such as the lungs or kidneys, and in which the heart suffers secondarily.

The most important field for the use of digitalis is in failure of cardiac compensation due to myocardial insufficiency which is frequently, but not invariably, associated with valvular disease. Among the earliest indications of decompensation are undue shortness of breath on exertion and œdema of the ankles. Digitalis is used here, no matter what valves may be involved, nor whether the disease consists in regurgitation or stenosis, or both together, so long as the compensation is inadequate; but it is contra-indicated when it is satisfactory, or when there is supercompensation. Thus the indications are not dependent on the particular nature or seat of the valvular disease, but on the relation between the filling of the arteries and that of the veins. The lengthening

and increase of the diastole draws the blood from the over-filled veins into the heart. The prolonged and powerful systole abolishes the stasis in the heart itself, and forces the blood out even through constricted orifices; regurgitation through incompetent valves decreases, as the valves close better when the transverse section of the orifice is diminished by a more complete ventricular contraction. If the incompetence is only relative, it may be altogether removed by reducing the dilatation of the heart.

The results are very frequently of surprisingly long duration; the compensation brought about by a few days of digitalis treatment may last for weeks, months or even years. The explanation is that the digitalis action interferes with a vicious circle. The circulation has become bad because the heart is weak, and the heart-weakness in its turn is increased by the bad circulation, for the organ whose nutrition suffers first of all from the overfilling of the heart, and the arterial anæmia is the heart itself. This chain, in which cause and effect continually and mutually aggravate one another, is broken by digitalis. When the heart is emptied, the overburdening against which it has worked with frequent but feeble contractions is removed; the great and continuous pressure that has rested on the walls is relieved; the improved nutrition which follows on the transference of the blood from the veins to the arteries benefits the heart as well as other organs, and occasions its hypertrophy, so that its muscle can hold its own against valvular disease, perhaps for a long time. So long as readjustment is possible by hypertrophy digitalis is superfluous.

Formerly it was believed that digitalis was contra-indicated in the presence of aortic regurgitation, the assumption being that a prolongation of diastole must inevitably embarrass still further the action of the left ventricle. In practice, however, it is found that digitalis often increases the cardiac reserve in patients suffering from aortic regurgitation.

Attempts have recently been made by the aid of a finer analysis of the arhythmia occurring in diseases of the heart, and of improved knowledge of the action of digitalis on the conductile tissue, to define more precise indications and contra-indications for the exhibition of this drug. A few of the more important results may be briefly mentioned.

The origin of the heart-beat is in the sinus venosus near the venous orifices in the right auricle. The regular impulses initiated here are transmitted to the auricles and thence by the bundle of His to the ventricles, thus determining the normal rhythm of the heart. The complete cardiac cycle is thus divided into three phases, separated by short intervals (see Fig. 14). The irregu-

larity in which the most brilliant results are obtained with digitalis is the so-called *auricular fibrillation*, which frequently occurs in chronic diseases of the heart, especially mitral disease (Mackenzie). The auricle may almost be considered as paralysed, and does not perform the normal contractions, but only irregular, rapid, fibrillary movements. The ventricle receives irregular and far too frequent impulses, and although it responds to only a fraction of these stimuli its action is totally irregular in time and force. Under the influence of digitalis, the ventricular rate, which is often about 130 per minute, may be approximately halved. Simultaneously, a greater degree of muscular relaxation takes place in diastole. Thus the heart is allowed to fill more completely, and in accordance with the physiological rule stronger contractions occur. Digitalis also increases the force of systole

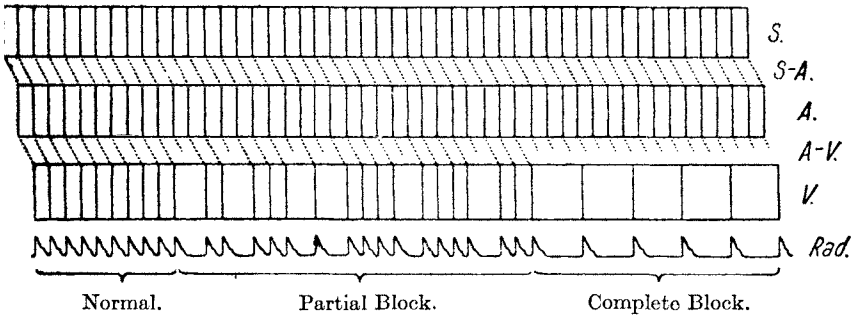


FIG. 14.—Diagram representing complete and partial heart-block. Conduction in dotted lines. *S.* Sinus. *S.-A.* Sinu-auricular conduction. *A.* Auricular contraction. *A.-V.* Auriculo-ventricular conduction. *V.* Ventricular contraction. *Rad.* Radial pulse.

by directly stimulating the heart-muscle. The combined effects on the conducting system and myocardium are particularly beneficial in the treatment of cardiac failure associated with auricular fibrillation ; symptoms and signs usually disappear in the course of 24—48 hours despite the persistence of fibrillation of the auricles.

Disturbances in the co-ordination, through the bundle of His, between auricle and ventricle, are also of special interest. If this conduction is quite interrupted, the normal impulses do not reach the ventricle, which begins to beat at its own automatic rhythm, *i.e.* in man about 30 to 40 contractions per minute. In this way there is a quickly-working auricle and a slowly-working ventricle. This condition is called *complete heart-block*. If the auriculo-ventricular bundle is not completely blocked, the ventricular movements will still be directed from the auricle ; but now and again the conduction fails, this being revealed by the lengthen-

ing of the interval between the auricular and ventricular contractions, or by the absence of one or more ventricular contractions, and constituting *incomplete* or *partial block* (Fig. 14). The treatment in such conditions must be conducted with judgment. Digitalis, as already stated, has an inhibitory action on the conductivity of the bundle of His, and in partial block may still further increase the lack of co-ordination. Nevertheless, in the presence of symptoms of cardiac insufficiency digitalis may be tried cautiously. Improvement not infrequently occurs because the beneficial effect of the drug on the heart-muscle in systole far outweighs the supposed disadvantages of an increased degree of heart-block. A patient may live in comparative well-being for many years with a complete block, and there is then no reason for giving digitalis. Sooner or later, however, symptoms of cardiac failure will occur, and sometimes under these conditions both digitalis and strophanthus induce stronger contractions in the automatically beating ventricle. Thus, the idio-ventricular rhythm may be unchanged at about 30 beats per minute while dropsy, dyspnœa and other evidence of cardiac failure steadily disappear (Mackenzie).

Premature beats are usually unaffected by digitalis. Occasionally, this irregularity heralds the onset of cardiac failure in chronic myocarditis and the employment of digitalis in these circumstances is justifiable. Paroxysmal tachycardia is a condition closely allied to premature beats and fleeting attacks of the disorder are not benefited by drugs of the digitalis series. If paroxysmal tachycardia lasts several days and signs of congestive failure appear, a large dose of digitalis, *e.g.* 2—3 fluid drachms of the tincture, often results in the resumption of the normal rhythm and the rapid disappearance of manifestations of cardiac failure.

In the myocardial weakness associated with chronic bronchitis and *emphysema* digitalis is rarely of much value. It must be remembered, however, that in these circumstances dyspnœa is often mainly pulmonary in origin. At a later stage, when œdema of the ankles occurs, digitalis may have a favourable action.

The diseases so far mentioned are, as a rule, associated with low arterial tension. Digitalis may also prove useful, however, when the heart is exhausted by working against high pressure, as in *arterio-sclerosis* and in chronic renal disease. Even in advanced stages of renal disease, digitalis may be tried ; but the result is often disappointing, especially when the heart is the seat of fibroid changes which render it incapable of further exertion.

For *cardiac weakness during acute febrile diseases*, digitalis is often prescribed. Recent observations tend to show that the

routine use of digitalis in pneumonia does not improve the prognosis. At the same time, drugs of the digitalis series can be used with good effect in individual cases should auricular fibrillation develop in the course of the disease. In *tachycardia*, which occurs at intervals, digitalis is nearly always without effect, and in *nervous palpitations* it is valueless. In the treatment of *beri-beri* digitalis is a very valuable remedy, often removing the cardiac symptoms and the œdema. In acute cases which are brought for treatment with cardiac failure already far advanced, this and all other drugs are useless.

Contra-indications. The first criterion for the action is that the heart shall be in a condition to perform increased work. Digitalis is therefore often useless when the *muscle is greatly degenerated*, but should, nevertheless, in most cases be given a trial, for if the muscle should prove to be equal to the increased demand upon it, and the circulation is improved, it is the most

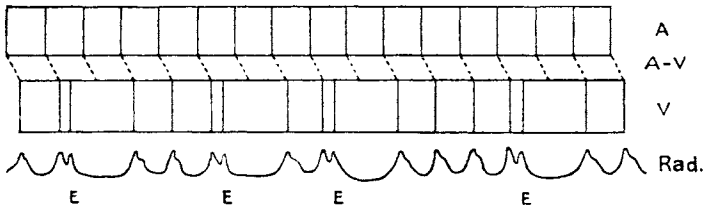


FIG. 15.—Diagram representing extra-systole. Conduction in dotted lines. *A.* Auricular contractions. *A.-V.* Auriculo-ventricular conduction. *V.* Ventricular contractions. *Rad.* Radial pulse. *E.* Extra-systole. This is followed, as in the normal heart-beat, by a refractory period, and therefore the ventricle does not contract with the first impulse from the auricle.

effectual means of preventing further degeneration. Attempts should first be made to remove *gastric disturbances*, if they are not symptoms of bad circulation, in which case digitalis is the best treatment. In order to avoid the irritant effects of digitalis upon a congested gastric mucosa, the drug may be administered rectally, the tincture being mixed with 2 or 3 ounces of normal saline for this purpose. *Albuminuria* forms no contra-indication. If the pulse becomes too slow (transition-stage), the employment of digitalis must be immediately stopped; and this applies even more to patients in whom a rapid pulse and other symptoms of poisoning proclaim the toxic stage. In these cases, as in the digitalis treatment of cases of valvular disease, it is of the greatest importance that the heart shall be spared by keeping the patient in bed, and that all muscular exertion, or sudden change to a sitting or standing posture, shall be avoided, as collapse and death may result.

Mode of Prescribing. The way in which digitalis is usually

prescribed in cardiac failure is to give for some days doses corresponding with 0·30—1·00 gramme of the leaves daily, 2—3 grammes in all. The effect does not appear until after 24 to 48 hours. If no result is obtained with these quantities it is useless to continue, and there is risk of poisoning. After a short time a fresh attempt may be made. Many cases react as if the digitalis were taking effect, but the action is brief, and dyspnœa, œdema, and the other symptoms of cardiac failure, reappear after 1—2 weeks ; when the treatment is resumed, there is again a short period of improvement. In such cases the *continuous digitalis treatment* is often beneficial ; when the compensation or improvement has begun, daily doses of 0·05—0·20 gramme, *i.e.* the smallest doses that prove capable of maintaining the action, are given continuously. The most frequent obstacles to the continuation of the treatment for an indefinite time are anorexia, nausea and diarrhœa. Cumulative action, even after continuous employment for years, is less to be feared than was formerly supposed, provided that the smallest effective doses are employed, always assuming, of course, that the patient's general health and the condition of his heart are under constant observation.

Remarks on the Preparations. Digitalis-leaves contain, according to Straub, about 1 per cent. of active glycosides. They are sometimes employed in the form of an *infusion*, which contains only very little of the insoluble *digitoxin*. Experience has shown that the preparation is good, but does not keep well. For this reason the fresh infusion of digitalis (B.P.) must be used within 12 hours of preparation. The powdered leaves act rather more powerfully than the infusion, as the glycosides are drawn out better in the intestinal canal than in the pharmacy. The *tincture* is also an efficient preparation, as the active constituents are soluble in alcohol.

It is a disadvantage that the strength of digitalis-leaves varies so much, both according to the locality in which the plant grows and still more to the care with which it is stored ; their activity may vary within the limits 1—5. For many years attempts to overcome this uncertainty in the dose of one of the most important of all drugs had no marked success. A sufficiently accurate estimation of pharmacological activity can, however, be made by the process of biological assay. The international unit is the activity of 0·08 gramme of the standard digitalis powder. Intravenous injections of a digitalis preparation are given to animals and the amount required to arrest the heart in systole is noted. The result is expressed as a comparison with the effects of the standard powder. Formerly, frogs were largely employed for the purpose of assay, but in recent years cats have been used for

the official estimation. General anæsthesia and artificial respiration are maintained throughout the test. One milligramme of 10 per cent. standard tincture contains 1 cat unit, *i.e.* 1 milligramme given intravenously arrests the action of the heart in a cat weighing 1 kilogramme.

Digitalin (Nativelle) in " granules " is one of several elegant preparations which have proved satisfactory in practice (see Preparations and Doses). Subcutaneous and intramuscular injection of the digitalis glycosides is an unreliable method of administration, as they are partly destroyed locally and absorption is irregular.

These remarks concerning action and use are applicable to the entire digitalis group of plants, but more especially to *Digitalis purpurea*. The other plants of therapeutic importance belonging to the group will be mentioned now.

Strophanthus

Many species of *Strophanthus* have presumably been employed from time immemorial as arrow-poisons in Africa and the Malay Archipelago. In Europe they first became known from Livingstone's travels. At the present time the seeds of *S. Kombé* are official in the British Pharmacopœia. From these Fraser, as early as 1870, isolated an amorphous glycoside, and Heffter later a crystalline one. An amorphous strophanthin occurs also in *S. hispidus*. These strophanthus glycosides are nearly related to one another, and exceedingly active. The third species is *S. gratus*, from which, in 1888, Arnaud produced the very crystalline ouabain, subsequently more carefully examined by Thoms, and called gratus-strophanthin. It acts upon the heart in the same way as, but more feebly than, the above-mentioned glycosides.

The *indications* for use are the same as for digitalis, which, however, is a far more certain drug, has a more lasting action, and cannot be replaced by strophanthus, although there may be cases which react better to the latter. The principal advantage of strophanthus lies in its more rapid action, which may make it useful in *heart-disease*, where it may be used to begin treatment which should be followed by digitalis. The quickly appearing action is also advantageous in the *heart-weakness of febrile diseases*, *e.g.* in auricular fibrillation occurring as a complication of pneumonia.

In heart-disease strophanthin is also employed for intravenous injections, and may even improve the pulse in the course of a few minutes. This method seems especially suitable in particularly

threatening cases of heart-weakness, in which the physician dare not wait for the slower results of oral administration. When the heart is already partly digitalised, however, strophanthin is contra-indicated.

Scilla

Scilla was formerly a much-esteemed remedy for dropsy. Its action upon the heart is similar to that of digitalis, but, probably owing to its action on the renal epithelium, it is more diuretic, and, moreover, irritates the stomach, so that vomiting is the invariable result of large doses. Like other emetics, scilla is employed as an *expectorant*, especially in the *bronchitis of children*. Of late its use in heart-disease has very much declined, but it is still worthy of attention in cases in which pathological accumulations of fluid are a prominent feature. Gross disease of the kidneys forbids its employment. The well-known Guy's pill contains equal parts of digitalis-leaf, squill and mercury pill.

Preparations and Doses

Digitalis Folia (B.P.), **Digitalis** (U.S.P.), the dried leaves of *D. purpurea*, foxglove, family *Scrophulariaceæ*, growing wild in Western Europe. The leaves are large, as much as 30 centimetres in length and 15 centimetres in width, ovate or ovate-lanceolate, crenate, gradually contracting at the base into winged petioles, the pale under-surface densely pubescent. **Digitalis Pulverata** (B.P., U.S.P.), a preparation standardised biologically (see text), and strength is expressed as cat units (B.P.) or frog units (U.S.P.). For technique employed in carrying out biological assay, the pharmacopœias should be consulted. *Doses*, 0·03—0·1 grm., ½—1½ grs.; single doses, 0·2—0·6 grm., 3—10 grs. (B.P.); 0·1 grm., 1½ grs. (U.S.P.).

Infusum Digitalis Recens (B.P.). 1 mil of fresh infusion is intended to possess 0·05 unit of activity, and in 4 fluid ounces 6 units of activity. Its strength is one-twentieth that of the tincture. The infusion should be used within 12 hours of its preparation. There is no official concentrated infusion of digitalis. *Dose*, 6—20 mils, 90—300 mins.; single doses, 30—120 mils, 1—4 fl. oz.

Tinctura Digitalis (B.P., U.S.P.), 1 mil possesses 1 unit of activity. *Dose*, 3—10 decimils, 5—15 mins.; single doses, 2—6 mils, 30—90 mins. (B.P.); 1 mil, 15 mins. (U.S.P.).

Fluidextractum Digitalis (U.S.P.). *Dose*, 0·05 mil, 1 min.

Unofficial Preparations of Digitalis

Digitoxinum Crystallisatum, $C_{34}H_{54}O_{11}$, colourless crystals soluble in alcohol, insoluble in water. 0·1—0·25 milligrm., $\frac{1}{600}$—$\frac{1}{250}$ gr. *per dosem*, up to 1 milligrm., $\frac{1}{60}$ gr., *per diem*. It is advisable after each milligramme to make a pause of a few days.

Digipuratum contains the glycosides in the form of tannates. One tablet answers to 10 centigrms. of *Dig. Fol.*

Digalenum, transparent, soluble, probably containing the glycosides that are soluble in water. 1 mil, 15 mins., several times daily; the same dose for use intravenously.

Strophanthus (B.P., U.S.P.), the seeds of *S. Kombé*, family *Apocynaceæ*, a woody climber, native of tropical Africa.

Tinctura Strophanthi (B.P.). Potency assayed biologically. *Dose*, 12—30 centimils, 2—5 mins.

Strophanthinum (B.P., U.S.P.), a glycoside or mixture of the glycosides of *S. Kombé*. A white or yellowish white powder, very soluble in water. *Dose*, ¼—1 milligrm., $\frac{1}{240}$—$\frac{1}{60}$ gr. (B.P.); ½ milligrm., $\frac{1}{120}$ gr. (U.S.P.). It is better to begin with ½ milligrm. Intravenous injections should not be employed while the patient is under the influence of other preparations of digitalis or strophanthus.

Ouabainum, G-Strophanthinum Crystallisatum, from *S. gratus*, colourless, square tablets, soluble in 100 parts of water. Intravenous up to ½ milligrm., $\frac{1}{120}$ gr. It is used as a standard for assaying the potency of strophanthin.

Scilla (B.P., U.S.P.), squill, the dried, fleshy inner scales of the bulb of *Urginea maritima* (*U. Scilla*), family *Liliaceæ*, growing wild in the countries surrounding the Mediterranean. *Dose*, 6—20 centigrms., 1—3 grs. (B.P.); 0·1 grm., 1½ grs. (U.S.P.). Prescribed in powders or pills as a diuretic.

Tinctura Scillæ (B.P., 10 per cent.; U.S.P., 10 per cent.). *Dose*, 3—20 decimils, 5—30 mins. (B.P.); 1 mil, 15 mins. (U.S.P.).

Acetum Scillæ (B.P., U.S.P.), vinegar of squill, is an unpractical preparation, as the acid diminishes the activity. *Dose*, 0·6—2 mils, 10—30 mins.

Syrupus Scillæ (B.P., U.S.P.). *Dose*, 2—4 mils, ½—1 fl. dr. (B.P.); 2 mils, 30 mins. (U.S.P.).

Oxymel Scillæ (B.P.). *Dose* as above. Prescribed for children.

The last two preparations are used as expectorants in bronchitis.

The root of *Apocynum cannabinum*, Canadian hemp, has the characteristic heart-action, but is more diuretic and, unfortunately, also more irritating to the stomach than digitalis (nausea). The *fluid extract* is employed in doses of 5—15 mins. A recently produced glycoside, related to strophanthin, *Cymarinum*, sometimes acts very strongly as a diuretic in heart-disease with dropsy. It is given by the mouth in doses of 0·3 milligrm., $\frac{1}{200}$ gr., *per diem* 1—2 milligrms., $\frac{1}{60}$—$\frac{1}{30}$ gr.; intramuscularly 0·3—1 milligrm. once a day for a few days in succession.

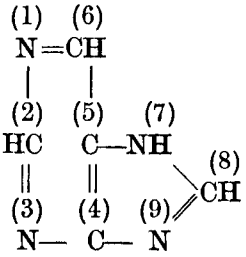
Convallaria. The rhizome of the lily-of-the-valley has been tried as a 2—3 per cent. infusion for heart-diseases, 1 tablespoonful several times a day. *Adonis vernalis* is used in the same way.

Digoxin is a glycoside obtained from the leaves of *Digitalis lanata*. The effects of digitalisation become apparent within 10 minutes of intravenous injection of ½—1 milligrm. of this active principle and reach a maximum in 1—2 hours. It is specially suitable for use in severe congestive cardiac failure, being preferable to strophanthin. Digoxin, being a pure glycoside, can be standardised by chemical methods. For preparations and doses special literature should be consulted.

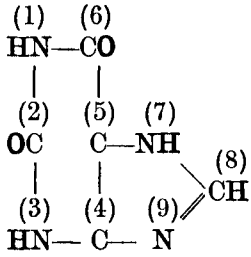
25. PURINE DERIVATIVES (THE CAFFEINE GROUP)

Caffeine and the other purine derivatives are worthy of interest both as valuable drugs and because similar compounds

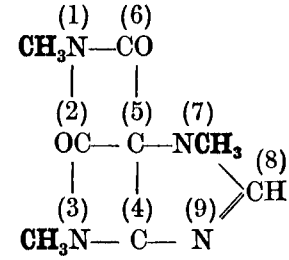
occur in the animal organism as the result of nitrogenous metabolism ; in particular xanthine and uric acid should be mentioned. The constitution of these bodies has been determined in a number of famous researches by Emil Fischer, who gives their constitution by reference to a nucleus called *purine*, of which the formula is given below. A great many other bodies originate from purine by the entrance of O or NH_3 at the places indicated by the even numbers (2, 4, 6, 8), while the alkyl radicals CH_3, C_2H_5, etc., enter at the odd numbers.



Purine.



2, 6. Dioxypurine = xanthine.



1, 3, 7. Trimethylxanthine = caffeine.

It will be seen from the above formulæ that caffeine is trimethylxanthine. According to the different places of the methyl groups, there may exist three different dimethylxanthines, which are known as *theobromine* (3, 7, dimethylxanthine), *theophylline* (1, 3, dimethylxanthine), and *paraxanthine* (1, 7, dimethylxanthine).

Action. The action of **caffeine** affects the central nervous system, the striated muscles, the heart and the kidneys.

Caffeine acts as a stimulant upon the **central nervous system.** In man small doses (0·10—0·20 gramme) are exhilarating and prevent sleep, an action which is utilised in everyday life, in which beverages containing caffeine are preferably drunk in the morning in order to drive away the remnants of the night's sleepiness, and after the heavier meals in order to combat the drowsiness that accompanies the process of digestion. According to Kraepelin, coffee and tea facilitate the association of ideas and the reception of sensory impressions. They thus act upon the very same psychical functions as alcohol, but in the opposite direction, a circumstance that has long been empirically recognised and utilised. Large doses of caffeine (0·50—1·00 gramme) induce, in a healthy subject, a frequent, hard pulse, restlessness, excitement and anxiety, accompanied by palpitations, noises in the ears, flickers of light, intoxication, delirium and tremor that may pass into convulsions. Whereas in man it is principally the brain that is affected by caffeine, in animals the spinal cord is the

part of the central nervous system that is chiefly attacked. The reflex irritability is increased ; convulsions occur, and after large doses violent tetanus. Death is caused by asphyxia during a fit of convulsions (arrest in inspiratory position), or by subsequent central paralysis.

The contractility of the **striated muscles** is increased, especially during fatigue. This is due to the central action and to direct action upon the contractile substance, for by direct electrical stimulation the contractility is also increased. That a reaction really takes place between caffeine and muscular tissue is evident from the fact that caffeine *in vitro* causes the fluid contents of the sarcolemma to coagulate. When freshly-excised, still living muscular fibrils are placed in a weak caffeine solution, they instantly become shorter, lose their structure, and stiffen as in boiling water. The same action can be traced in the living animal. If a few drops of caffeine solution are injected into the lymph-sacs surrounding the muscles of the leg or thigh of a frog (*Rana temporaria*), the muscles stiffen as the solution reaches them, the limb is fixed in the position in which it was held during the injection, and on being released the animal jumps about with a stiff leg. If quite small quantities of a very dilute solution are injected, the muscular action appears after absorption in a less dramatic but more useful manner, as the following easily-performed experiment shows. A gastrocnemius muscle is prepared in such a way that the Achilles tendon is free, while above the muscle remains attached and retains its normal blood-supply. Various weights are then fastened to the tendon, and the muscle is made to contract by an induction current. By a few experiments the absolute strength of the muscle can thus be determined, that is to say, the weight that is just sufficient to prevent contraction. In the normal frog's gastrocnemius this is 600—800 grammes. If the muscle is now carefully replaced and a very small quantity of caffeine injected somewhere into the animal, and the absolute strength is then once more determined, it will be seen that the muscle, far from being exhausted by its previous exertions, is capable of lifting about double the weight (Dreser).

The **circulation** is affected in a complex manner. The results obtained by various investigators (Hedbom, Santesson, Bock, Cushny, Sollmann) may be briefly summed up as follows : Caffeine increases the absolute strength of the heart as of the skeletal muscles, so that the heart is enabled to overcome greater resistance. Unlike digitalis, however, it occasions no increase in the diastolic relaxation, which, on the contrary, is reduced after toxic doses, because the tonic contraction of the heart-muscle anta-

gonises relaxation and the filling of the heart during diastole. The pulse-frequency is affected in two ways, namely, by central vagus stimulation—slow pulse—and by stimulation of the muscle or the excitomotor apparatus—quick pulse. In man the former action is seen after small doses, the latter after large doses. The vessels are also affected in a twofold and opposite manner, as the stimulation of the vasomotor centre induces contraction, especially in the splanchnic area, while peripheral influence on the vascular walls produces dilatation of the renal vessels (see below), and those of the brain and the heart. The dilatation of the coronary arteries is of special value, as the nutrition and work of the heart is thereby promoted.

The **respiration** is quickened and strengthened by caffeine, while at the same time the reflex irritability is increased.

Caffeine and allied bodies exert a very important practical effect upon the **kidneys**. It has long been known that after drinking coffee or tea there is often great increase in the secretion of urine, far greater than after corresponding quantities of hot water. For a long time it was thought, with von Schröder (1886—1887), that caffeine directed its action exclusively on the secreting renal epithelium, which was thus supposed to be roused to greater activity. Loewi subsequently showed (1905) that caffeine has a pronounced effect upon the renal vessels, causing them to dilate ; after intravenous caffeine injections the volume of the kidney is increased, and there is an indication of more rapid circulation in the brighter, almost arterial, colour assumed by the blood returning through the renal vein. From these experiments it seems probable that the increased secretion of urine is due, in great part at any rate, to a more copious flow of blood. Enlargement of the kidney and increased diuresis still occur even after section of the nerves passing to the kidney and their consequent degeneration ; from this it may be concluded that the action is of a peripheral nature, affecting the vascular walls themselves.

Fate in the Organism. Only a small proportion of caffeine is excreted as such in the urine. The greater part is resolved through dimethyl- and monomethyl-xanthines down to xanthine. The same fate is shared by the dimethylxanthines mentioned below.

Among the *dimethylxanthines*, **theobromine**, like caffeine, is found in the seeds of cacao (chocolate), but differs from caffeine in having little or no effect on the central nervous system, while its action on the muscles, heart, coronary arteries and kidneys is similar to, and on the last-named organ even stronger and more certain than, that of caffeine. The presence of **theophylline**—also called *theocine*—in the leaves of the tea-plant was demonstrated

by Kossel in 1888, but the drug is now produced synthetically. Its action is still more pronounced, being about twice as strong on the kidneys as that of theobromine ; but it possesses a stimulant action on the central nervous system, and in large doses may elicit convulsions both in man and in animals. *Paraxanthine* has also a powerful diuretic action, but cannot compare with theophylline.

Therapeutic Uses. **Caffeine** is employed as a cardiac stimulant during symptoms of cardiac failure in *chronic heart-diseases*, often simultaneously, or alternating, with digitalis. Besides raising the blood-pressure and improving the pulse, it may sometimes have a regulating action, but in this respect can by no means supersede digitalis. In *acute heart-weakness in febrile diseases*, *e.g.* in *pneumonia*, *œdema of the lungs* and *far-advanced asystolism*, hypodermic injections of large doses may be of great service. Owing to its influence on circulation, respiration and cerebrum, caffeine is indicated in cases of *poisoning* with narcotic poisons such as morphine or opium, chloroform, ether, chloral and alcohol. It is given both hypodermically and in the form of tea or black coffee, which have the advantage of also containing tannic acid, which precipitates many poisons (metallic salts, alkaloids) as sparingly soluble and non-absorbable compounds. Typical *migraine* affords a frequent indication for caffeine, the attacks being as a rule relieved by that drug, or, better still, by caffeine + antipyrine ; sometimes they are entirely banished when the remedy is given soon after the pain has begun. The fully-developed attack is influenced less. The effect is perhaps connected with its dilatation of the cerebral vessels.

Theobromine or its compound with salicylate of soda (diuretine), which is absorbed better than pure theobromine, is a powerful diuretic, which is useful when there is a pathological accumulation of fluid, since it can bring the flow of urine up to many quarts in the course of 24 hours. Its best action is exhibited in cases of œdema of *cardiac origin*, where it may often elicit an abundant diuresis, even when digitalis fails, though the reverse effect has also been experienced. In *angina pectoris*, moderate doses, continued over a considerable period, often give great relief (dilatation of the coronary arteries). This also applies to other symptoms probably due to vaso-constriction, such as headache. In the dropsy of *chronic disease of the kidneys*, too, the theobromine compounds are frequently effective, and do not increase albuminuria when present. In other diseases, such as pleurisy, peritonitis and hepatic diseases, the action is uncertain.

Theophylline (theocine) is the most active of all previously known diuretics and takes effect very quickly ; but the diuresis

decreases soon after the drug is left off. Unfortunately its stimulating action on the central nervous system has several times been evidenced by violent epileptiform convulsions. A case has been described that ended fatally after a day's dose of 1·60 gramme. It is therefore necessary to handle this drug with caution ; the maximal doses given below should not be exceeded, nor should it be given for more than one day at a time, alternating, if desired, with theobromine preparations. Some unpleasant and not infrequent secondary effects, common to both theobromine and theophylline, are intense headache, nausea, vomiting and diarrhœa.

It is a fact of great practical importance that the above-mentioned diuretics, as Dreser and Katsuyama have demonstrated, not only remove fluid, but also cause a great increase in the *excretion of salts in the urine.* This is of importance in connection with the duration of the action. The accumulation of liquid in dropsy has, like the blood, a constant concentration of salts corresponding with a freezing-point of — 0·56, or a 0·91 per cent. sodium chloride solution ; that is to say, every gramme of salt fixes 100—110 grammes of water. If only the water were excreted and the salts were left behind, the organism, which always endeavours to adjust itself to the normal concentration, would behave like a hygroscopic body ; as soon as the effect of the remedy given was over, the water introduced by the mouth would be retained until the salts had once more the same amount of water as before, and the œdema would quickly return. It also follows from this that the value of diuretics is increased, and the occurrence of œdema reduced, by a diet that contains little salt (Finsen).

Preparations and Doses

Caffeina (B.P., U.S.P.), colourless crystals with a silky lustre, bitter taste, soluble in 80 parts of cold water. *Dose*, 12—30 centigrms., 2—5 grs. (B.P.) ; 0·2 grm., 3 grs. (U.S.P.). As a diuretic small doses of 10 centigrms. are given several times a day. For migraine caffeine 0·1 grm., antipyrine 1 grm., in cachets, 1—2 cachets to be taken at the beginning of the attack.

Caffeinæ Citras (B.P.C.), an unstable combination of caffeine and citric acid. Gives a clear syrupy solution with a small quantity of water, but the caffeine is precipitated on dilution. The precipitate dissolves on the further addition of water. *Dose*, 12—60 centigrms., 2—10 grs.

Caffeinæ Citras Effervescens (B.P.C.), a granulated mixture of caffeine (about 2 per cent.) with sodium carbonate, tartaric and citric acids. *Dose*, 4—8 grms., 60—120 grs.

Caffeina et Sodii Benzoas (B.P.), **Caffeina cum Sodii Benzoate** (U.S.P.), a mixture of caffeine (about 48 per cent.) and sodium benzoate, a white powder, very soluble in water, and suitable for hypodermic use. *Dose*, 0·3—1 grm., 5—15 grs. ; 12—30 centigrms., 2—5 grs. by injection (B.P.)

internally, 0·3 grm., 5 grs. ; hypodermically 0·2 grm., 3 grs. (U.S.P.). In acute cardiac weakness 0·2 grm. is injected every 1 or 2 hours. Maximum dose, 1 grm.

Theobromina (not official), almost insoluble in water, and absorbed slowly, is not very practical. *Dose*, 50 centigrms., 3—5 grms., *per diem*.

Theobrominæ et Sodii Salicylas (B.P.), **Theobromina cum Sodii Salicylate** (U.S.P.), diuretine, a compound of sodium-theobromine and sodium salicylate, a white powder with an unpleasant, sweetish, alkaline taste, very soluble in water. *Dose*, 6—12 decigrms., 10—20 grs. (B.P.) ; 1 grm., 15 grs. (U.S.P.). For dropsy 4—6 grms. daily, in cachets or dissolved in peppermint water ; for angina pectoris 0·6 grm. 3 times a day for 2 or 3 weeks.

Theophyllina (B.P., U.S.P.), a white, crystalline powder, soluble in 100 parts of water. *Dose*, 0·25 grm., 4 grs. (U.S.P.). Maximum dose *per diem*, 1·2 grm. Also called *theocine*. Used in *Injectio Mersalyli* to prevent decomposition of the mercurial complex.

Theophyllina et Sodii Acetas (B.P., U.S.P.), is more readily soluble in water. Contains about 60 per cent. of theophylline. *Doses*, 12—30 centigrms., 2—5 grs. (B.P.) ; 20 centigrms., 3 grs. (U.S.P.).

Theophyllina cum Ethylenediamina (U.S.P.), contains 75—85 per cent. anhydrous theophylline. One grm. of the preparation is soluble in 5 mils of water at 25° C. Insol. in alcohol and ether. *Dose*, 1 decigrm., 1½ grs.

Intravenous injection rapidly abolishes Cheyne-Stokes' respiration by central action.

Coffee and Tea

The importance of plants containing caffeine is very great. The leaves of the Chinese tea-plant (*Thea Chinensis*) and the seeds of the African coffee-tree (*Coffea Arabica*) and the chocolate-tree of Central America (*Theobroma cacao*) are used all over the world, and make some of the most important beverages known to man. The so-called guarana, prepared from the seeds of *Paullinia sorbilis*, which contain caffeine, and the leaves of *Ilex Paraguayensis*, which has found its way to the shops of our tea-dealers under the name of Paraguay tea, are highly esteemed in South America. North American Indians make their tea from the leaves of *Ilex cassine*, and the tribes of tropical West Africa have the *Kola acuminata* as their caffeine-plant, its seeds—the well-known kola nuts—having even superseded coined money. Caffeine has recently been found in very small quantities in the scilla, but, with this exception, all recent search for caffeine in plants other than those that have already supplied beverages from the earliest ages has proved fruitless. We are thus faced by the interesting fact that, among all the plants that cover the surface of the earth, savage tribes, standing at the lowest stage of civilisation, have, quite independently of one another and with infallible certainty, guided solely by the effect, found and made use of the few plants that contain caffeine. None of these are indigenous to Europe, and when coffee and tea were imported from the East about the middle of the seventeenth century, many objections were made to their introduction, one of these being that coffee would make the women sterile. Notwithstanding these objections, however, and the opposition to everything new that was customary on the part of the clergy, both tea and coffee rapidly became popular, and the first coffee-houses were started. In their defence it was even then urged, as it has

been so often since, that the new beverages reduced the consumption of alcohol. "Were there no other use in tea and coffee, they are nevertheless useful in that they have caused drunkenness, which was formerly so prevalent, to go out of fashion. Our wives and daughters can now pay ten visits in one morning, and yet come home quite sober" (Holberg, 1748).

Tea-leaves contain on an average 2 per cent. of caffeine and 10—12 per cent. of tannic acid; their aroma arises from the presence of a very small quantity of a volatile oil, and from substances that are formed by the slight heating and fermenting to which the fresh leaves are subjected. In coffee-beans there is 0·6—2 per cent. (on an average 1·2 per cent.) of caffeine, 5—6 per cent. of tannic acid, besides albumin, sugar and a fixed oil. When the beans are roasted, empyreumatic substances are formed, which by distillation can be obtained in the form of a clear, pale yellow oil, of which the composition is not fully known. In man the caffeine-free distillates increase the volume of air inspired and expired in the unit of time by quickening the respiration, and produce slight excitement and restlessness. In animals, too, that have been paralysed by large doses of alcohol, the respiration is improved. The aromatic constituents thus support the action of the caffeine.

According to many authors, chronic cases of tea and coffee poisoning are of frequent occurrence, but unless the indulgence is carried to great excess, they are among the most harmless of poisoning cases. Some of the symptoms, which consist in palpitation, anxiety, tremor, restlessness and "nervousness," arise from the aromatic substances, and principally from the caffeine, of which an ordinary cup of coffee contains 0·10—0·15 grm., while anorexia, dyspepsia, cardialgic pains and constipation must be ascribed to the tannic acids.

Attention was first directed to the *kola nut* by accounts of its employment by West African negroes as an indispensable condiment, which enabled them with ease to go through the greatest exertion, desert wanderings under a burning sun, etc. Its praises found an echo in Europe and resulted in the production of numerous preparations—kola wine, kola biscuits, etc. These, however, can hardly have had other action than that of caffeine, which is present in the much-talked-of "nuts" as a glucoside, *kolanin*, which is easily decomposed into caffeine and tannic acid.

26. ADRENALINE (EPINEPHRINE) AND EPHEDRINE

After Addison in 1855 had described the disease that was called after him, and in every case had found morbid changes in the suprarenal glands, and Brown-Séquard in 1857 had shown that animals survive only a few hours the extirpation of these glands, their physiology became a subject of the greatest interest. It was not until 1894, however, that a firmer foundation was obtained for their physiology in the discovery by Oliver and Schäfer that an extract of suprarenal gland has the property of eliciting a great rise in blood-pressure. All previous attempts to find the active constituent had failed, but they were now resumed and were soon crowned with success. Abel (1897) very nearly arrived at the goal with his *epinephrine*, and Aldrich, von Fürth,

and the Japanese chemist Takamine (1901), reached it by the production of *adrenaline*, $C_9H_{13}O_3N$. The history of this drug bears proud testimony to the powers of chemical research in the present day. Though not much more than 25 years since the search for this unknown substance began, not only has it been found, but its chemical constitution has been determined, and the final result is the synthetic production of a substance that is identical with the natural. In the synthetic production it was discovered that adrenaline, like many other organic compounds, occurs in two optical modifications (*re* optical antipodes, see under "Hyoscyamine," p. 107), which are physiologically quite different. The action is associated with the lævo-rotatory form, which is that occurring in the suprarenal glands, whilst the dextro-rotatory form is almost inert. The synthetic product is called *suprarenine*.

Adrenaline is a derivative of the bivalent phenol or dioxybenzol pyrocatechin, and has the following comparatively simple constitution: $(OH)_2C_6H_3CH(OH)CH_2.NH.CH_3$ = dihydroxyphenylethanolmethylamine. Adrenaline, especially in alkaline solutions, like the parent substance, pyrocatechin, is easily affected by the atmospheric oxygen, or by substances giving off oxygen (oxidisers) or transmitting oxygen (ferric chloride) forming dark-coloured oxidation products; by ferric chloride it is coloured green, by chromic acid almost black. Even the medulla of the adrenals exhibits this sensitive reaction, whence the name chromaffine tissue. From the suprarenal glands, whose content of adrenaline in man is estimated by colorimetric determination to be 4—5 milligrms., the adrenaline passes into the circulation. If the conditions found in the cat might be applied to man, the daily production would amount to about 20 centigrms. The adrenaline-concentration of the blood is not known; it is, in any case, very small, in the rabbit at the most 1 in 1 milliard. A new, very interesting occurrence has recently been discovered by Abel, who found adrenaline in considerable quantities in the poison-glands of *Bufo agua*, the large toad of tropical America.

Action. The action of adrenaline shows itself in all organs as a *stimulation of the sympathetic nerves*. In some organs this leads to contraction or increased activity, in other organs to the reverse conditions. The action of adrenaline is, therefore, of a manifold and apparently very complex nature. The following description will include only the principal, and in practice most important, particulars that have up to the present been obtained.

The most conspicuous property of adrenaline is that it acts upon the **vascular walls** in such a manner as to cause constriction and local anæmia. The vaso-constriction, which affects veins and capillaries as well as arteries, is very intense, and with direct local application also protracted. Mucous membranes surcharged with blood immediately become pale on being painted with even very dilute solutions, and bleeding from wounds is arrested if arising from small vessels. This peripheral action

also takes place after intravenous injection, but is then of very short duration. As the site of attack is peripheral, the arteries are contracted, and the circulation becomes slow, even in isolated surviving extremities. Excised pieces of artery preserved in Ringer's solution at body temperature also contract on the addition of adrenaline. All vessels do not, however, behave in the same manner. Those of the skin and the mucous membranes are, as already mentioned, readily affected, and still more the intestinal arteries innervated by the splanchnic. The pulmonary arteries, on the other hand, are not constricted, or only very little. In various mammals, including man, the cerebral arteries and the coronary arteries of the heart are dilated.

Continued intravenous injections produce in rabbits degeneration of the muscles and elastic fibres in the tunica media of the arteries. As a consequence of this, aneurysms occur, especially in the aorta, and may rupture and cause sudden death. The production of this condition is not peculiar to adrenaline, however, for similar, although not so constant and marked, vascular changes have been observed after a number of other poisons.

In consequence of the peripheral vaso-constriction, especially of the extensive vascular plexus of the abdomen, adrenaline has a great, though very transitory, influence on the **blood-pressure.** After intravenous injection of only $\frac{1}{50}$ milligramme in rabbits and corresponding doses in other animals, it rises for a few seconds or half a minute to twice or three times its normal height.

On the **heart** adrenaline injected directly into the blood has a powerful effect. As a consequence of stimulation of the terminations of the accelerator nerves, the pulse becomes frequent and the contractions stronger and more complete. This may at first be masked by stimulation of the vagus control, which acts in the reverse manner. This vagal effect, however, is produced not directly by the adrenaline, but by the high blood-pressure ; and as soon as the latter falls the accelerator action once more gains the upper hand.

In addition to the vessels, numerous other organs with **unstriated muscles** are affected by adrenaline, some of them in an opposite way. The *radiating iris-muscles* innervated by the sympathetic are contracted (*i.e.* the pupil is dilated), and the same thing occurs in the case of several pelvic organs, *e.g.* the pregnant *uterus*, *vagina* and *vesiculæ seminales ;* the movements of the *bladder*, and also the *stomach* and *intestine*, are inhibited by adrenaline. All this is explained by the fact that the sympathetic, as already mentioned, in some organs acts as a motor, in others as an inhibitory nerve. The relaxation is especially evident when the organs are already in a state of tonic contraction, even in

exceedingly dilute adrenaline solutions (1 in many millions. See Fig. 16).

The *uterus* is exceedingly sensitive to adrenaline. Even very dilute solutions cause strong contractions of the excised organ. *Dilatation of the pupil*, which is due to stimulation of the sympathetic in the dilatator pupillæ, takes place in most animals after minimal doses of adrenaline, injected directly into the blood. In the healthy human subject, on the contrary, there is no dilatation of the pupil when adrenaline is dropped into the eye. The explanation of this is that the dilatator pupillæ, through the superior cervical ganglion, also receives inhibitory nerves, and that this normal inhibition cannot be overcome by the exceedingly small amount of adrenaline absorbed. Under special circumstances mydriasis occurs. This is seen in conditions in which there is increased irritability of the sympathetic, such as hyper-thyroidism, Graves' disease, after previous employment of cocaine, and in many diabetics. In these diabetic cases,

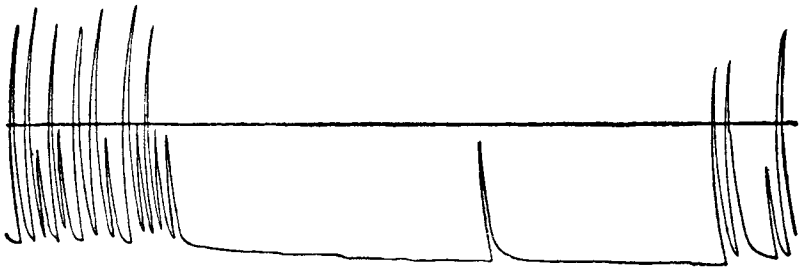


FIG. 16.—A strip of muscle from the small intestine of a cat, in Ringer's solution of body-warmth, makes vigorous movements under the influence of strophanthin. After the addition of adrenaline (1 in 2,000,000), 10 minutes' standstill. Mechanical stimulation with forceps elicits a powerful contraction. The standstill is thus not caused by muscle-paralysis, but by action on nerve-apparatuses. (Magnus.)

mydriasis confirms the presence of some abnormality of the pancreas, for extirpation of this organ makes the pupil sensitive to adrenaline in animals (cats, dogs), which in normal condition, like man, are refractory (Loewi). Further experience will decide whether adrenaline can acquire diagnostic importance as a reagent to pancreatic diabetes.

Many **glands** are also affected by adrenaline, but in different ways. The secretion from lachrymal glands, salivary glands, and the little mucus-glands in the mouth and throat is increased; and in man, as also in dogs, there is an increase in the free hydrochloric acid contained in the gastric juice. In the frog it produces a more abundant cutaneous secretion. With the pancreas the conditions are reversed, the secretion being diminished, according to observations on dogs with a Pawlow's fistula, without any weakening of the enzyme action. The amount of bile is likewise reduced, and that of urine always decreases.

After intravenous or subcutaneous injections, and still more after intraperitoneal injections, there is increased glycogenolysis

in the liver and other glycogen-depots of the body. This may be sufficiently marked to result in glycosuria.

Large intravenous doses induce paresis of the hind limbs, strong convulsions and death, in some species of animals by paralysis of the respiration, in others by cardiac paralysis.

Almost nothing is known of the **fate** of adrenaline **in the body.** It is supposed that it is very easily oxidised into unknown compounds which no longer possess the characteristic action, and that this explains its transient effect and the fact that general action (with ordinary doses) is hardly noticeable unless the drug is introduced directly into the blood, for when not otherwise expressly stated, all that has been said above refers only to intravenous injections. Even if only a fraction of a tenth part of a milligramme is injected, the effects are pronounced. After subcutaneous injections absorption into the general circulation is insignificant, and when taken by the mouth adrenaline is robbed of almost all general effect. Man, however, is perhaps somewhat peculiar in this respect. As the subcutaneous injection has acquired therapeutic importance, it is interesting to learn how great this loss is. Ritzmann has endeavoured to solve the problem by comparing the intravenous and subcutaneous doses that produce equal excretions of sugar. The result showed that only 6 per cent. of that administered subcutaneously took effect, 94 per cent. being destroyed. It is this instability that makes all the effects of adrenaline so fugitive. A small portion of the subcutaneously injected drug is, however, absorbed. After injection of 1—1·5 c.c. of the ordinary solution, 1 in 1,000 (*i.e.* 1—1·5 milligrammes), palpitations with rapid pulse and a feeling of weakness may occur. After intraperitoneal injection of large doses (10 c.c. = 1 centigramme) a higher blood-pressure has been observed, and after injection of still larger amounts into the bladder and uterus serious collapse. Death occurred after injection of 10 c.c. of 10 per cent. solution. No general poisonous effects have been seen after local employment on mucous membranes.

Therapeutic Uses. Adrenaline is the most active of all vasoconstricting substances, and is now one of the drugs in daily employment in surgical practice.

Its greatest importance is as an *addition to local anæsthetic solutions*, such as procaine and cocaine ; the local anæmia produced by adrenaline prevents absorption and thus prolongs the anæsthesia, while at the same time the toxicity of the cocaine or other bodies is reduced, as explained more fully in the chapter on cocaine.

Adrenaline is further employed, together with the above-

mentioned drugs or alone, to prevent or *arrest bleeding in operations in the nose, mouth and throat,* though there is some liability to secondary hæmorrhages, as dilatation may follow the constriction of the vessels. The vaso-constriction enlarges the lumen of narrow passages and facilitates their examination; it also relieves for a time various troublesome symptoms in *catarrh of the Eustachian tube, ordinary cold in the head, and hay fever.* In other cases of bleeding, adrenaline is efficient where the bleeding does not arise from a single large vessel, but from many small vessels, and where the drug can be applied directly. It has been successfully employed in *parenchymatous hæmorrhage after operations,* in *hæmophilia* and in *vesical and uterine hæmorrhage.* For hæmorrhage in *gastric ulcer* and in *typhoid ulcer* the results are uncertain. In anaphylactic shock, which is very occasionally seen following the administration of horse-serum to sensitive individuals, adrenaline should be injected immediately. The urticaria and other manifestations of " serum-sickness " are also amenable to repeated small doses of adrenaline.

Adrenaline is used in operations on the *eye* and for removing congestion in *conjunctivitis* and *iritis.* In *glaucoma* it may diminish the tension and the pain.

Intravenous injections of adrenaline are recommended as the most powerfully stimulating treatment for *heart-failure* with *low blood-pressure* during *anæsthesia,* in *febrile diseases, post-operative shock,* and in *hæmorrhage.* The effect is brief, however, and there is a danger of producing ventricular fibrillation—a condition which is invariably fatal in man. For this reason adrenaline is contra-indicated in circulatory failure due to chloroform poisoning. A few deaths have been accounted for in this way. Many have therefore adopted subcutaneous injections, which act far more mildly, may be repeated many times and do excellent service. In serious cases of collapse, 1—3 milligrammes may be given without danger every one or two hours for several days in succession. When normal saline is administered intravenously in cases of surgical shock, a small quantity of adrenaline may with advantage be added to the injection, *e.g.* 2 drops of a 0·1 per cent. solution to 1—2 pints of saline. The newest method is that of intracardiac injections (1 milligramme). Several cases have been reported in which patients have been brought back to life several minutes after the heart action seems to have ceased. In hypoglycæmic coma the injection of 5 minims of the solution of adrenaline hydrochloride hypodermically rapidly restores consciousness for a short time. This valuable action is brought about by increased glycogenolysis and lasts long enough to enable the patient to take sugar by mouth.

As a *uterine drug* adrenaline has not much reputation. It elicits powerful contractions, it is true, but its action is brief and therefore of little use.

Attacks of *bronchial asthma* cease instantly with the subcutaneous injection of 1—2 milligrammes of adrenaline, which relaxes the bronchial spasm.

The symptoms of Addison's disease are unaffected by adrenaline, but improvement has been recorded following the feeding of whole adrenal glands. In recent years it has been shown that the suprarenal medulla is not essential to life, a sufficiency of adrenaline being supplied by the accessory chromaffin tissue of the body. On the other hand, animals deprived of their suprarenal cortex steadily deteriorate and die in a state of profound asthenia. Swingle and Pfeiffner have prepared from the suprarenal gland an extract which rapidly relieves these symptoms. Application of these findings to the treatment of Addison's disease in man have met with gratifying results. The active principle known as the cortical hormone can be recovered from the medulla as well as the cortex of the suprarenal gland. Its mode of action is not yet understood, but it would appear that absence of the hormone seriously disorganises the sodium metabolism of the body. This hypothesis is supported by the fact that the administration of common salt in Addison's disease is also effective in relieving the symptoms.

EPHEDRINE

Ephedrine is an alkaloid obtained from the plant Ma Huang. This plant was known to the Chinese at least 2,000 years ago as a therapeutic agent, but in the light of present knowledge it is doubtful whether it was used rationally.

Ephedrine is a sympatheticomimetic drug having the same actions in general as adrenaline, but the effects of ephedrine are slower in onset and much more prolonged. Furthermore, ephedrine possesses a more stable molecule than adrenaline; it is usually administered by mouth and, if necessary, it can be sterilised by boiling for parenteral injection. The site of action of the two drugs is probably identical, *i.e.* the sympathetic nerve-endings; it has been claimed, however, that ephedrine also stimulates the involuntary muscle fibres supplied by the sympathetic.

Following a dose of 1 grain of ephedrine hydrochloride there is a temporary increase in the heart-rate and in the force of the beat. As a result of vaso-constriction, especially in the splanchnic region, the blood-pressure rises and this rapidly brings about a reflex slowing of the heart. In man this compensatory bradycardia predominates and the preliminary acceleration of the heart-rate is negligible. The bronchi are relaxed, and this is most marked when spasm of the bronchial muscle has been produced by pathological conditions or as a result of the administration of

drugs. Results of observations on the action of ephedrine upon the alimentary canal are conflicting ; at all events, relief of spasm of the stomach and bowel does not occur consistently following the use of ephedrine. In contrast to adrenaline, a solution of ephedrine hydrochloride instilled into the conjunctival sac causes dilatation of the pupil ; this is brought about by a direct action on the iris. This drug has no effect of any importance upon glandular secretions. In experimental animals uterine movements are increased by ephedrine.

The most important use of ephedrine is in the symptomatic treatment of asthma. Small doses of the hydrochloride (*e.g.* half a grain thrice daily) are often used with good results in preventing the paroxysms. As the drug takes about 15 minutes to act it is less suitable than adrenaline for dealing with an asthmatic attack once this has developed. Ephedrine hydrochloride in solution is also used as a nasal spray in acute rhinitis and in hay-fever. Applied in an ointment base it is an effective remedy for relieving congestion of the nasal mucosa in the early stages of a common cold. In shock and collapse ephedrine may be administered in order to raise the blood-pressure and increase the force of ventricular systole. It also stimulates the medullary centres.

Untoward effects of overdosage include vasomotor disturbances with palpitation, and throbbing in the head. Prolonged administration is said to cause myocardial degeneration. Excitement and apprehension are sometimes seen in high-strung individuals owing to cerebral stimulation.

Preparations and Doses

Adrenalina (B.P.), *Epinephrina* (U.S.P.), a light brown, or nearly white, minutely crystalline powder, very slightly soluble in water. Combines with acids to form readily soluble salts. The synthetic product, now extensively employed, is identical with that produced from the suprarenal gland. *Dose*, 0·0001—0·0005 grm., $\frac{1}{6\,0\,0}$—$\frac{1}{1\,2\,0}$ gr. (B.P.) ; 0·5 milligrm., $\frac{1}{1\,2\,0}$ gr. (U.S.P.).

Liquor Adrenalinæ Hydrochloridi (B.P.), **Liquor Epinephrinæ Hydrochloridi** (U.S.P.), contains adrenaline (0.1 per cent.), hydrochloric acid, sodium chloride (0·9 per cent.), and as a preservative a little chlorbutol. *Dose*, 0·12—0·5 mil, 2—8 mins. by subcutaneous injection (B.P.) ; 0·5 mil, 8 mins. by parenteral injection (U.S.P.) ; externally in nose, mouth, throat, etc., in concentrations of from 1 in 5,000 to 1 in 1,000, *i.e.* the official solution undiluted or diluted with up to 4 parts of water ; in the eye and bladder 1 in 10,000 to 1 in 5,000. For large doses in collapse see above.

Ephedrina (U.S.P.) ; **Ephedrinæ Hydrochloridum** (B.P., U.S.P.), $C_6H_5.CH(OH).CH(NH.CH_3).CH_3.HCl$. The hydrochloride of an alkaloid from various species of ephedra (China). Colourless crystals, soluble in water. A sympatheticomimetic drug ; action resembles that of adrenaline but is slower in onset and of longer duration. Active when

given by mouth. *Doses*, 0·016—0·1 grm., ¼—1½ grs. (B.P.); 0·025 grm., ⅜ gr. (U.S.P.).

Ephedrinæ Sulphas (U.S.P.). *Dose*, as above.

Addendum

Uzara is the name given by the natives to a species of *Gomphocarpus* (*Asclepiadaceæ*) growing in the regions surrounding the great African lakes. Its root is used for dysentery and dysmenorrhœa. According to Gürber and Bachem, uzara contains active crystalline glucosides and amorphous bodies. The extract has a central stimulating action and a digitalis-like action upon the heart; it stimulates also the peripheral sympathetic, acting upon the vessels, intestine and uterus like adrenaline, but more slowly and with more lasting effect. According to various clinical reports of recent years, uzara is often effectual in acute and chronic diarrhœa. *Liquor Uzaræ*, a bitter liquid. *Dose* for adults 30 mins., for children 6—20 mins., every 2 hours or less frequently, also tablets a few times daily.

27. ERGOT

The official ergot is the hibernating stage or winter mycelium (sclerotium) of *Claviceps purpurea*, a fungus which is parasitic on many species of grass, and especially on rye, where it forms the well-known long, black bodies that after wet summers are often seen in the ears of rye among the normal grain.

As ergot contains all the very varied products of metabolism that the fungus forms from the nutritive substances that flow to the ovary, it will be easily understood that the chemical composition of this drug is very complex. There is scarcely any other drug of which the constituents have so frequently been sought for in vain. As far back as 1865 it was shown by Wenzell that ergot owed its activity to its alkaloidal content. Ten years later Tanret discovered the crystalline alkaloid ergotinine, and Buchheim put forward the assumption that decomposition or putrefaction products of albumin were of vital importance. Ergotinine proved, however, to be inert, research abandoned these clues, and three decades passed before Barger and Dale and their co-workers, and independently of them Kraft, in 1906 succeeded in isolating the highly active alkaloid *ergotoxine*, $C_{35}H_{41}N_5O_6$, a hydrate of, and therefore very nearly related to, ergotinine. Another alkaloid, *ergotamine*, which is closely allied to ergotoxine, was found by Stoll in 1921. For nearly 30 years ergotoxine was accepted as the most important active principle of ergot, and as recently as 1932 this alkaloid was officially adopted for the purposes of standardisation. It had been pointed out repeatedly, however, that many preparations of ergot which were potent clinically contained no ergotoxine. This apparent discrepancy was investigated by Moir and Dudley (1932—1935), and a new alkaloid, *ergometrine*, was isolated. It is now established

beyond doubt that the clinical value of preparations of ergot is almost entirely due to this alkaloid. Its isomer ergometrinine is inert. A number of very active amines have also been produced from aqueous ergot extracts, which contain but little ergotoxine. The most important are *p-hydroxyphenylethylamine*, which arises from the influence of bacteria on tyrosine, and has therefore received the name *tyramine*, and *β-imino-azolylethylamine*, which is formed in the same way from histidine, and, for the sake of brevity, is called *histamine* or *ergamine*. By the demonstration of these amines, which are also formed by the putrefaction of meat, the old assumptions have been corroborated. Ergot further contains other amines, choline, and about 30 per cent. of a fixed oil.

Action. As at present it is chiefly various extracts of ergot that are employed, the action of these will first be described, and then a brief mention will be made of its active constituents. The most important sites of action are the *arteries* and the *uterus*.

Ergot produces a prolonged tonic contraction of all small **arteries.** This is due to its action upon the vaso-motor nerves. The peripheral nature of the action is shown by the rise of blood-pressure from vaso-constriction after section of the cervical spinal cord, and by the fact that the flow of blood in excised living organs is greatly reduced when an ergot preparation is added to the blood (Jacobi). In the pulmonary circulation, too, which generally possesses a certain immunity from vaso-motor drugs, a considerable and prolonged rise of pressure occurs, produced by the contraction of the small pulmonary arteries (Bradford and Dean, Mellin).

In close connection with the influence on the vessels there is a very peculiar effect, namely, **gangrene.** This appears in a somewhat different manner in the various classes of animals. The typical gangrene is most easily produced in cocks. Only a couple of hours after administration of a sufficient amount of ergot the comb and wattles show signs of arrested arterial circulation, as they lose their normal red colour and assume a bluish hue. If the dose is not too large, the discoloration disappears in the course of twenty-four hours. After large quantities, on the other hand, and in chronic poisoning, the circulation ceases completely, the entire comb and other peripherally situated parts, such as the tongue and the epiglottis, shrivel up, are attacked by a dry gangrene, and at last fall off. Even larger members, *e.g.* the wings, may gradually fall away spontaneously without bleeding. In the intestine there are numerous extravasations of blood, and, as in typhoid fever, swelling and necrosis, leading to deep ulceration, which may perforate and give rise to peritonitis. In all the

necrotic parts, according to von Recklinghausen's investigations, there are hyaline thrombi, some of which lie fixed to the vascular walls, leaving only a small central lumen open, and some completely fill the arteries. Ergot probably produces changes in the intima of the vessels, which give the impulse to the hyaline deposits ; and the contraction of the arteries also contributes to the complete closing of the vessels, so that the parts in question are quite cut off from the circulation and doomed to mortification. This first affects the most peripheral parts, in man the fingers and toes, because here the conditions of circulation are the most difficult.

Several species of animals exhibit a remarkable immunity from this gangrene. In cats, rabbits, guinea-pigs and monkeys, even after the largest doses, or after they have been fed a long time on ergot, necrosis is hardly ever seen, but only hæmorrhage in various organs, especially the stomach and intestine. Animals, too (cocks), that have once got over the gangrene, subsequently show a comparative insusceptibility.

In less than toxic doses, ergot causes, in animals, contractions of the **uterus**, especially in pregnancy, and more distinctly in the more advanced stages. The contractions may be of varied nature, judging from the different descriptions. Periodical contractions often occur which exactly resemble the normal pains and end in abortion or, if the fœtus is almost full-grown, in a birth in regular course. In other cases the contractions are for the most part of tonic nature and prolonged, so that the fœtus dies from pressure, in which case abortion takes place, but generally only after a few days. The contractions are due to a peripheral action on the uterus. As little as one-tenth of a milligramme of *ergometrine* injected intravenously causes strong contractions of the uterus in less than 1 minute. Doses of 1 milligramme may be given by mouth and act in about 5 minutes. Ergometrine has no action on the motor sympathetic nerves and it does not produce gangrene. Ergotoxine increases the frequency and force of the uterine contractions during pregnancy and parturition. It does not act so rapidly as ergometrine and it is not nearly so reliable for therapeutic purposes. Following oral administration, ergotoxine takes about half an hour to act, but by intravenous injection of the æthane sulphonate this interval can be reduced to about a quarter of an hour. Many of the motor effects of adrenaline are abolished by ergotoxine. The phenomenon known as vasomotor reversal is an interesting illustration of this : if a dose of ergotoxine be given to an experimental animal the blood-pressure rises owing to stimulation of the motor sympathetic nerve-endings. If, while the blood-pressure is elevated, a dose of adrenaline is

injected, the blood-pressure *falls*. This is due to stimulation of the vaso-dilator fibres, the vaso-constrictors having been paralysed by the ergotoxine. Ergotamine closely resembles ergotoxine in its action on the uterus. This alkaloid has the remarkable property of relieving the intense headache of migraine. Its mode of action is not understood. For this purpose ergotamine is administered as the tartrate intravenously (see Preparations and Doses). Ergotaminine is an isomer of ergotamine but its action is comparatively weak.

In large doses, in both higher and lower animals, ergot produces first clonic, afterwards also tonic, *convulsions*, which may closely resemble epileptic attacks. The convulsions are preceded by violent contractions of the stomach and intestine, with diarrhœa and vomiting. General paralysis follows, and respiration ceases.

Acute ergot poisoning seldom occurs, but when it does it is generally in consequence of attempts to bring about abortion. The toxic symptoms begin as a rule with great thirst, vomiting and diarrhœa, headache and confusion of mind, followed later by epileptiform convulsions ; gangrene is exceptional. Hæmorrhage from the uterus and abortion are of frequent occurrence. Even if there were life in the fœtus, it is generally born dead, as it is asphyxiated during the prolonged contractions of the uterus.

A far more important part was played during the Middle Ages and to the end of the eighteenth century by **chronic ergot poisoning,** *ergotismus chronicus*, which after wet summers would ravage large districts and attack thousands, principally of the poorer inhabitants. As the cause was unknown, the sufferers were defenceless against the disease ; but during the last century it has almost disappeared from all civilised countries, where the grain is now carefully cleansed.

Chronic ergot poisoning occurred in two forms, *ergotismus gangrœnosus* and *ergotismus convulsivus*, which made their appearance sometimes immediately, sometimes several weeks, after the patient had partaken of the infected grain.

The *gangrenous form* in many places was called " ignis sacer," because the limbs were consumed as if by an invisible fire, which ceased to burn when the sufferers resorted to the churches (and were fed with wholesome bread). It was characterised by painful bullæ on the extremities, which at first contained a serous fluid, this afterwards becoming discoloured ; fingers and toes turned black and withered, and after a long time fell off at the demarcation ; or, if the same food was continued, the gangrene spread centripetally, so that entire limbs would necrose and at last fall off. " One saw people who consisted only of head and

body." Many of the sufferers died of exhaustion in consequence of prolonged suppuration or of pyæmia, but the majority recovered with the loss of one or more limbs. Others became blind as a consequence of peculiar, milk-white opacities of the lens. Gangrene of the lung was seldom the cause of death.

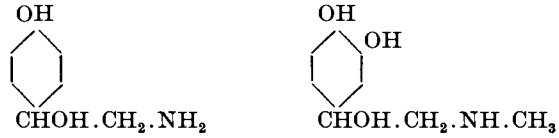
The *convulsive form*, " miserabilis et omnino terribilis morbus pestilentialis convulsivus," commenced after indefinite prodromata such as headache, giddiness and general malaise, with formication and numbness or complete anæsthesia, which spread from fingers and toes all over the body. This was accompanied by unquenchable thirst and ravenous hunger, after which the pathognomonic symptoms appeared in the form of slow, prolonged and very painful tonic contractions of various groups of muscles, especially the flexors of the extremities, which left behind muscular atrophy and permanent contraction. In the more serious cases, convulsions resembling those of chorea or epilepsy occurred, which in a few days or weeks might end in death or insanity.

The two forms of chronic ergotism might occur side by side in the same epidemic, but in general had different geographical distributions, the convulsive form being prevalent in Northern and Eastern Europe (Scandinavia, Germany, Russia), the gangrenous in the western and southern countries (England, France, Spain). This seems to indicate that climatic conditions have an influence upon the chemical composition of ergot.

Concerning the active principles the following additional facts may be stated :—

The alkaloids *ergotoxine* and *ergotamine* produce in animals contraction of the arteries, rise in blood-pressure, uterine movements and gangrene, by a peripheral action.

p-Hydroxyphenylethylamine, or *tyramine*, is of great interest, because both chemically and physiologically it resembles adrenaline, and even occurs analogously in the animal kingdom, where it is the active constituent in the poison-glands of some Cephalopoda (*cf.* the occurrence of adrenaline in the South American toad, *Bufo agua*, p. 177). Tyramine possesses most of



p-Hydroxyphenylethylamine — Adrenaline

the characteristic action of adrenaline, *e.g.* contraction of the gravid uterus, energetic stimulation of the heart, and arterial contraction. The action is feebler, however, and more prolonged than that of adrenaline ; it is also far less poisonous and a more stable compound, so that it also acts when taken internally. In man (Barger and Dale's experiments on themselves), after 10 milligrms. the blood-pressure rose in 15 minutes from 115 to 149 mm., and was as much as 139 even after 1½ hours. According to

Mayor and Wiki, the lethal dose by intravenous injection in animals is 25—30 centigrms. per kilo of body-weight. Death ensues from paralysis of the heart, preceded by epileptiform convulsions.

β-Imino-azolylethylamine, or *histidine* (ergamine), $\begin{matrix} CH = N \\ | \quad\quad \diagdown \\ NH \cdot CH \diagup\!\!\diagup \end{matrix} C \cdot CH_2 \cdot$

$CH_2 \cdot NH_2$, is a very active substance, which kills animals in intravenous doses of only a few milligrammes. The action exhibits a striking resemblance to the anaphylactic complex of symptoms so much discussed of late years. It should be especially noted that it causes vaso-dilatation (lowering of the blood-pressure) and bronchial spasm (dyspnœa), and has so powerful an action upon the isolated uterus that contractions take place even with a solution of 1 in 250,000,000. Extracts of the intestinal mucosa have a similar action. A hypothetical substance that has not been isolated, vasodilatine, is perhaps identical with histidine.

In the crude ergot, the action of ergotoxine and tyramine (raising of the blood-pressure) is as a rule predominant, although occasionally a fall in blood-pressure is seen.

Therapeutic Uses. The frequent occurrence of abortion in cases of poisoning induced first midwives and then doctors to employ ergot in the expectation that during pregnancy it would more or less certainly procure abortion, and in parturition strengthen the contractions already begun. This is not the case, however. Abortifacients in the sense of drugs that can free the uterus from its contents without general poisoning, just as an emetic empties the stomach and a cathartic the intestine, are not known. Nor can one venture to reckon on an advantageous influence on labour already commenced. From the very numerous, extremely contradictory, statements on the subject, it appears that ergot *may* increase the movements while retaining the necessary intervals of relaxation that are characteristic of physiological labour, but that there is also a risk of the action taking the form of a continued tonic contraction, a prolonged "tetanus uteri," which prevents the birth, because the uterus is like a hand closed upon its contents, and thus endangers the life of the child (asphyxia). During parturition, therefore, ergot is a two-edged weapon. It is contra-indicated during the dilatation period, and only permitted during the expulsion period when the surgeon is prepared at a moment's notice to undertake artificial delivery. It is indicated, on the other hand, in *hæmorrhage that is due to atony of the uterus when the birth is over*, and afterwards in *subinvolution*. The curves shown in Figs. 17 and 18 have been taken by registration of the movements of the human uterus *in situ* (Rübsamen), and illustrate the various kinds of contractions. A long-continued tonic contraction (Fig. 17, the ergot type) is very effectual against hæmorrhage, while periodic contractions (Fig. 18, the pituitary extract type) assist the birth. In all

other kinds of uterine hæmorrhage not connected with pregnancy or parturition, ergot is much employed, and often with good effect.

Ergot is also frequently prescribed for *hæmorrhage from other organs, e.g.* from kidneys and intestine, and in hæmoptysis, but is of doubtful benefit. It is very difficult to judge of the activity of a drug with these hæmorrhages, which as a rule cease spontaneously. Ergot must originally have been employed for lung hæmorrhage on account of its action on uterine hæmorrhage, but the conditions for its hæmostatic action are really quite different in these two organs. As it has been proved that ergot causes the pressure in the pulmonary circulation to rise by contracting the small pulmonary arteries, it would be most natural to look upon

FIG. 17.—After-birth period. Woman of 24, quadripara. After-pains at intervals of about 13 minutes. After the injection ↓, prolonged tonic contraction.

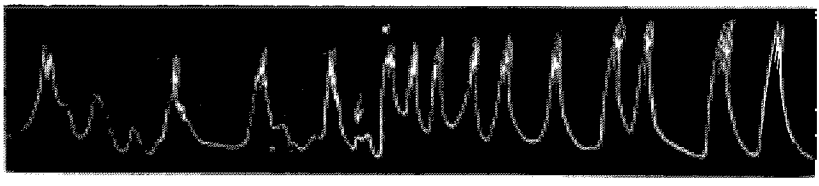


FIG. 18.—Expulsion period. Primipara. Slight pains at irregular intervals. At ↓ injection of a preparation of pituitary extract, immediately followed by strong contractions and rapid progress in the birth.

the drug as harmful in all more serious hæmoptysis originating in large vessels which certainly do not share to any great extent in the contraction. The conditions are otherwise in the uterus, where it is not necessary for the arteries to be constricted independently, but only to be passively compressed by the contraction of the surrounding muscle.

Ergot has been recommended at various times as a remedy for *diseases of all kinds*, such as spinal complaints, chorea and epilepsy, cystoparalysis and enuresis, prolapsus recti, aneurysms, varix and telangiectasis, struma, intestinal catarrh, whooping-cough, and diabetes. Needless to say, these uses are merely of historical interest.

PREPARATIONS AND DOSES

Ergota (B.P., U.S.P.). The dried sclerotium is about 2 cm. long, and from 3 to 5 mm. in thickness, subtriangular, generally curved, purplish

black without, white or pinkish white within. *Dose*, 2 grms., 30 grs. (U.S.P.). *Ergota Præparata* (B.P.). Ergot which has been powdered and immediately defatted with light petroleum. Contains 0·1 per cent. of the total alkaloids of ergot calculated as ergotoxine. *Dose*, 0·3—1 grm., 5—15 grs. Is prescribed in the form of powder or infusion. Ergot is the most unstable of all drugs, and in some ways, at any rate, has little activity after being kept for a few months. Ergotismus gangrænosus occurred only during the first four months after harvest.

Extractum Ergotæ Liquidum (B.P.). *Dose*, 6—12 decimils, 10—20 mins. **Fluidextractum Ergotæ** (U.S.P.). *Dose*, 2 mils, 30 mins.

Ergometrina (B.P.), the most potent alkaloid of ergot, $C_{19}H_{23}O_2N_3$. Colourless crystals, odourless, slightly bitter taste, almost insoluble in water, moderately soluble in dehydrated alcohol. *Doses*, 0·25—0·5 milligrm., $\frac{1}{240}$—$\frac{1}{120}$ gr. by intramuscular injection; 0·125—0·25 milligrm., $\frac{1}{480}$—$\frac{1}{240}$ gr. by intravenous injection.

Ergotoxinæ Æthanosulphonas (B.P.), contains approximately 83·6 per cent. of ergotoxine. Colourless acicular crystals, sparingly soluble in water. An aqueous solution has a blue fluorescence and is acid to litmus. *Dose*, 0·0005—0·001 grm., $\frac{1}{120}$—$\frac{1}{60}$ gr. by subcutaneous or intramuscular injection.

Ergotamine Tartrate (not official). Used exclusively in the treatment of migraine. *Dose*, $\frac{1}{2}$—1 milligrm. injected intravenously at the first warning of a paroxysm. Relief of headache in a high proportion of cases, but nausea and vomiting are fairly common sequelæ.

28. THE PITUITARY GLAND

Much attention is being given at the present time to the hypophysis cerebri (corpus pituitarium). For long nothing was known about it physiologically, but it is now regarded as a gland with very important internal secretions.

The pituitary body consists of two lobes, the anterior and the posterior. The anterior lobe develops from Rathke's pouch, which is a diverticulum of the buccal ectoderm. This lobe is further differentiated into an anterior part containing numerous epithelial cells, and a posterior portion called the *pars intermedia* which presents entirely different histological appearances. The posterior lobe or *pars nervosa* of the pituitary body develops independently, originating as a downgrowth from the anterior cerebral vesicle. It consists of spindle-shaped cells called *pituicytes*. The anterior and posterior lobes of the pituitary gland, although closely associated anatomically, are therefore totally unrelated as regards development and structure.

The internal secretions which enter the cerebro-spinal fluid from the posterior lobe of the pituitary body probably originate in the pars intermedia. They are all contained in a watery extract of posterior lobe which is known by various trade-names, *e.g.* Pituitrin, Infundin, Pituglandol, etc. Parenteral injection of pituitrin stimulates directly (without the aid of nerves) nearly all the involuntary muscle of the body. One of the hormones, *Vaso-*

pressin, when injected intravenously, constricts the arterioles and causes a moderate but prolonged rise of the blood-pressure. Another hormone, *Oxytocin*, increases the tone and rhythmic contractions of the uterus. In addition, pituitrin produces increased intestinal peristalsis, constriction of the bronchi and increased contractility of the bladder and ureters. The cardiac output is diminished owing to constriction of the coronary arteries. One very striking effect is that the quantity of milk—in the human subject as well as in animals—is greatly increased immediately after an injection. The reason is, perhaps, that the milk is forced out by the stronger contractions of the smooth muscle of the lactating gland ; the amount of milk secreted daily does not appear to be increased following the administration of pituitrin.

Owing to the higher blood-pressure the urinary output may rise for a short time following the intravenous injection of pituitrin into animals, but this effect is negligible in man. Later, however, there is a well-marked anti-diuretic action and this lasts about 8 hours. The effect is attributed to a separate hormone in the posterior pituitary, and the diminution in diuresis is still observed when large volumes of fluid are taken at the same time. Repeated administration of the anti-diuretic hormone over a period of several days while the intake of fluid is unrestricted may produce the pathological condition known as " water-poisoning."

Parenteral injections of pituitrin increase the sugar content of the blood as a result of an action which is antagonistic to that of insulin.

A fourth hormone is known to exist in pituitrin, but it is only of pharmacological interest at present ; it causes dilatation of the pigment cells of the skin when injected into frogs.

Uses of Pituitrin. The most important application of pituitrin is in obstetric practice. Owing to its rapid action on the uterus it is invaluable for the treatment of post-partum hæmorrhage. For this purpose 0·5—1 mil is injected subcutaneously and the action upon the uterus appears within half a minute. In primary uterine inertia the activity of the uterus may be stimulated by the use of small doses of pituitrin, *e.g.* 0·2 mil. Considerable experience, however, is necessary in deciding whether this form of interference is necessary. If pituitrin be injected too early in labour there is a serious risk of prolonged tonic contraction of the uterus causing asphyxia of the child. In no circumstances, therefore, should pituitrin be given before the os uteri is fully dilated, neither must there be any obstruction to the passage of the child. Pituitrin may be employed cautiously where the placenta has been retained for an abnormally long period of time through sluggishness of the uterine movements ; the danger of eversion

of the uterus must, however, be borne in mind. The effect of subcutaneous injections on *diabetes insipidus* is often to cause a great decrease in the quantity of urine, and to diminish the thirst. Unfortunately the action is only temporary (see Fig. 19), but the treatment, in any case, affords a very welcome relief to the patient, whose rest and general condition suffer from the incessant micturition. Pituitary extract has also been tried in *collapse* and *low blood-pressure* in peritonitis, pneumonia, diphtheria, and other infectious diseases, in post-operative *hæmorrhage* from small vessels, and in hæmophilia. It should be noted that a second injection before the effect of the first is over is followed by little or no rise in blood-pressure. The uterus responds again sooner than the vessels, and the injection may therefore be repeated several times during parturition. The combination of pituitary extract with ergot is also recommended, as the action of the former begins quickly, but also disappears quickly, while the latter takes effect more slowly, but the effect lasts longer.

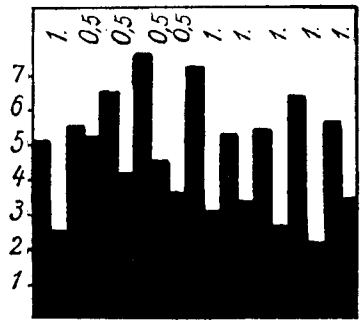


FIG. 19.—Effect of treatment with pituitary extract on a patient of 42 (in a hospital in Christiania), who had suffered for 1½ years from diabetes insipidus. The vertical series of figures indicates the daily amount of urine in litres, the horizontal series the pituitary extract in cubic centimetres (mils). Each injection greatly reduces the flow of urine, but the very next day it is again very abundant.

In *asthma* the pituitary extract treatment is not indicated, as the bronchial muscles are contracted like other involuntary muscles.

PREPARATIONS AND DOSES

Pituitarium Posterior (U.S.P.), the dried and powdered posterior lobe of the pituitary body of cattle. *Dose*, 0·03 grm., ½ gr.

Extractum Pituitarii Liquidum (B.P.), **Liquor Pituitarii Posterii** (U.S.P.), extract or solution of posterior pituitary. An aqueous extract of posterior lobes of pituitary bodies of oxen or other mammals. Biologically assayed. Contains 10 units in 1 mil. The unit is the specific activity yielded by 0·5 milligrm. of the standard preparation and is the same as the international unit. The strength of the U.S.P. preparation is such that 1 mil has between 80 and 120 per cent. of the activity of 5 milligrms. of the standard Powdered Posterior Pituitary, U.S.P. In both cases the biological assay is carried out on the isolated uterus of the virgin guinea-pig. The preparation is a clear colourless liquid with a faint odour. Should not be used later than 18 months after the date of manufacture. *Dose*, by subcutaneous injection, 2—5 units, 0·2—0·5 mil (B.P.); 1 mil, 15 mins. (U.S.P.).

Pituitrin, *Glanduitrin*, *Pituglandol*, *Infundibulin*, are the names of various commercial extracts that are employed subcutaneously or intra-

muscularly in doses of 0·5—1 c.c. (mil). *Hypophysin* is a sterile solution of the sulphates of the four active bases. It is employed in the same way and in the same doses as the other preparations.

Anterior Pituitary

The anterior lobe of the pituitary gland produces numerous important internal secretions. Only a brief reference will be made to these; for more details regarding this interesting subject reference should be made to recent publications on the physiology of the endocrine glands. At least six hormones are known to originate in the anterior lobe.

(1) *The Growth Hormone.* Absence of the growth hormone in early life leads to one form of dwarfism. Excess of this secretion before puberty results in "gigantism," and over-secretion after puberty causes acromegaly. The hormone is produced by the eosinophile cells of the anterior pituitary (see below).

(2) Separate hormones are secreted each having a specific effect on the activity of certain other ductless glands. Thus, there are the thyrotropic, the adrenotropic and the gonadotropic hormones; possibly still another exists to control the parathyroids. Hypersecretion of any one of these hormones results in hyperplasia and over-secretion of the corresponding ductless gland.

(3) The metabolism of carbohydrates and fats is partly governed by hormones produced in the anterior pituitary. When the gland is over-active, *e.g.* in acromegaly, there is often hyperglycæmia and glycosuria, whereas hyposecretion of the anterior pituitary is accompanied by increased carbohydrate tolerance. These effects are explained by postulating a *diabetogenic hormone* in the anterior pituitary. When sodium hydroxide is used to extract anterior lobe the product contains a substance which, on injection into animals, increases the ketone-bodies in the blood and urine. The hormone responsible for this is called the *ketogenic hormone.* It will be evident that a condition closely resembling clinical diabetes can therefore be simulated by injecting extracts of anterior pituitary containing both of these metabolic hormones.

Under clinical conditions the manifestations of disease of the anterior lobe of the pituitary gland are often complex. This is easily understood when it is realised that the cells secreting the various hormones may not be affected to the same extent. Therefore, although a number of syndromes have been described our views on the symptomatology of diseases of the pituitary are likely to be modified as experience increases. Atrophy of the whole anterior lobe causes *progeria* characterised by an extraordinary appearance of senility. Reports have been published of syndromes of this type which have been treated successfully with preparations of anterior pituitary.

Lack of secretion from the eosinophile cells results in dwarfism, but this is almost invariably accompanied by the results of hyposecretion of other hormones. Thus, in Frolich's syndrome there is adiposity, delay in sexual development (frigidity or impotence in adult life), and mental apathy. In the Lorain-Levi type dwarfism is also accompanied by sexual infantilism. The childish stature and proportions are retained but the intelligence is normal. Cushing's syndrome is usually associated with a basophil adenoma of the pituitary. In addition to absence of sexual functions, there are the following manifestations: obesity of the face, neck and trunk, hypertrichosis, pigmentation of the face, hypertension and glycosuria.

Sex Hormones

There are at least two gonadotropic hormones secreted by the basophil cells of the anterior pituitary :

(1) Prolan A. This stimulates ovulation and also the production of *Œstrin*—the follicular hormone of the ovary. Œstrin produces maturation of the uterus and under its influence animals develop periodically the state of œstrus or " heat."

(2) Prolan B presides over the formation of the hormone which originates in the corpus luteum, hence it is also known as Progestin. In pregnancy progestin ensures quiescence of the uterus by antagonising the oxytocin of the posterior lobe of the pituitary. Under its influence, too, proliferation of the uterine mucosa occurs and this favours implantation and retention of the fertilised ovum. Corpus luteum hormone also stimulates hypertrophy of the uterine mucosa and development of the breasts.

Prolan B is found in the urine only during gestation. This is the basis of the *Aschheim-Zondek* and other tests for pregnancy.

Therapeutic Uses of the Sex Hormones. Preparations of œstrin are used therapeutically in the treatment of sexual frigidity, primary amenorrhœa and certain forms of dysmenorrhœa which are attributed to an absolute or relative deficiency of œstrin. Progynon, Menoformon, etc., are extracts of ovarian gland whereas Theelin is an aqueous solution of crystalline œstrin. Preparations are standardised in rat units, one unit being the amount required to induce œstrus when injected into a mature ovarotomised rat, characteristic changes occurring in the vaginal epithelium which are recognisable on examination of smears. The placenta has been found to be particularly rich in this hormone and extracts of placenta are now used commercially in the preparation of œstrogenic substances for therapeutic purposes. Progestin has limited uses in practice. As it favours embedding of the ovum, it has been used with some success in cases of habitual abortion. The same effects can be obtained more directly by giving corpus luteum hormone.

29. INSULIN

As early as 1889 von Mering and Minkowski showed that removal of the pancreas in animals produced a condition apparently identical with diabetes in man. Further experiments indicated that the controlling influence of the pancreas over carbohydrate metabolism was due to an antidiabetic hormone. In 1922 Banting and Best succeeded in producing a potent extract of the pancreas which could be used in the treatment of human diabetes, and the preparation was named Insulin, because it is secreted by the islets of Langerhans. Although it is accepted that diabetes mellitus is ordinarily associated with disease of the pancreas, disorders of other ductless glands, especially the anterior lobe of the pituitary, may play an important part in the ætiology of this disease in some cases.

Chemically, insulin is a complex protein-like substance, the empirical formula of which is stated to be $C_{45}H_{69}O_{14}N_{11}S.3H_2O$. According to Abel, the antidiabetic potency of the product is specially related to the sulphur content. Insulin is readily

destroyed by the action of the proteolytic enzymes in the stomach and duodenum, and it is therefore without effect when given by mouth. Injected subcutaneously, insulin diminishes the quantity of sugar in the blood and other tissues. This is brought about by (1) an increased rate of oxidation in the tissues, and (2) more rapid removal of sugar from the blood-stream by the liver and muscles to be stored as glycogen. The action begins after about 20 minutes and the blood-sugar continues to fall for about 2 hours. Thereafter, the effect gradually diminishes and the concentration of sugar in the blood after 6 hours is approximately the same as before insulin was given. The transient nature of the action of insulin makes it necessary to administer two or more injections daily for therapeutic purposes. Insulin is excreted unchanged in the urine. Excessive doses of insulin produce toxic effects which are the result of hypoglycæmia. When the blood-sugar in man is lowered to about 70 milligrammes per cent. a feeling of great muscular weakness develops, accompanied by giddiness, tremor, inco-ordination, pallor (more rarely flushing), and often profuse sweating. In severe cases coma may develop, and in exceptional circumstances convulsions ending fatally have been reported. The manifestations of hypoglycæmia can be rapidly relieved by giving cane-sugar or, better still, glucose, by mouth. When swallowing is impossible, about 20 mils of 50 per cent. dextrose solution should be injected intravenously. A hypodermic injection of adrenaline, by increasing glycogenolysis, suffices to cause the patient to recover temporarily from coma, and sugar may then be given orally. Pituitrin, which is an antagonist to insulin, may be administered with similar temporary improvement.

Insulin in Diabetes Mellitus. Diabetes is primarily a disorder of the carbohydrate metabolism which results from diminished secretion of insulin by the pancreas (see, however, reference above to the anterior pituitary). Inadequate combustion of sugar in the tissues leads to incomplete metabolism of protein and fat also. The effects upon the body as a whole are therefore serious and far-reaching. Thus, in addition to glycosuria, ketone bodies may appear in the urine, indicating the well marked tendency to acidosis. Some degree of emaciation is almost invariable in untreated diabetes and in severe cases wasting is extreme.

In the treatment of diabetes the amount of food consumed daily must be sufficient to meet the demands of the basal metabolism. In addition to this, an allowance must be made for the energy expended by the patient in carrying out his occupation. Diets are usually prescribed to supply a stated number of calories per kilogramme of body weight. The basal requirement is 25 calories per kilogramme of body weight ; 30—35 calories per kilo-

gramme may therefore suffice for a sedentary worker, and 35—40 may be required for a more active life. A much greater allowance than this is necessary in the case of patients engaged in strenuous manual labour. From the patient's weight and the nature of his occupation the daily requirements expressed in calories can be readily calculated by reference to Tables.[1] The next step is to distribute the calories suitably among the various types of foodstuffs—carbohydrate, protein and fat. In view of the nature of the disease, it seems reasonable to prescribe a minimum of carbohydrate and a maximum quantity of fat. It must be remembered, however, that the metabolism of fat tends to produce ketosis, whereas carbohydrates are completely non-ketogenic and proteins occupy an intermediate position. Furthermore, an insufficiency of carbohydrate in the diet increases the ketogenic property of fats. A convenient system of dieting is known as the Line Ration Scheme. Every ration is really a miniature meal in which the proportions of carbohydrate, protein and fat are suitably balanced and every ration has a calorific value of 210 calories. Thus the patient can readily make up his daily allowance, *e.g.* 3,000 calories, by selecting the appropriate number of rations and distributing these over the meals of the day. Reference to this Scheme will show the extraordinary flexibility of the method employed, which virtually eliminates monotony of diet. The Line Ration Scheme can be easily adapted to provide the *high carbohydrate and lower fat diet* which has been advocated in recent years. The Scheme can also be used by the mild diabetic whose chief concern is the avoidance of foods specially rich in carbohydrate ; it is simply explained to the patient that when selecting carbohydrate foods he should choose those which are relatively poor in carbohydrate. For this purpose, however, Lawrence's " Unweighed Diabetic Diet " is preferable.

If, when a suitable diet has been arranged, insulin proves to be necessary, a sufficient quantity should be prescribed to keep the urine free from sugar *and ketones*. The injections are given about 20 minutes before meals twice or thrice daily. A rough estimate of the amount of insulin required can be made by assuming that 1 unit should be given for every 2 grammes of sugar excreted in the urine *per diem*. From time to time the diet and dosage with insulin call for readjustment, especially in children. Temporary alterations of diet are necessary during febrile illnesses, and at these times also, relatively larger doses of insulin are required. In difficult circumstances the estimation of the fasting blood-sugar often gives very helpful information.

[1] The "Line Ration" Diet Scheme by R. D. Lawrence, M.A., M.D., F.R.C.P. London : H. K. Lewis & Co. Ltd., 1935.

Diabetic Coma. The indications in diabetic coma are to abolish glycosuria and ketonuria, and to replace the tissue-fluids. Large doses of insulin are required as a rule. Fifty units may be injected subcutaneously immediately and at intervals of four hours until the patient's condition and urinary findings show considerable improvement. Insulin-resistance is often so marked in these cases that even larger doses, *e.g.* 100 units or more, may be needed at a time. The patient should also receive 3 pints of normal saline by slow intravenous injection during the first few hours of treatment. When the patient recovers from coma the diet can be built up gradually, using the Lawrence Line Ration Scheme.

Slow-acting Insulins. Owing to the transient nature of the action of ordinary insulin it is impossible, in practice, to keep the diabetic condition completely under control throughout the 24 hours. During the night the blood-sugar gradually rises, and in the 2 or 3 hours preceding breakfast more or less glycosuria frequently occurs. With zinc protamine insulin the maximum depression of the blood-sugar occurs in about 12 hours, and 24—30 hours elapse before the effect completely disappears. A dose administered early in the day will therefore carry on the insulin effect throughout the following night, and usually glycosuria will be prevented. The best technique for the employment of this and other slow-acting insulins has not yet been established, but it is probable that the best results will be obtained in moderate and severe cases of diabetes by combining the use of ordinary insulin and the newer preparations. Thus if a mixture of the two be administered before breakfast, by the time the effects of the ordinary insulin have disappeared the action of the other insulin will have become apparent. Zinc protamine insulin must not be regarded as a substitute for ordinary insulin ; the two varieties are, in fact, complementary in the therapeutics of diabetes. Patients suffering from the disease in a mild form, yet requiring insulin, may, however, be effectively treated by giving a single dose of zinc protamine insulin provided that the time of injection is decided carefully. The slow-acting insulins have their disadvantages and dangers, and these arise out of the same circumstances which have made the new insulins such valuable therapeutic agents. Thus they come more definitely into the category of cumulative drugs, and unless the injections are properly spaced frequent bouts of hypoglycæmic coma are inevitable. Zinc protamine insulin must be injected subcutaneously to produce a sustained action ; by the intravenous route its effects are almost identical with those of ordinary insulin. Although the new insulins are very recent additions to therapeutics, it is certain that substances of this type will be extensively employed in the future.

Preparation and Dose

Insulinum (B.P.), insulin. The solution is a colourless liquid, free from turbidity, containing 20 units in 1 mil. The date of manufacture is stated and the preparation should not be used more than 18 months after. Also obtainable in tablet form, the number of units in 1 tablet being specified. When insulin is prescribed insulin in solution shall be dispensed unless tablet form is specified. The unit is the specific activity contained in such an amount of the standard preparation as the Medical Research Council may from time to time determine. *Dose*, by subcutaneous injection, 5—100 units.

30. LIVER PREPARATIONS

Pernicious anæmia is thought to be due to the absence of a substance which normally ensures the full maturation of the erythrocytes. In consequence, the red blood cells are relatively very scanty, but as there is no lack of material for hæmopoiesis the cells are overloaded with hæmoglobin and are mostly larger than normal. This type of anæmia is therefore also called "megalocytic" and "hyperchromic," and the colour index is high, usually about 1·1 or 1·2.

The hæmopoietic substance which presides over maturation of the red cells is probably formed by a reaction which occurs between an "extrinsic factor" contained in protein food and an "intrinsic factor" secreted by the gastric mucosa. The product resulting from this reaction is evidently stored in the liver, and it is likely that further chemical changes occur here before the synthesis is complete. The constitution of this principle is not definitely established, but it is thought to be the dipeptide of β-hydroxyglutamic acid and γ-hydroxyproline. Vitamin B complex is also believed to play a part in the formation of the active principle. The liver being the organ in which the hæmopoietic substance is stored, the rationale of liver-therapy in pernicious anæmia is clear. It is interesting to recall, however, that the experiments which led up to this important discovery were carried out by Whipple and Robscheit-Robbins in 1920 and 1925, who were investigating the effects of feeding various foodstuffs to dogs suffering from *secondary anæmia* induced artificially. In 1926 these observations were applied empirically by Minot and Murphy to the treatment of patients suffering from pernicious anæmia, and the value of liver-therapy in this disease was immediately accepted. Half a pound of raw or lightly cooked liver taken daily produces subjective improvement in a patient in 3 or 4 days. By the end of a week the blood contains a large proportion of reticulocytes.

When the anæmia is profound, *e.g.* only 600,000 red blood cells per cubic millimetre, the reticulocytosis may amount to 50

per cent. of the circulating erythrocytes. A higher initial count of red cells is accompanied by a lower reticulocytosis. In the course of 3 or 4 weeks the number of erythrocytes in the blood is often trebled or quadrupled. Microscopic examination of the blood shows that the cells have simultaneously reverted to the normal morphology. As the number of red cells rises rapidly the iron supply of the body may be depleted and the colour-index may fall considerably below unity. Thus a stage may be reached at which iron therapy may be indicated. When the " blood-picture " has returned to normal—say, 5,000,000 red cells and 90 per cent. of hæmoglobin—an adequate maintenance dose of liver should be given.

Following the use of liver, concentrated extracts were soon available for oral administration. In recent years, however, liver preparations have been produced for parenteral administration—intramuscularly and intravenously—*e.g.* Anahæmin, Campolon, Hepatex, etc. Anahæmin is particularly potent even in small doses injected intramuscularly. A severe case of pernicious anæmia will respond satisfactorily to an initial injection of 2 mils of this preparation followed by 1 mil at weekly intervals for about 6 weeks, in which time the " blood-picture " has usually reverted to the normal state. Thereafter 1 mil is injected *monthly* as a maintenance dose.

As achylia gastrica is invariably present in pernicious anæmia, ½-drachm doses of dilute hydrochloric acid should be given 3 or 4 times daily after food ; suitable flavouring agents are natural lemonade or syrup of cherry.

It is doubtful whether liver preparations have any effect upon subacute combined degeneration of the cord, which is so often associated with pernicious anæmia. Improvement is, however, recorded following large doses of extracts administered parenterally. The peripheral neuritis which is so troublesome a feature of subacute combined degeneration of the cord, is said to improve when Vitamin B_1 is given in addition to liver-therapy. This claim, however, has not yet been fully confirmed.

Stomach Preparations. A hæmopoietic principle is also present in other body tissues, including the stomach wall. Hog's stomach, chopped fine, desiccated and defatted, has therefore been employed therapeutically in pernicious anæmia. The dose recommended is 10 grammes for every million deficit in the red cell count, followed by a daily (maintenance) dose of about 15 grammes.

Controlled observations show that the hæmopoietic factor is of no value in microcytic (hypochromic) anæmia. The beneficial results following the administration of large quantities of raw or

lightly cooked liver in this form of anæmia are due to the high iron content of this food.

Preparations for the treatment of pernicious anæmia are tested for potency by their effect in curing the disease in the human subject. This is a cumbersome method, but, unfortunately, neither chemical assay nor tests upon laboratory animals are practicable as yet. The beneficial effects of potent preparations upon the blood (reticulocytosis) in patients suffering from pernicious anæmia are unmistakable. Conversely, in doubtful cases, a potent liver preparation given parenterally, may be used as a therapeutic test for the presence of pernicious anæmia.

Preparations and Doses

Extractum Hepatis Siccum (B.P.), **Extractum Hepatis** (U.S.P.), an alcoholic extract of ox or sheep liver. It contains the specific principle which increases the number of red corpuscles of persons suffering from pernicious anæmia. A light brown, very hygroscopic powder, faintly meat-like odour, saltish taste, soluble in water. The dried powder is mixed with $\frac{1}{10}$ of its weight of dry sodium chloride and transferred to tubes which are then hermetically sealed. Each tube contains the equivalent of 225 grms., or about $\frac{1}{2}$ lb. of fresh liver. This description applies to the B.P. preparation, but the U.S.P. extract is similar. *Dose*, the contents of 1 tube (B.P.); dosage to be stated on the label of the container (U.S.P.).

Extractum Hepatis Liquidum (B.P.), **Liquor Hepatis** (U.S.P.), liquid extract or solution of liver. The dry extract dissolved in a mixture of glycerin, alcohol and distilled water. One ounce is the equivalent of 8 oz. of liver. This description applies to the B.P. preparation; the U.S.P. extract is similar. *Dose*, 30 mils, 1 oz. (B.P.); dosage to be stated on the label of the container (U.S.P.).

Liquor Hepatis Purificatus (U.S.P.), a solution of liver for parenteral injection. Action and uses are the same as those of the preparations of liver which are given by mouth. Dose to be stated on the label of the container.

There are numerous proprietary preparations of liver suitable for intramuscular or intravenous administration, *e.g. Anahæmin, dose*, 2 mils intramuscularly, followed by 1 mil at intervals of 1 week until the "blood-picture" becomes normal (usually about 6 weeks); thereafter, a maintenance dose of 1 mil per month suffices as a general rule. Other preparations are *Hepastab, Pernæmon Forte, Hepatex, Campolon*, etc.

Stomachus (U.S.P.), dried and defatted wall of the stomach of hogs. Taste and odour distinctly unpleasant. It is used in the treatment of pernicious anæmia. The *dose* is that stated on the label of the container.

31. THYROID GLAND

Among the operations that were more frequently performed after the introduction of the new antiseptic methods in the seventies of last century was the extirpation of the thyroid gland. Doubt was soon felt, however, regarding the justification of the operation when J. L. and A. Reverdin, in 1882, drew attention to

the fact that it was not infrequently followed by a peculiar disease identical with the spontaneous myxœdema (*myxœdème post-opératoire*), and Kocher, in the following year, published his famous studies of the general condition produced by the extirpation, to which he gave the name of cachexia strumipriva. The sequelæ appear in two forms, one beginning immediately after the operation, the other some time later. The first, *tetany*, consists of tonic convulsions, which at first are situated in the flexors of the upper extremities, and, by passing on to the respiratory muscles, may end fatally in the course of a few days. The true significance of this was appreciated only when the parathyroid glands were discovered (see p. 388). The other form, which comes on insidiously through weeks or months after an apparently successful operation, is characterised by œdema of the subcutaneous tissue, anæmia, mental and physical dulness, loss of memory, slowness of speech, etc., in short, the symptoms peculiar to *myxœdema*.

These observations were not new, however. Almost 30 years previously, Schiff had described similar symptoms and death from tetanus, in thyroidectomised animals, and physiologists had pointed out, but in vain, the great dangers of the operation. It was only after the experiment had been made on a large scale on man, often with the most unfortunate results, that a perception of the great physiological importance of the thyroid gland was obtained, and new animal-experiments were made, which soon yielded very important therapeutic results. These showed that in animals the consequences of extirpation could be averted by previously transplanting a piece of thyroid gland in the subcutaneous tissue or in the peritoneal cavity. The result was dependent on the fate of the transplanted fragment of gland. If it was vascularised and continued to live, there were only slight, if any, sequelæ. In the reverse case, the protective action continued only as long as any of the transplanted piece of gland remained ; when, in the course of a few weeks, it was all absorbed, convulsions came on, which rapidly ended in death.

These and similar experiments form the basis of modern thyroid therapy. At first, efforts were directed towards the transplantation of pieces of gland, but the treatment was soon simplified when Mackenzie and Howitz pointed out that myxœdema could be influenced by simply letting the patient eat the raw or boiled glands. From this it was clear that the gland contained an active substance which resisted both digestion and a boiling-temperature, an assumption that was confirmed by Baumann's production (1895-96) of *iodothyrine*, an organic body containing iodine, which proved to possess the characteristic

action of the gland. It was subsequently shown by Oswald that iodothyrine did not occur in a free state, but in combination with a globulin, as *thyreoglobulin*, which is found in the colloid substance that fills the follicles of the glands. The varying percentage (9—13) of iodine in iodothyrine has raised doubts, however, as to whether it were a simple hormone. This has at last (1919) been solved by Kendall, who, after working on an enormous amount of material—3,000 kilogrammes of the gland—has succeeded in isolating, in colourless crystals, a new substance, *thyroxine*, an indol derivative containing 65 per cent. of iodine, which even in milligramme doses elicits the typical action on metabolism, and myxœdema, and in larger doses hyperthyroidism in the normal subject. This result was in fact to be expected. The hormones are formed in their several organs and conveyed in the blood to other organs, and must, therefore, be able to pass through the cell-walls. It is, therefore, probable that they are not amorphous, colloid, albuminoid substances, but crystalline, dialysable, comparatively simple chemical compounds. The hormones, moreover, have no " zoological " specificity. When the glands in man are insufficient, glands of some animal or other may be used—the thyroid gland from the sheep, the pituitary body from the ox, and so forth. This also clearly calls in question their albuminoid character, for albumin and allied bodies are each specific to one species, and in other species elicit strong reactions, " serum disease," anaphylaxis, etc.

The reason of the variation in the consequences of excision of the gland has been widely discussed. Animals (dogs) soon succumb in convulsions, while in man the slowly supervening myxœdema is the prevailing effect. The question has now been solved by the discovery of the previously overlooked parathyroid glands, which in dogs are situated just behind, and embedded in, the principal gland, and are removed with it in the operation, whereas in man they are farther to one side, and are therefore generally left. It is now believed that the function of the thyroid gland consists in furnishing one or more of the substances necessary to the normal metabolism and the normal growth of the body, while the parathyroids exert a controlling influence over the calcium metabolism (see below). Removal of the thyroid gland alone before puberty results in cretinism, but in the adult deficiency of thyroid secretion produces myxœdema. If the parathyroids are excised, even though the thyroid gland is left intact, tetanic convulsions supervene and, if untreated, terminate fatally in the course of a few days.

Action. The therapeutic employment of thyroid preparations has taught us that the individual reaction varies greatly. Several

investigators, in experiments on themselves, have consumed large quantities without ill effects, and a child of 2½ has been known to eat tablets answering to 27 grammes of thyroid without noticeable effect ; but in other cases a long series of toxic symptom appears. Among the most general are **disturbances of circulation** corresponding with those in Graves' disease, namely, *palpitation* and a *rapid pulse*. Patients suffering from hyperthyroidism are very subject to attacks of tachycardia, with a pulse of 150 or more, and considerable cardiac weakness. Other symptoms are *headache* and *congestion*, *profuse sweating*, *tremor*, *nervousness* and *glycosuria*. Excessive doses of thyroid do not cause exophthalmos, although this condition is nearly always present to some extent in Graves' disease.

Still more peculiar and very constant is the influence on **metabolism,** which consists in a great increase in katabolism. The amount of urine is increased, and the elimination of nitrogen is so great that it exceeds the amount of nitrogen taken in the food, that is to say, the protein of the tissues is affected. Even when fat and carbohydrates are given in abundance they are unable, as in normal conditions, to protect the protein. It is only by taking a surplus of albumin in the food that the abnormal consumption of tissue proteins can be arrested and nitrogenous equilibrium once more established. As a consequence of the destruction of protein, the phosphates also increase in quantity. A great amount of fat is oxidised, more oxygen is taken up, and more carbonic acid is excreted through the lungs. It is not known whether the diuresis is due to a direct action upon the kidneys or to changes in the circulation. These three factors together—protein-destruction, oxidation of fat, and increased loss of fluid—especially in myxœdematous or very corpulent persons, bring about a rapid wasting and a loss of weight that may amount to several kilogrammes weekly.

In addition to these symptoms of increased metabolism there are also effects of an opposite nature. In dogs, for instance, that have undergone thyroidectomy, the post-mortem autolysis is less than in the organs of normal animals. In white mice, even minute doses considerably increase the resistance to acetonitril, CH_3CN, as they prevent the liberation of prussic acid, which in normal animals quickly brings death (Reid Hunt's acetonitril reaction). The emaciation in man is probably partly due to a reduction in the normal conversion of carbohydrates into fat. Gudernatsch found a very singular effect on tadpoles. When fed with thyroid their growth ceased and metamorphosis began at once ; and in 7 days, tadpoles that had been limbless developed fore and hind extremities and lost their tail, the result being miniature frogs.

Therapeutic Uses. Thyroid is the specific remedy for *myxœdema*. The characteristic symptoms of the disease usually

begin to disappear in a few days. The cutaneous œdema decreases, the face loses its dull apathetic expression and reassumes its ordinary appearance, the movements are quicker, the voice is more natural and the skin once more pliable, the secretion of sweat recommences, and with an abundant flow of urine the body-weight is reduced. In the course of a few weeks the improvement may be so great that the dull, bloated patient is a changed being, both mentally and physically. A permanent cure is not attained, however, by one course of medication. Some time after the hormone administered is used up, there is generally a return of the disease ; and in order to maintain the good result, the treatment must be continued with a suitable dose now and then, *e.g.* once a week or fortnight, or as often as it appears to be necessary. As already mentioned, myxœdematous patients are very sensitive to thyroid, and liable to react with pronounced cardiac symptoms and loss of weight, and it is therefore necessary to begin with small doses and increase them gradually. *Operative myxœdema* and *sporadic cretinism* (infantile myxœdema) are similarly influenced by thyroid medication. Excellent results are obtained in cases of cretinism if treatment is begun in infancy. In older children, some stigmata of hypothyroidism—usually a degree of mental dulness—persist throughout life despite the continuance of treatment. Even *endemic cretinism* is somewhat benefited by prolonged treatment.

Among the various forms of enlargement of the thyroid, the *simple hyperplastic goitre* in young persons is most influenced. The effect is similar to that mentioned under potassium iodide (p. 426). Whatever result is attainable is obtained in the course of 3 or 4 weeks, after which an intermittent treatment is kept up to prevent recurrence. The active principle is excreted in the milk. I. Bang records the case of an infant at the breast, with a congenitally abnormal thyroid gland, that improved rapidly when the mother was treated with thyroid.

Thyroid has also been tried in *exophthalmic goitre ;* but when it is remembered that the symptoms in this disease are somewhat similar to those of thyroidism, it is not surprising that the result has often been unfortunate. Indeed, the disease is now treated with success in a large proportion of cases by surgical removal of a part of the gland, or by diminishing its activity by means of radium or deep X-ray therapy.

Thyroid is also employed for *obesity*, and a great reduction in weight can often be attained very quickly (10 kilogrammes in 14 days). The treatment has thus become popular, but unjustly so. It is irrational, because the reduction is due not only to diuresis and oxidation of fat, but to a great extent to the destruc-

tion of proteins. The results, moreover, are of brief duration, the body-weight in most cases increases rapidly after the treatment is concluded, and serious secondary effects are often seen, such as cardiac symptoms, glycosuria, great exhaustion and neurasthenia. Thyroid should therefore be employed with great caution as a subsidiary remedy to the dietetic treatment, and under continual medical observation. The uncontrolled use of the drug has been the cause of fatal cases of poisoning.

The good effect that thyroid has had upon the nutrition of the skin in myxœdema has led to its being tried in various *skin-diseases*, such as ichthyosis, lupus, eczema, and above all psoriasis; in the last-named disease good results are described. Improvement has also been reported in obstinate cases of syphilitic eruptions (psoriasis luetica) and ulceration that iodine and mercury failed to cure.

It should be remembered that the action of thyroid comes on slowly and lasts a long time, and therefore, in order to run no risk of being surprised by unwelcome symptoms, the commencing doses should be small and increase slowly, with occasional intervals of a few days. The effects described above, including the therapeutic action, are found in pure thyroxine, and can be estimated quantitatively by the influence of the drug on the nitrogenous exchange, this being increased 2 per cent. by 1 milligramme, and 20 per cent. by 10 milligrammes, so that the doses can be regulated with exactitude.

Preparations and Doses

Thyroideum (B.P., U.S.P.), dry thyroid, a powder prepared from the fresh gland of oxen, sheep or pigs (or other animals used for human food, U.S.P.). It contains 0·1 per cent. of iodine (0·2 per cent., U.S.P.) in combination as thyroxine. *Dose*, 3—30 centigrms., $\frac{1}{2}$—5 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.).

Thyroxinsodium (B.P.), *Thyroxinum* (U.S.P.), the active principle of thyroid gland prepared synthetically. Both are white crystalline powders almost insoluble in water. Used with the same indications as thyroid, over which it has no advantages for clinical purposes. *Dose*, 0·1—1 milligrm., $\frac{1}{640}$—$\frac{1}{64}$ gr. (B.P.); 0·5 milligrm., $\frac{1}{120}$ gr. (U.S.P.).

In recent years much research has been undertaken to determine whether antihormonal substances can be produced in the tissues under certain conditions. This would now appear to be established, and it is possible that this discovery will find some therapeutic application.

Addendum

Other Preparations from Organs of Animals

At about the time when the first transplantations of the thyroid gland and the first injections of an extract of the gland were tried upon man, Brown-Séquard (1890) announced that in the testicles of young, strong,

adult animals he had found a substance that was capable of restoring to the ageing organism some of the vigour of youth, both mental and physical. At first he employed subcutaneous injections of an emulsion prepared by the triturating of the testicles in water, and which thus included spermatozoa and all other formed elements. As the danger of septic poisoning was great, extracts were subsequently made instead of the emulsion, and were said to give the same results, namely, increased energy, sexual desire, and a temporary return of lost power, in short, all specifically masculine properties. The famous physiologist's statements aroused extraordinary interest, and soon also contradiction ; and since then, sober investigation has shown that the testicle extract is not the long-sought elixir of life. This does not, of course, preclude the possibility that, in addition to the secretion necessary to propagation, the testicles may furnish other products of great physiological importance.

In connection with the therapeutics of testicle extract, Brown-Séquard put forward the theory of the twofold secretion of glands, one external, with its outlet through passages, and of which the purpose is generally manifest, the other an *internal secretion*, which may take place in closed organs, and of which the products, called by Starling *hormones* (from ὁρμαω = I urge on), pass into the blood to perform important, to some extent little known, functions. Upon this theory the so-called *opotherapy* (ὀπος = juice), *hormotherapy* or *organotherapy* rests. This branch of the healing art has its origin far back in history. The idea that certain effects or properties accompanied certain organs, and that these could be transmitted by the consumption of those organs, has been cherished from time immemorial by all races down to the existing wild tribes, who eat the heart of their fallen foe in order to acquire his courage. (The centaur, Cheiron, reared Achilles on lions' hearts and bears' marrow.) After having been abandoned for centuries by medical science, this branch of therapeutics is now returning in rational form, a renascence to which we are already indebted for such valuable drugs as the suprarenal, thyroid, pituitary, and liver extracts.

Numerous other preparations offered for sale are nothing but indiscriminate quack medicines. All sorts of mystic productions have been called to life by organotherapy, and manufacturers with a keen eye to business have very willingly fallen in with the demand for a specific remedy for each organ. In this way one can obtain cerebrine for diseases of the brain, pulmonine for pneumonia and tuberculosis, cardine for heart-disease, oculine for eye-diseases, prostatine for hypertrophy of the prostate gland, kidney tablets for nephritis, etc., etc., etc. Discussion of these absurdities is superfluous.

THE PARATHYROID GLANDS. See Chapter on Calcium.

32. NITRITES (AMYL NITRITE)

Amyl nitrite, sodium nitrite, potassium nitrite and other *nitrous anhydride compounds* paralyse directly all the smooth muscles of the body, this effect being due to the group O — N = O. Amyl, sodium, etc., only play the part of carriers, and share in the action only in so far as they affect the stability of the compound. The less stable and more volatile these compounds are, the more quickly is the active group given off, and the more rapidly does

the action appear and subside, whereas the nitrites which are decomposed more slowly in the body have a more prolonged action.

Amyl nitrite, like other esters, is very prone to saponification, and is even decomposed by water into amyl alcohol and nitrous anhydride, $C_5H_{11}.O.NO + H_2O = C_5H_{11}OH + HNO_2$. It accordingly acts very quickly. When 3—5 drops of amyl nitrite are inhaled, after a few seconds a strong throbbing in the arteries of the neck is felt, the head becomes hot and the face *flushes* brightly with a colour between that of arterial and venous blood. The vaso-dilatation spreads from the face downwards over the neck, forming an irregular boundary-line on the chest ; sometimes red marbling and irregular patches may extend as far as the inguinal region. The dilatation is always most pronounced in the face, however, and in this respect resembles natural blushing, which is similarly localised. The susceptibility of people to the effect of nitrite varies greatly—yet another point of resemblance to the blush of bashfulness or embarrassment ; in some people it may never appear, and in others appears all too readily. In the course of two or three minutes after inhalation of only a few drops, the entire effect has disappeared. Continued inhalation may lead to dizziness, intoxication and loss of consciousness.

The injection of the skin is due to dilatation of both arterioles and veins. The action upon the vessel walls may be demonstrated by artificial perfusion experiments through isolated organs or amputated extremities ; if a few drops of amyl nitrite be added to the blood flowing into the arteries, the output of blood from the vein is immediately increased, because the calibre of the vessels is enlarged. Animal experiments show that, besides the vessels of the face, the arteries on the surface of the brain are also dilated, but no change can be seen in the retinal vessels. Simultaneously with the vaso-dilatation there is a fall of the blood-pressure, and as a consequence of this the *pulse-frequency* increases, and in man may amount to twice the normal rate.

The *respiration* is at first, as the expression of a reflex action from the nasal mucous membrane, often arrested, as it is with inhalation of other irritant gases, but subsequently increases in depth and frequency.

If animals are made to inhale large quantities of amyl nitrite, or if *blood* is treated with amyl nitrite in a test-tube, the blood assumes a dark chocolate colour ; there is formation of methæmoglobin, which does not benefit the respiration, as it firmly fixes oxygen and only very slowly gives it off again to reducing substances. The cause of death is partly due to this change in the blood and partly to respiratory failure.

Erythrityl tetranitrate produces a powerful nitrite action as the effective ion is slowly liberated in the tissues. The blood-pressure may fall as much as 35 millimetres Hg. The maximum effect is attained in about half an hour and persists for 2—3 hours ; thereafter the blood-pressure gradually increases to the original level, although this may take as long as 6 hours. In the official preparation lactose is used as a diluent.

Sodium nitrite, which as a solid compound is given internally, is far weaker in action, as it is absorbed more slowly. It produces the same symptoms as amyl nitrite, but the effect is of longer duration ($\frac{1}{2}$ to 1 hour). Amyl nitrite taken internally also has far slighter action than when inhaled, and recovery may therefore be seen even after enormous doses (1 teaspoonful to 1 tablespoonful).

Nitroglycerin, $C_3H_5(NO_3)_3$, as the formula shows, is a nitrate, but is partly reduced in the body to nitrite, and acts even more powerfully than amyl nitrite. Even 1 milligramme produces flushing of the face, a feeling of intense heat, and a quick pulse. It differs from amyl nitrite in that its action is often accompanied by severe headache. Differences also appear (convulsions after nitroglycerin) in cases of poisoning in animals. In spite of the great toxicity, tolerance is often established, so that the doses may be increased. In poisoning with large quantities, the red colour of the face gradually changes into dark cyanosis, and death supervenes in the course of a few hours, preceded by diminished respiratory and pulse frequency, and coma. Both amyl nitrite and nitroglycerin may occasion glycosuria.

Therapeutic Uses. The basis for the employment of amyl nitrite is determined by its marked effects. It has been tried for all diseases in which the symptoms indicate *vascular spasm,* especially where there is supposed to be tonic contraction of the coronary arteries of the heart, *i.e.* in angina pectoris. In a considerable proportion of cases there is rapid relief of substernal pain which accompanies this condition. When the coronary vessels have become sclerosed, and therefore unable to dilate, amyl nitrite is much less likely to give relief. In the presence of coronary thrombosis administration of nitrites is contra-indicated, as further clotting may be precipitated by the sudden lowering of blood-pressure. Amyl nitrite has also been employed in such acute spasmodic conditions as asthma and certain types of dysmenorrhœa. Epileptic and eclamptic fits can occasionally be aborted by the inhalation of full doses of amyl nitrite at the first warning of the onset of convulsions. Migraine and sea-sickness have also responded to this treatment in a small proportion of cases. In general, however, it may be said that, apart from its

use in angina pectoris, the therapeutic value of amyl nitrite is very limited.

Sodium nitrite and other slowly acting compounds are usually employed to reduce arterial hypertension, the effect lasting 2—4 hours. It is well known that many patients feel worse as a result of over-energetic treatment of this kind and caution should be exercised regarding dosage.

A tablet containing 0·5 milligramme of nitroglycerin crushed and retained beneath the tongue is often as effective as amyl nitrite in relieving angina pectoris. With nitroglycerin there are the additional advantages that dosage is more accurately controlled and palpitation, flushing, headache, etc., are less troublesome.

There is no reliable evidence that nitrites lessen the frequency of the paroxysms of angina pectoris, although individual patients may maintain that the number is reduced while taking nitrites in small doses several times daily.

Nitrites are contra-indicated in aortic incompetence and any other conditions in which the diastolic pressure is low, for in these circumstances syncope may occur. Sudden changes of blood-pressure are also undesirable in patients suffering from atheroma.

Preparations and Doses

Amylis Nitris (B.P., U.S.P.), $C_5H_{11}NO_2$, a clear, yellow, volatile liquid, with spicy taste and a fruity odour like that of an over-ripe pear. *Dose* for inhalation, 12—30 centimils, 2—5 mins. (B.P.); 0·2 mil, 3 mins. (U.S.P.). A convenient form is the tiny, thin glass capsules containing about 3 mins., which can be broken with slight pressure in the handkerchief.

Sodii Nitris (B.P., U.S.P.). $NaNO_2$, white sticks or crystals, very readily soluble in water. *Dose*, 3—12 centigrms., ½—2 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.).

Spiritus Ætheris Nitrosi (B.P.); *Spiritus Æthylis Nitritis* (U.S.P.). This antiquated preparation, which is an alcoholic solution of ethyl nitrite, is still official in several pharmacopœias. It deteriorates rapidly. *Dose*, 1—4 mils, 15—60 mins. (B.P.); 2 mils, 30 mins. (U.S.P.).

Liquor Glycerylis Trinitratis (B.P.), **Spiritus Glycerylis Trinitratis** (U.S.P.), a 1 per cent. alcoholic solution of nitroglycerin. *Dose*, 3—12 centimils, ½—2 mins. (B.P.); 0·05 mil, 1 min. (U.S.P.). These small doses are given to begin with, and if tolerated well may be increased to 10—30 mins. daily.

Tabella Glycerylis Trinitratis (B.P., U.S.P.), tablets, each containing 0·5 milligrm. of nitroglycerin. *Dose*, 1—2 tablets (B.P.); an amount corresponding to 0·0006 grm., $\frac{1}{100}$ gr. of glyceryl trinitrate (U.S.P.). Not a very practical preparation, as the nitroglycerin diminishes with keeping.

Erythritylis Tetranitras Dilutus (B.P., U.S.P.). Diluted Erythrityl Tetranitrate, Erythrol Tetranitrate (50 per cent.). $C_4H_6(NO_3)_4$. A white powder, odourless, tasteless except for slight sweet taste of lactose which is the diluent. *Dose*, 0·03—0·12 grm., ½—2 grs. (B.P.); 0·03 grm., ½ gr.

(U.S.P.). Is employed as a vaso-dilator in cardiac diseases, angina pectoris, and chronic disease of the kidneys. For very susceptible persons even ½ tablet is sufficient to produce strong congestion.

Benzyl Benzoate, $C_6H_5.CH_2O_2C.C_6H_5$. The opium alkaloid papaverine, which is a benzyl-isoquinoline derivative, is also remarkable for its paralysing action on unstriated muscle (see pp. 84 and 88). According to Macht's investigations, several of the simpler benzyl derivatives also have the same action. Of these benzyl benzoate is especially suitable for clinical use, as it has little toxicity, and is converted into hippuric acid in the organism. It has shown itself efficient in many cases of spasm in smooth muscle, *e.g.* in *asthma*, *pyloric spasm* and other kinds of *intestinal spasm*, *biliary and renal colic*, *spastic dysmenorrhœa*. *Hypertenion* of varied origin is also treated successfully; when once the blood-pressure has been lowered by a suitable dose, a continuation of smaller doses is sufficient to keep it down. In *whooping-cough* it often causes the attacks to become less frequent and severe. Benzyl benzoate is a colourless or yellowish liquid, with an unpleasant taste; boils at a high temperature. It is employed in a 20 per cent. alcoholic solution, of which the taste can be improved by a few drops of benzaldehyde (oil of bitter almonds). *Dose*, 20—40 drops 2 or 3 times a day, for young children beginning with 5 drops in milk or sugar and water. Benzyl benzoate may be taken for weeks or months.

Addendum

Yohbinime is an alkaloid found in the bark of *Corynanthe yohimbe* (*Rubiaceæ*), which is used as an aphrodisiac by the natives of Western Africa during the hottest season, when the heat of the sun is said to weaken the power of coition. According to Franz Müller's investigations, yohimbine produces, by its action on the vessel walls, dilatation of the vessels of the skin, intestine, kidneys, and especially of the genital organs. The blood-pressure consequently falls, and the increased amount of blood in the genitalia, together with increased reflex irritability in the sacral region of the spinal cord (erection-centre), explains its aphrodisiac action. Mammals exhibit liveliness after small doses, hyperæmia in various peripheral parts, turgescence of the testes, and erections; after large doses great excitement, with prolonged erections, salivation, diarrhœa and convulsions. In man yohimbine has been employed with varying results in cases of neurasthenic impotency, and has recently also been tried in arterio-sclerosis, to dilate the vessels and lower the blood-pressure. For impotency 5—15 milligrms., $\frac{1}{12}$—$\frac{1}{4}$ gr., of the hydrochloride, *Yohimbinæ Hydrochloridum*, is given 3 times a day; in obstinate cases, 10—20 milligrms., $\frac{1}{6}$—$\frac{1}{3}$ gr., may be injected subcutaneously.

Mistletoe, *Viscum album*, a plant growing parasitically on various trees, is employed in France for arterio-sclerosis, as, in a way not quite understood, it causes the blood-pressure to fall. Two substances of the nature of saponin are considered to be the active principles. It is prescribed as an aqueous extract (Guipsine) in doses of 0·3—0·5 grm. daily.

33. QUININE

Cinchona bark contains about 20 different alkaloids, of which, however, only *quinine* is of any great medicinal importance, and quinotannic acid, which behaves like other tannic acids.

Action. Quinine occupies a special position among the vegetable alkaloids. Most of the others have more or less clearly-defined points of attack in the body, and act upon special tissue, *e.g.* those of the nervous system, while they spare others. Quinine, on the contrary, is a universal **protoplasm poison**, which in sufficient concentration is fatal to almost all cells, including those in which only purely vegetative processes take place. The action generally commences with a temporary augmentation of the activity of the protoplasm, this being followed by a diminution in all vital processes, and finally by death. The same thing is seen with other protoplasm poisons, such as the aromatic antiseptics, which in many respects quinine resembles.

The influence upon the living protoplasm may be very clearly seen in lower organisms that have independent movements, the activity of which can be watched under the microscope and provides a gauge of their vitality. Most organisms such as these die quickly, even in very dilute quinine solutions (fundamental investigations of Binz, 1867). It appears to act most strongly upon comparatively large protoplasmic micro-organisms. If a drop of a putrid hay infusion, or something similar, that is swarming with actively-moving *infusoria*, be placed upon the object-glass of a microscope together with a drop of 1 per cent. quinine solution, it will be seen that the infusoria are instantly paralysed; their rapid ciliary movements immediately cease, the protoplasm becomes dark and granulated, and in a short time has dissolved into amorphous granules. Even in a dilution of 1 in 20,000 infusoria become sluggish after 5 minutes, after 2 or 3 hours all movement has ceased, and a few hours later there is nothing to be seen but granular detritus. There is a similar susceptibility in *amœbæ*, *e.g.* the malaria amœba, the development of which is checked by the presence of a mere trace of quinine. The vegetable micro-organisms, *cocci*, *bacilli* and *bacteria*, exhibit very varied behaviour, a few being very sensitive, others comparatively insusceptible, to quinine. Among the most resistant of all micro-organisms are moulds, which thrive well in quinine solutions (prepared from the sulphate of quinine), and the spirillum of relapsing fever, which is not affected by quinine solutions weaker than $\frac{1}{2}$ per cent., this according well with the teaching of clinical experience, which shows that quinine has no effect upon that fever.

The protoplasm of the higher organisms also reacts in various ways to quinine. The *white blood-corpuscles*, like the morphologically-allied amœbæ, are remarkable for their extreme sensitiveness. Even in a solution of 1 in 20,000 they evince distinct symptoms of paralysis; if quinine be added in the proportion of

1 to 10,000 in the warm, moist chamber to such leucocytes, they immediately become motionless. Even in the concentration in which quinine circulates in the blood after large doses, it so acts upon the leucocytes that, as Binz has demonstrated by observations of the frog's mesentery, they lose the power of passing out of the vessels (the formation of pus is checked). In man after large doses $\frac{1}{200}$ of body-weight), the number of white blood-corpuscles falls to $\frac{1}{4}$ of the normal amount.

The diminution in *chemical activity* goes hand in hand with the cessation of the movements of the protoplasm. If turpentine containing ozone and guaiacum tincture are mixed with a few drops of blood, they immediately assume a blue colour (oxidation), but if only a minute quantity of quinine (1 in 20,000) be added, the reaction is checked.

Freshly excised, still living kidneys, perfused with blood containing glycocoll, convert benzoic acid into hippuric acid ; when a little quinine is added to the blood, this synthesis is prevented. It is probable that the principal effect of quinine in the living organism also is to restrict many of the normal chemical changes, syntheses, oxidation and decomposition, and thus to diminish the metabolism (Schmiedeberg), the reason probably being that the quinine paralyses the intracellular enzymes by whose aid the chemical changes are wrought. The *nitrogenous metabolism* especially is checked. In a healthy person, after 1·6 grammes of quinine hydrochloride, the total amount of nitrogen in the urine was diminished by 24 per cent. The other solid constituents of the urine are also decreased. Prior, experimenting on himself and on dogs, found an average increase of 11—12 per cent. in the flow of urine, but the amount of urea was nevertheless diminished by 19—20 per cent., of uric acid by 72 per cent., of sodium by 9 per cent., sulphuric acid by 34 and phosphoric acid by 23 per cent.

In the healthy subject quinine has little influence upon the **body-temperature.** In most febrile diseases, however, average non-toxic doses occasion great fall of temperature. It seems natural to connect this action with the above-mentioned influence on metabolism, and consequently to regard the fall of temperature as a result of *diminished production of heat.* Against this view it may be urged that quinine, as far as may be judged by the experiments hitherto made, does not seem to have a marked influence on the consumption of oxygen and the giving off of carbonic acid, *i.e.* on the oxidation which is the body's principal source of heat, and that the fall of temperature might also be due to increased loss of heat. The body-temperature also decreases, however, after quinine in febrile animals, when all increased loss of heat is

prevented ; and careful calorimetric experiments even show that, far from increasing the loss of heat from the surface of the body, quinine diminishes it. As the temperature nevertheless falls, the only possible explanation is that it is due to a reduced production of heat. The action of quinine is thus the reverse of that of the numerous newer antipyretics, antipyrine, phenacetine, etc., all of which, as will be shown in the next chapter, produce a fall in temperature by increasing the loss of heat. The reduction of temperature by means of quinine may be compared to letting the fire burn low, or go out, in a room that is too hot, while to give antipyrine is like opening the windows. It is clear that these are two entirely different ways of cooling. The first is at once a more radical, more causal, but, as the temperature falls quite gradually, in many respects a milder treatment ; the second causes greater and more sudden changes of temperature. Thus, in spite of the attractive, often summary, action of the newer antipyretics on high temperatures, quinine, which not long since was thrown too much into the shade, retains its peculiar and great value. If, with Liebermeister, we understand by " antipyretic " a drug that diminishes the production of heat, it is the only antipyretic, for all the other temperature-reducing drugs are merely " antithermics," which cool in the same way as a cold bath.

The effects of quinine are represented above as they appear in the amounts usually employed in febrile diseases. According to several observers, after small doses there is a slight rise in temperature before the fall, and a corresponding small increase in the amount of the nitrogenous constituents of the urine before their diminution. It is also seen how very dilute solutions increase the movements of infusoria and white blood-corpuscles for a short time before the paralysing action ensues.

Quinine acts in an analogous manner upon **striated muscle.** It first causes a temporary increase and then a decrease in the absolute strength and the working capacity, and finally death, followed immediately by rigor. The results are the same whether the muscles are curarised or not ; the action affects the contractile substance itself independently of the nerves.

The **heart** is probably acted upon in the same way as the skeletal muscles. Small quantities of the drug accelerate the pulse and raise the blood-pressure ; with large quantities the pulse becomes slower and the blood-pressure falls. As atropine does not then alter the pulse-frequency, it may be assumed that there is a weakening of the motor-apparatus of the heart. The reduced work of the heart has no doubt its share in the collapse-temperatures that very large doses may occasion in fever-patients.

Smooth Muscle. In pathological spleen-enlargements, as well

as in animals under normal conditions, the volume of the spleen decreases during the employment of quinine, whether as a consequence of contraction of its muscles has not, however, been determined. Contractions of the uterus are strengthened by quinine. In quinine-factories the women-packers, who are constantly breathing quinine-dust, are said to be very liable to abort.

Large doses of quinine produce in man symptoms from the **central nervous system,** principally the brain—giddiness, headache, frequent noises in the ears and deafness, amblyopia or even total blindness, confusion of ideas (quinine intoxication) and somnolence. In rare cases loss of consciousness has been seen, accompanied by delirium and convulsions, and death following symptoms of collapse, *i.e.* paralysis of the central nervous system and heart. Weakening of the heart is the main cause of the fatal result, but the respiration stops before the heart. Deaths have been recorded after 2 grammes, but as a rule the lethal dose is estimated at 8—10 grammes or more. As quinine is rapidly excreted, recovery generally takes place, but deafness and weakness of sight or blindness may remain for weeks or even months.

Local Action. Quinine has a very intense and persistent *bitter taste* (noticeable even in a solution of 1 in 10,000), which reflexly causes some increase in salivation. The digestion seems to be little affected by small doses. The prolonged employment of large doses may call forth catarrhal symptoms, tenderness in the epigastrium, nausea and vomiting, although they can often be taken for a long time without such effects. In subcutaneous injection it has been observed that after the injection pain is over quinine has a prolonged *local anæsthetising action.*

Absorption and Excretion. Quinine is easily absorbed, both from mucous membranes and from the subcutaneous tissue. In the body 60—70 per cent. disappears, *i.e.* is destroyed, the remainder being found unchanged in the urine. The greater part is excreted within 24 hours, a little during the next 24 hours, and after 72 hours there is scarcely a trace, if any, left in the body.

Now and then a pronounced **idiosyncrasy** with regard to quinine is met with, expressed in some variety of skin eruption, such as scarlatina-like erythema, which may be accompanied by fever, eczema, local œdema, extravasation of blood in the skin, and perhaps also in the intestine and kidneys. Some patients are so sensitive that 2 or 3 decigrammes of quinine is sufficient to produce universal urticaria attended by intolerable itching. Idiosyncrasy may suddenly appear in persons who have formerly taken large doses of quinine without any disagreeable consequences, and may also declare itself by the occurrence, after small doses, of the toxic symptoms (deafness, amblyopia, etc.) that very large doses

may produce. If serum from a person with idiosyncrasy be injected intraperitoneally into a guinea-pig, the animal's susceptibility to quinine is greatly increased. The rarely-occurring *contrary* or *paradoxical action* that quinine has in common with other antipyretics, consisting in an enormous rise in temperature accompanied by rigors, instead of the expected fall in temperature, remains unexplained.

Therapeutic Uses. Quinine is the ideal *specific for malaria*. It fulfils the requirement that must be the highest aim of the treatment of diseases produced by micro-organisms, namely, that it should kill the latter without injury to the host. Before the parasitic nature of the malarial fevers was known the action was ascribed to some influence on the nervous system. We now know that it is due to the fact that quinine is so strong a poison for most of the malaria parasites that they are killed by the exceedingly dilute solution in which it may circulate in the blood without harm to the patient. Quinine acts best in the ordinary regularly intermittent fever of the quotidian, tertian or quartan type, and is given during the apyrexia stage, either in several doses of ½ gramme or in larger, single doses (1—2 grammes). The time for administration is so chosen that the greatest possible amount of quinine shall be in the blood during the next attack, *i.e.* 4 to 6 hours before the rise in temperature is expected, for then the spores (the merozoïtes) are moving freely in the blood, and are easily reached by the alkaloid. The next attack after the administration of quinine may be arrested, although this is not usual; but with continued treatment the attacks become weaker and weaker and soon cease. In a week the treatment is repeated to prevent a relapse. Some physicians deviate from this method, and give 0·2 gramme every 2 hours with good results. Quinine is not given during the paroxysms of fever, as it has no effect upon the already developed attack, and is excreted too rapidly to prevent the next. It has the same specific action on other types such as those in which there is intermittent neuralgia, instead of the regular fever. Malignant malaria (febris tropica), in which the protozoa have crescentic stages of development and seem to be far less susceptible to the action of quinine, and also remittent and continued fevers, require very large doses of quinine, and intravenous injections are desirable. In malignant cases, hæmolysis, with the excretion of hæmoglobin in the urine (black-water fever), may occur during the employment of quinine.

It follows from the nature of the action that quinine can also be employed *prophylactically* for malaria, but as it is quickly eliminated, the immunity is only brief, and a fresh dose is necessary soon after the first has left the body. Opinions differ as to the

mode of procedure for prophylaxis; some recommend ½—1 gramme every 1 or 2 days, others larger doses (1—2 grammes) once a week. It should be noted, however, that quinine has no effect on the sexual forms of the malarial parasite. Thus, although it is possible to prevent or abort the paroxysms of the disease by taking quinine daily, the individual is none the less liable to infect mosquitoes with gametocytes. From the point of view of public health the practice is therefore to be deprecated. In recent years certain quinoline derivatives, *e.g.* atebrin and plasmoquine, have been used to eradicate sexual forms and offer hope of rational prophylactic measures in malaria. Quinine has little effect upon the cachexia remaining after recovery from malaria.

In *other febrile diseases* the employment of quinine has of late become very limited, partly because antipyretic treatment has lost its adherents, and partly because many newer drugs have rival claims. It falls to the lot of text-books on therapeutics to decide between the claimants; here we will only repeat that quinine acts in a way quite different from antipyrine and similar substances, and that it produces a more prolonged action. After doses of 1—1·5 grammes the temperature gradually falls for some 3 or 4 hours, and after remaining low for 6—9 hours once more rises slowly during 3—4 hours; these times are, however, only approximate, as the action varies with the nature of the fever. No specific action on febrile diseases other than malaria has been demonstrated. Like other antipyretics, quinine is best administered in the evening, so that the action shall coincide with the normal fall in temperature commencing in the course of the night.

As an analgesic for *neuralgia* and *cephalalgia*, quinine is decidedly inferior to antipyrine, phenacetine and other newer antipyretics. It may, however, in cases of regularly recurrent pain, even when the possibility of malaria seems excluded, act in a manner that may almost be called specific.

Quinine is much employed for its tonic and bitter action in all *conditions of weakness* after acute and chronic diseases, after loss of blood, and in diseases that produce anæmia: this effect is much over-rated. It is indicated where the weakness or loss of appetite is due to causes which quinine can remove, such as diseases following malaria, or convalescence from fever, where it may indirectly stimulate the appetite by curing the fever that causes the want of it. It is probably also beneficial in its inhibitory action on metabolism, whereby albumin is spared.

In *uterine inertia*, doses of ½ gramme are given to elicit more powerful contractions. The effect is produced only at full term when the onset of labour is imminent or is actually overdue.

Quinine tannate, quinine ethyl carbonate, or one of the newer compounds mentioned below, are all either very sparingly soluble or insoluble, and are therefore tasteless or nearly so. They are therefore suitable for administration to children and others who may be intolerant of the extremely bitter taste of the ordinary quinine salts.

The ordinary salts of quinine cannot be used alone as *local anæsthetics*, because they are too irritant. By the addition of urea the irritation is lessened, while at the same time the anæsthesia is strengthened and prolonged. Such a combination is now often employed in minor surgical operations.

Other alkaloids occurring in cinchona bark have been only partially investigated. As far as we know, they act in the main like quinine. One of them, **quinidine**, is of special interest for its effects upon the heart in auricular fibrillation and auricular flutter. These disorders of the cardiac rhythm are satisfactorily explained on the hypothesis of "circus movement" in the auricle, *i.e.* the normal cardiac impulse arising periodically in the sino-auricular node is replaced by one which travels around the auricle at a rate of about 200—500 circuits per minute. At the slower rates auricular flutter occurs. The auricle contracts as a whole and the ventricle responds to a definite proportion of these auricular beats—a half, a third or a quarter—according to the degree of auriculo-ventricular block present. At the higher rates of circus movement (about 500 per minute) the auricle fails to contract as a whole and is thrown into a condition of fibrillary twitching known as auricular fibrillation. The response of the ventricle is totally irregular in time and force, and where the condition is associated with cardiac decompensation the rate is often between 120 and 160 per minute.

Quinidine therapy will convert auricular fibrillation into a normal rhythm in about 50 per cent. of cases, provided that the condition is of recent onset and there is no evidence of gross congestive cardiac failure. The drug acts by depressing the auricular muscle and slowing the rate of passage of the abnormal stimulus. This effect can be watched in a series of electro-cardiograms taken during the treatment; the fibrillæ representing auricular activity become more and more coarse and begin to resemble the waves associated with contraction of the auricle. In some cases normal rhythm suddenly supervenes at this stage. In auricular flutter, the value of quinidine therapy depends upon the effect of the drug in increasing the refractory period of the auricular muscle, thereby tending to bring the circus movements to an end. If this were the only action of quinidine success would be attained more frequently; unfortunately, the drug also slows

the rate of conduction, and in the longer period of time which elapses during the completion of the circus movement the muscle sometimes recovers from the refractory state and becomes excitable, thus allowing the impulse to pass on. This accounts for the not infrequent failure of quinidine therapy in auricular flutter. As the auricular rate is slowed by the depressant effect of quinidine, the ventricular rate tends to draw level with that of the auricle, *i.e.* ventricular tachycardia occurs, and occasionally this may be somewhat alarming in its effects. This disadvantage can be minimised and, in addition, the chances of the success of the treatment increased by previously digitalising the heart. The sudden change from auricular fibrillation to a normal rhythm is liable to dislodge blood-clot from the right auricular appendix and thus result in fatal pulmonary embolism. Fortunately, this is a rare complication.

Quinine has also been tried in cases of cardiac arhythmia, but is less effectual.

Newer Quinine Derivatives. The constitution of quinine is now in all essentials known. The parent-substance is the alkaloid cupreine, occurring in the same vegetable family, its nucleus consisting of piperidine (formula, p. 131) and quinoline (formula, p. 223). It is further known that quinine is methylcupreine, and that the methylation is important, because the cupreine is much less active than the quinine. Synthetic chemistry has of late been directing its efforts towards the development, by changes in the molecule, of its parasiticidal properties so that they shall act upon other micro-organisms besides the malarial amœba (Morgenroth). It has been found that the hydro-compounds obtained by the addition of hydrogen atoms are very active, and that the bactericidal properties are still further increased when methyl is replaced by other alkyl radicals. The following table shows the dilution in which some of the new compounds kill streptococci and staphylococci in the course of 24 hours :—

Methylcupreine (Quinine) . .	1 in 1,000— 4,000
Methylhydrocupreine (Hydroquinine)	1 in 4,000— 6,000
Ethylhydrocupreine (Optochine) .	1 in 2,000— 8,000
Isoamylhydrocupreine (Eucupine) .	1 in 20,000—40,000
Isoctylhydrocupreine (Vucine) .	1 in 40,000—80,000

The increase in local anæsthetising action is more or less parallel with that of bactericidal power, but its utilisation is restricted by the injury these compounds inflict upon the tissues.

The above particulars apply to streptococci and staphylococci. Some of the compounds also possess a selective toxicity for certain micro-organisms. Ethylhydrocupreine, or optochine,

surpasses quinine in its very powerful action on pneumococci, which it kills even in a concentration of 1 in 300,000—400,000. The new alkaloid is therefore a valuable drug in cases of *pneumococcus infection in the eye* (*ulcus serpens corneæ*). It has been tried internally for *pneumonia*, but here its curative value is much disputed, and its use is still further restricted by its affinity for the optic nerve, which is far stronger than that of quinine. Ethylhydrocupreine has in many cases occasioned permanent weakness of vision. *Eucupine* and *vucine* are used in surgery as antiseptics. Eucupine has also been tried internally for *malaria*.

Preparations and Doses

Cinchona (B.P., U.S.P.), red cinchona, the bark of *Cinchona rubra*, **Cinchona** (U.S.P.), yellow cinchona, the bark of *Cinchona Ledgeriana*, *Calisaya*, and hybrids of these and other species of *Cinchona* (order *Rubiaceæ*). *Dose*, 0·3—1 grm., 5—15 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). The bark now used officially is obtained from cultivated trees. It was formerly imported exclusively from South America, where numerous species of the genus *Cinchona* grow wild, especially in the eastern highlands of the Andes, where they are found in the misty region (3,000—10,000 feet above sea-level), growing singly or in little groups without forming continuous forests. The genus received its name from the Spanish Viceroy of Peru, Don Geronimo Hernandez de Cabrera Bobadilla y Mendoza, Count of Chinchon, whose countess was cured of intermittent fever by the bark in 1638. As the native collectors' ruthless felling of the trees gave rise to fears of their extermination, the Dutch and English, in 1850—60, began to make plantations in their Asiatic colonies, whence the Old World now obtains its supplies. By rational cultivation the alkaloid percentage has been raised to 15 and more, but only 5 per cent. is required in the official bark.

Quinina (U.S.P.), an alkaloid obtained from cinchona. *Dose*, 1 grm., 15 grs.

Totaquina (B.P.), a mixture of alkaloids of cinchona. A nearly colourless, or pale yellowish-grey, or pale brown powder. Taste bitter. Almost insoluble in water. *Dose*, 0·06—0·6 grm., 1—10 grs. A cheap but effective preparation for use in epidemics.

Tinctura Cinchonæ (B.P.). *Dose*, 2—4 mils, ½—1 fl. dr.

Tinctura Cinchonæ Composita (B.P., U.S.P.) contains cinchona, serpentaria and bitter orange peel. *Dose*, ½—1 fl. dr. in a little water 3 times a day before food (to give appetite).

Extractum Cinchonæ (B.P.), adjusted to contain 10 per cent. of the alkaloids of cinchona. *Dose*, 0·12—0·5 grm., 2—8 grs.

Extractum Cinchonæ Liquidum (B.P.), *Fluidextractum Cinchonæ* (U.S.P.). *Dose*, 3—10 decimils, 5—15 mins. (B.P.); 1 mil, 15 mins. (U.S.P.).

Quininæ Hydrochloridum (B.P., U.S.P.), $C_{20}H_{24}N_2O_2.HCl+2H_2O$.

Quininæ Dihydrochloridum (B.P., U.S.P.).

Quininæ Sulphas (B.P., U.S.P.), $(C_{20}H_{24}N_2O_2)_2.H_2SO_4+7H_2O$.

Quininæ Bisulphas (B.P., U.S.P.).

Quininæ Salicylas (U.S.P.).

All these salts of quinine are white crystals with an exceedingly bitter

taste, and are all given in the same doses, 0·06—0·6 grm., 1—10 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). The most practical is the *hydrochloride*, which contains 85 per cent. of alkaloid, and is soluble in 35 parts of water. The non-fluorescent solutions remain pure, whereas solutions of the sulphate contain only 72 per cent. of the alkaloid, and are very liable to become mouldy. *Dose* as a tonic, 10 centigrms., 1½ gr., 3 or 4 times a day; as an antipyretic, 0·5—1—2 grms., 7—30 grs., in the evening. The doses in malaria have already been given. For children as many centigrammes (⅙ gr.) as the age in months, or as many decigrammes (1½ gr.) as the age in years. For adults quinine is prescribed in pills, cachets or capsules, for children in solution or powders with sugar; but nothing can conceal the bitter taste. The *sulphate* is very sparingly soluble in water (800 parts), but is easily dissolved, with strong fluorescence, by the addition of a little sulphuric acid, which forms the acid salt.

Liquor Quininæ Ammoniatus (B.P.) contains 2 per cent. of the hydrochloride and of the sulphate. *Dose*, 2—4 mils, ½—1 fl. dr.

Tinctura Antiperiodica (not official), Warburg's tincture, used in India for malaria, contains, in addition to 2 per cent. of quinine sulphate, aloes, rhubarb, camphor, a little opium, and several bitters and aromatics. A remarkable example of polypharmacy, the quinine is the only essential constituent. *Dose*, 4 mils, 1 fl. dr.

Ferri et Quininæ Citras (B.P.), a mixture of the constituents indicated by the name, its aim being to unite the actions of iron and quinine. Thin scales of a greenish-yellow colour, very soluble in water. *Dose*, 3—10 decigrms., 5—15 grs.

For children the following may be substituted for the bitter salts :—

Quininæ Tannas (B.P., U.S.P.), a pale yellow amorphous powder, slightly soluble in water, and almost tasteless. *Dose*, 0·1—1 grm., 1½—15 grs. (B.P.); 1 grm., 15 grs. (U.S.P.).

Quininæ et Æthylis Carbonas (B.P.), *Quininæ Ethylcarbonas* (U.S.P.), *Euquinine*, the ethyl ester of quinine carbonic acid, may also be used. White, very insoluble needles, with slightly bitter taste. Given in the same doses as the tannate. *Aristochine*, diquinine carbonic ester, and *Chinaphenine*, a compound of quinine and phenetidine, are compounds of a similar nature, and are also given in the same doses.

Quinidinæ Sulphas (B.P., U.S.P.), colourless crystals, sparingly soluble in water. Average *dose* for arhythmia (see text), 0·2 grm., 3 grs., 3 times a day for a few days in succession. The attack often ceases after two or three doses. Action partly due to the presence of *hydroquinidine*.

Quininæ et Ureæ Hydrochloridum (U.S.P.), a compound of the hydrochlorides of the substances named, not less than 58 per cent. being quinine. Colourless crystals or a white powder, very soluble in water. *Dose*, hypodermic, 1 grm. 15 grs. once a day. The solutions are irritant, as they have an acid reaction. As a local anæsthetic, quinine and urea hydrochloride has a potency about one-quarter that of cocaine, but it is remarkable for the fact that anæsthesia may last for several days. Strengths suitable for intracutaneous injection are ⅛—¼ per cent.; concentrations greater than these cause irritation and may even produce sloughing. On mucous membranes up to 20 per cent., which may also be used for intramuscular injection in pernicious malaria.

Æthylhydrocupreinæ Hydrochloridum (U.S.P.), "Optochine," a white, almost insoluble powder. *Dose* for pneumonia, 20 centigrms., 3 grs., every 4 hours, but not more than 1·2 grm. in 24 hours; in the eye (ulcus serpens), 1—2 per cent. ointment or solution in olive oil. The soluble hydrochloride

is used in a 1 per cent. aqueous solution for dropping into the eye several times a day.

Eucupinum, a white powder, soluble in olive oil. *Dose* for malaria, 0·5—1 grm. daily; externally, in a 5 per cent. ointment, as an analgesic and disinfectant in ulcerating carcinoma. The *soluble bi-hydrochloride* is used as an antiseptic for wounds in a $\frac{1}{5}$ per cent. solution.

Plasmoquine is a synthetic amino-quinoline compound. It is more effective than quinine in benign tertian and in quartan malaria. Quinine, however, is superior to plasmoquine in the treatment of malignant malaria. Administered with quinine, it destroys the sexual forms of the malarial parasite in all types of the disease. Its most important application is therefore in malaria-prophylaxis. *Dose*, 0·06—0·09 grm., 1—1½ grs.

Atebrin. Action and uses similar to those of plasmoquine but less effective as a prophylactic. *Dose*, 0·3 grm., 5 grs., daily.

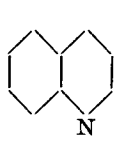
34. THE ANTIPYRINE GROUP

Antipyrine, Acetanilide, Phenacetine

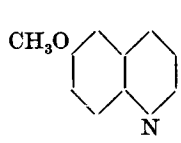
Chemical Survey. Introductory Remarks. After the introduction of cinchona bark into Europe in 1640, that drug, and later quinine, were for long the only reliable antipyretics known to medicine. It was not until 1875 that salicylic acid also came to be used, its influence on fever-temperatures being discovered in that year. During the rage for antipyretics that prevailed 30 or 40 years ago in the treatment of fever, quinine and salicylic acid were very extensively employed, but, with the large and frequent doses then considered necessary, often produced unwelcome secondary effects. The great need of better febrifuges than the old ones, which would reduce the temperature and yet be harmless, was instrumental in initiating very important investigations, the aim of which was to find by synthesis substances that possessed the desired properties. Notwithstanding that the age of strict antipyresis is past, these investigations have been continued up to the present day, and have given to practical medicine several of its most valuable and most frequently employed remedies, which, although they are now as a rule used for other purposes than reducing high temperature, are comprised under the title of "the new antipyretics." These fall historically, chemically and pharmacologically, into groups.

1. *Quinoline Derivatives.* Endeavours were first made to become acquainted with the structure of the quinine molecule, in order, by chemical changes, to modify its action in the desired direction. They did not succeed in elucidating the composition of quinine, but they showed that among the decomposition-products *quinoline* always appeared, this being a colourless liquid, quickly turning yellow in the air, which forms crystalline salts with acids. These salts acted both as antiseptics and antipyretics, but easily produced collapse. Continued investigations led to the view that the quinoline in the quinine molecule occurred as para-methoxy-

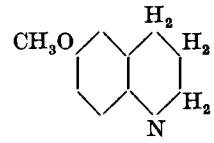
quinoline, and the abundance of hydrogen in quinine was explained by the assumption that the quinoline must be hydrated. From this *Thalline* arose, its formula giving a very clear expression of the efforts to produce an improved quinine.



Quinoline



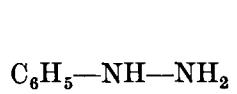
Para-methoxyquinoline



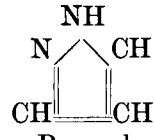
Thalline.

Thalline, like its ally, *Kairine*, once (1884 and 1882) aroused extraordinary attention. Both these quickly reduce temperature, but only for a couple of hours and with marked secondary effects (rigors, profuse sweating, collapse). Their fame was short-lived, as they were soon completely overshadowed by antipyrine.

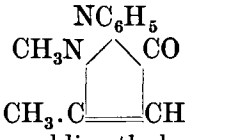
2. *Antipyrine* (Knorr-Filehne, 1884). This was also produced in the endeavour to arrive synthetically at a quinine-like body. That the result was such a valuable remedy as antipyrine was in reality a lucky chance, for both the conception of the composition of quinine, which served as a type, and the conception of the composition of the antipyrine first obtained, were erroneous. It was produced from phenylhydrazine, and was supposed to contain that compound in its molecule. A new ring, pyrazol, was formed, however, which does not give off phenylhydrazine in the organism. Were this to take place, antipyrine would be of little use, for phenylhydrazine, like its simpler derivatives, is far too toxic. Such bodies act as antipyretics, but produce collapse and serious changes in the blood.



Phenylhydrazine



Pyrazol



Phenyldimethylpyrazolon. Antipyrine.

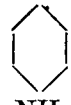
3. *Acetanilide* or *Antifebrine*. The synthesis of antipyretics acquired a fresh starting-point in acetanilide. Its introduction is due to the important observation of the antipyretic action of aniline derivatives (Cahn and Hepp, 1886). Pure aniline and its salts act far too violently, and, like phenylhydrazine, produce serious collapse and destruction of the red blood-corpuscles. If, instead of one H of the amino group, an acid radical is introduced, *e.g.* acetyl, the toxicity diminishes, but the character remains the same, for aniline is gradually regenerated in the organism. The action of acetanilide becomes therefore a subdued and protracted

aniline action, and in large doses, or with too long employment, it may exhibit the dangerous properties of aniline.

Aniline

Acetanilide.

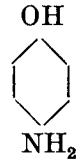
4. *Paramino-phenol Derivatives, Phenacetine.* This newest group of antipyretics originated from the study of the breakdown products of acetanilide or aniline. In the body, aniline is oxidised in the para position in such a manner as to produce paramino-phenol, which is eliminated in combination with sulphuric or glycuronic acid.



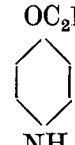
Aniline

Paramino-phenol.

This oxidation is of benefit to the organism, for paramino-phenol is less poisonous and has less effect upon the hæmoglobin than aniline. Febrifuges that are based upon paramino-phenol are, therefore, less harmful than the aniline compounds. Pure paramino-phenol, however, is still too toxic to permit of employment, but it may, without loss of its antipyretic power, be made less injurious by substituting for the hydrogen of the hydroxyl an alkyl radical, *e.g.* ethyl (phenetidine), or an acid radical, *e.g.* acetyl, for its amino hydrogen, or, better still, by making substitutions in both side chains, as in phenacetine, which represents the latest important advance in the synthesis of antipyretics :—



Paramino-phenol



Phenetidine

Phenacetine
(Acetophenetidine).

The great majority of the still newer antipyretics are only superfluous variations of the phenacetine idea. The paramino-phenol derivatives may be almost endlessly modified, as the hydrogen of both hydroxyl and amino may be replaced by all kinds of alkyl and acid radicals. The fundamental action remains

the same, however, as it is ultimately the paramino-phenol split off in the organism that is the active constituent. The lateral chains must, however, give definite properties ; they must make the compound so stable that the decomposition in the body will take place with a sufficient slowness to ward off the deleterious consequences of a sudden liberation of paramino-phenol, but must not fix it too firmly, as the activity would then be too much weakened. None of the numerous imitations of phenacetine has up to the present superseded that drug. A few of these compounds will be briefly mentioned below.

Action. Antipyrine, acetanilide, phenacetine, and the numerous allied substances have so many properties in common that separate descriptions of their action would cause needless repetition. Their main action will, therefore, be described as one.

Like quinine, the newer antipyretics have little influence on the **temperature** in healthy animals and man, but reduce very promptly—even quicker than quinine—abnormal temperature in nearly all febrile diseases ; they act better, however, when the fever is of an intermittent or remittent type than when it is continued. The action runs its course more quickly than that of quinine. The temperature falls rapidly for 1—3 hours, remains low only 2—6 hours, and then rises a little more slowly than it fell. The quinoline derivatives are especially remarkable for the sudden changes of temperature they produce, while antipyrine in this respect stands half-way between them and quinine.

Opinions have differed as to the *cause of the fall of temperature*. The newer antipyretics were originally supposed to reduce the temperature in the same way as quinine by decreasing the production of heat. Investigations of the *metabolism* do not point in this direction, however, for no regular or great diminution of oxidation processes or of other chemical changes can be demonstrated. As far as may be concluded from the somewhat conflicting results of investigations, ordinary doses seem to increase slightly the excretion of urea and nitrogen. Nor is the characteristic action of quinine on protoplasm found in antipyrine, acetanilide, etc. ; they are not very antiseptic, do not kill protozoa until the concentration is comparatively high, and do not prevent the emigration of the white blood-corpuscles. All this taken together indicates that the cause of the fall of temperature must be *increased loss of heat*, and not diminished production of heat, an explanation which is fully confirmed by calorimetric experiments. If a febrile rabbit be placed in a calorimeter and given antipyrine, as soon as the animal's body-temperature begins to fall, the temperature of the surrounding air rises much more rapidly than in a calorimeter in which there is a control animal.

By accurate measurement, Gottlieb found that the loss of heat in healthy animals increased 10—20 per cent., in animals with high temperature up to 55 per cent. In fever patients, in whom only a partial calorimetry can be carried out, Rosenthal has similarly shown that the radiation of heat from a limited area, *e.g.* an arm, increases greatly after antipyrine.

Even direct observation shows that the great loss of heat is due to *dilatation of the cutaneous vessels*. During the fall of the temperature there is a feeling of external heat, the face is not infrequently distinctly injected, and the skin feels warm to the

Diagrammatic Temperature—curves.

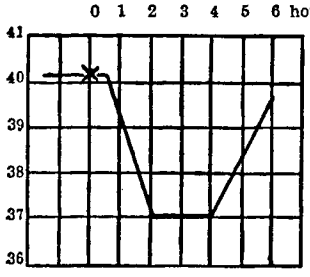


FIG. 20.— × indicates ¼—½ gramme thalline.

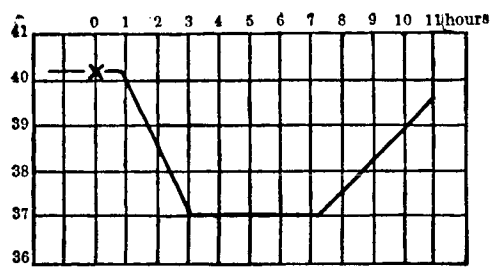


FIG. 21.— × indicates 2—4 grammes antipyrine.

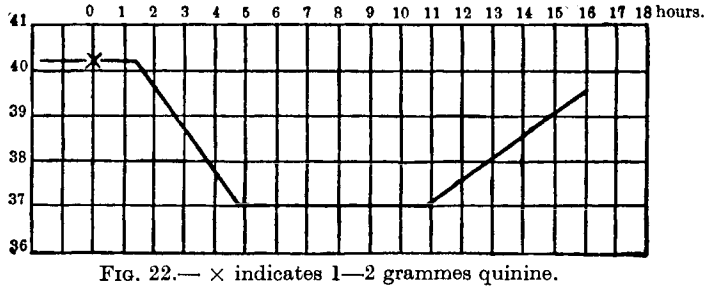


FIG. 22.— × indicates 1—2 grammes quinine.

touch ; and, in addition to this, electrothermic and plethysmographic measurements have proved its increased temperature and the dilatation of the vessels respectively. The internal vessels of the body do not share in the dilatation. This difference between the external and the internal vessels is of great significance. When all the vessels of the body are dilated, the blood-pressure falls, the skin becomes bloodless, pale and cold, and gives off little heat ; but if the cutaneous vessels are relaxed while the tension in the large arteries is unchanged, large quantities of blood are driven through the skin, where it is cooled.

It is, moreover, highly probable that the temperature-lowering action of antipyrine and allied drugs consists essentially in

paralysis of certain parts of the brain which govern the heat-economy. The temperature of the warm-blooded animal is kept constant under the most varying conditions by the continual maintenance of balance between production and loss of heat. With a large increase in metabolism, as after great muscular exertion, the body-temperature rises only slightly, because a compensating loss of heat is immediately brought about, principally by the filling of the cutaneous vessels which are exposed to the influence of the outer air, partly also by the evaporation of moisture (sweat) from the surface of the body. When, on the contrary, external cold causes cooling, heat is saved by the skin becoming anæmic. This strict maintenance of balance between income and expenditure of heat, which ensures to man his 98° F., whether he lives beneath the equator or in the polar regions, presupposes a central regulating mechanism that is set, like a thermostat, at a certain temperature, and, like its regulator, reacts

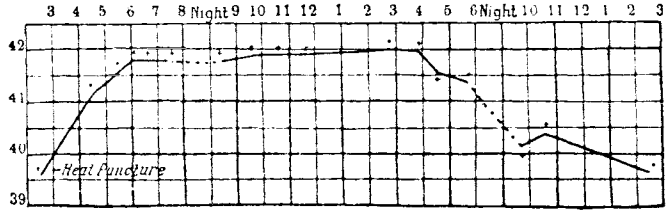


FIG. 23.—Temperature-curve after heat-puncture (Gottlieb). The curve begins at 103° (39·5° C.), the rabbit's normal temperature.

even to small changes of temperature. By poisoning, especially with bacterial poisons (febrile diseases) and by operative procedure, the regulating centre of the central nervous system may be so acted upon that the whole adjustment is raised to a higher level, and the centre now endeavours to maintain the new level. The regulating centre, or one of them, seems to be situated in or near the corpus striatum. If a rabbit is trephined in the corner between the coronal and the sagittal sutures, the dura mater divided with a small transverse cut, and a thin glass rod inserted perpendicularly down to the base of the skull, the corpus striatum is injured, a condition of stimulation arises round the puncture, and the temperature immediately begins to rise. That it is stimulation, and not paralysis, is apparent from the fact that electric stimulation acts in the same way. The temperature often reaches 107·6° (42° C.), and when the " heat-puncture " is successful, remains at this height for many hours, and then falls slowly to the normal. The animal has no true fever, however, but only the solitary symptom of heightened temperature, for it evidently

feels well, moves about as usual, and retains its customary good appetite.

The result of the heat-puncture is shown by the calorimeter to be a disturbance of the regulating mechanism, in which the loss of heat is considerably diminished and subsequently the production of heat increased. The regulating mechanism is set at a higher level, and the animal then endeavours, when artificially cooled or heated, to defend its new temperature as it had formerly done the old, but now does not succeed so well. This reveals the pathological side of the condition: whereas antipyrine cannot greatly lower the temperature in the normal animal, it easily reduces that raised by heat-puncture. It is accordingly most natural to explain the temperature-lowering action of antipyrine as a *paralysing of those parts of the brain the stimulation of which elicits a rise of temperature.* Its action is thus of a narcotic character, a view that finds cogent support in the fact that

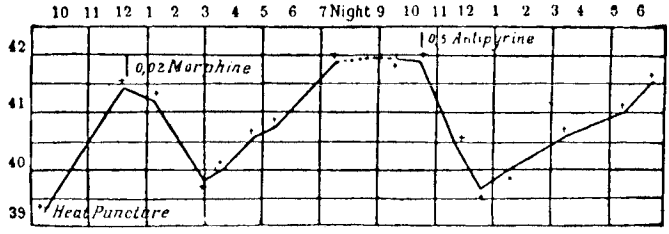


FIG. 24.—Temperature-curve after heat-puncture, morphine and antipyrine.

morphine alters the heat-puncture curve in the very same way. This is clearly seen in Fig. 24.

In other ways, too, the newer antipyretics prove to be slight anæsthetics; they have *analgesic, sedative, and soporific* properties, which are now quite as much utilised as their antipyretic action.

On the **heart** antipyrine and its allies have no special action in the ordinary doses. Considerable cardiac weakness is of rare occurrence. It will be mentioned later under "Secondary Effects."

The three types, antipyrine, phenacetine, and acetanilide, are all different in their action upon the **blood.** Antipyrine has almost no deleterious effect upon the red blood-corpuscles. Although it is produced from phenylhydrazine, which is a strong blood poison, it is physiologically not a phenylhydrazine derivative, on account of the formation of the pyrazolon ring (*cf.* p. 223). Phenacetine is almost as harmless as antipyrine. Paraminophenol is split off in the body so slowly and continuously that a deleterious effect is avoided. It therefore seldom occasions the formation of methæmoglobin. Acetanilide and other anilides

are more dangerous. In large doses the liberated aniline may lead to the formation of methæmoglobin, which is dissolved in plasma and appears in the urine. *Cyanosis* may occur after large doses of all these antipyretics, but far more rarely after antipyrine and phenacetine than after the aniline compounds. Its origin is somewhat obscure. It seems to be in some way connected with the appearance of methæmoglobin, but may also occur where methæmoglobin cannot be detected.

Secondary Effects. Antipyretics are remarkable in that they produce more frequently than most other drugs unpleasant secondary effects. Among the most usual, especially after large doses and considerable variations in temperature, are *profuse sweating* when the temperature falls, and *rigor* when it rises again. These symptoms, however, are not directly due to the drugs, as Liebermeister and Filehne have endeavoured to show by the following argument. When the temperature of a fever-patient is 104° (40° C.), his heat-mechanism is set at that height, and this it endeavours to maintain. If he is given a drug which suddenly sets the mechanism 5° (3° C.) lower, he is not able, like the healthy individual, to withstand its influence, and has to respond as quickly as possible to its action ; all the sluices are opened for the escaping heat, great quantities of blood are received into the dilated cutaneous vessels, and thus come nearer to the surrounding cool air, the skin becomes hot and turgescent, and the vessels surrounding the sweat-glands are filled ; the abundant perspiration and its evaporation aid in the cooling process (not much, however, for the fall of temperature is about the same even when the secretion of sweat is suppressed by atropine or agaricine). At last the 99° (37° C.) aimed at is reached, and all is well. After a time, however, the antipyretic given is converted into inert compounds or eliminated from the organism, its influence ceases, and the morbid temperature-level of 104° (40° C.) once more gains the ascendancy. The patient is now in an unpleasant condition : he is 5° (3° C.) too cold, and therefore begins to shiver and shake like a healthy person who has been too much cooled by a cold bath. His temperature must be raised again to 104° (40° C.). This is attained by the contraction of all superficial vessels, so that the heat is shut in ; the pallor of the skin and the shivering during the renewed rise of temperature may easily have the appearance of a collapse, which in reality it is not. All these symptoms are only elicited by considerable and rapid changes of temperature ; they occur in the same manner in all abrupt rises and falls of temperature from any cause whatsoever, *e.g.* in malaria, only here the consecutive order of events is reversed (Figs. 25 and 26).

The most important of all the untoward effects which are

directly due to antipyretics is *collapse*. Large quantities, and, in especially sensitive or already enfeebled persons, even the ordinary doses, may in rare cases produce the most alarming cardiac weakness; the pulse becomes small and irregular, the temperature subnormal; the patient is drowsy, his pallid skin is covered with cold sweat, and death may occur from failing circulation. The paleness is a consequence of insufficient heart-action, and must be distinguished from that which appears as a result of the contraction of the cutaneous vessels when the temperature rises again after the period of apyrexia is over.

There may also appear, especially after antipyrine, a great many less dangerous but very unpleasant effects, such as *skin eruptions*, which, when accompanied by fever, may be mistaken for acute infectious diseases (measles, scarlet fever), burning pain in the mouth and throat, swelling of the mucous membrane of the mouth, œdema of the eyelids, salivation and flow of tears, swelling of the mammæ with cessation of the secretion of milk in nursing

Temperature-curves.

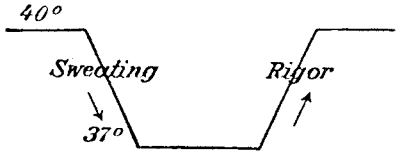


FIG. 25.—After ½ gramme thalline.

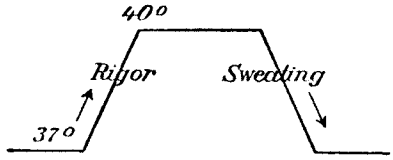


FIG. 26.—A malarial attack.

women, and many other, often very peculiar, symptoms. Some persons, for instance, cannot be treated with antipyrine, because even ½—1 gramme causes prolonged paroxysms of convulsive sneezing. *Contrary action* is also now and then seen. It may appear in the most unexpected manner in persons who have formerly shown normal response to the drug, as in the case of a consumptive described by Laache, who for a long time had taken 5 grammes daily without unpleasant consequences, but who one day after 2 grammes suddenly had an attack of shivering and a rise of temperature from 100·7° (38·2° C.) to 105·4° (40·8° C.).

Therapeutic Uses. Antipyrine, phenacetine, etc., are prescribed in febrile diseases as antipyretics in cases in which a great rise of temperature, or long-continued high temperature, makes action necessary. They are now, as a rule, preferred to quinine, as the effect is generally more certain and attended with fewer disadvantages. It is advisable, however, before resorting to large doses, to give a small trial dose. Special caution should be observed in diseases that are subject to critical falls of temperature. If a strong antipyretic is given just before the crisis, the physio-

logical fall of temperature and that produced by the drug may together amount to a dangerous collapse. A detailed explanation of the employment of antipyretics in the various febrile diseases is to be found in text-books on medicine. It will here only be stated that in the present day, since experience has shown that most febrile diseases do not change their character and are not shortened by artificial lowering of temperature, antipyresis in general has lost ground and is practised far less than it was thirty years ago, when high temperature was regarded as a fire that at all costs must be extinguished either with water or with medicines.

What antipyretics have lost in one direction they have more than gained in another. They are still prescribed extensively in almost all febrile diseases, not to reduce temperature, but as *alleviating remedies*. Doses that have no great influence on the temperature—*e.g.* 1 gramme antipyrine, $\frac{1}{3}$ gramme acetanilide, or $\frac{1}{2}$ gramme phenacetine a few times a day—are generally sufficient to relieve many of the troublesome symptoms that are the constant attendants upon most kinds of fever. The slight perspiration they cause lessens the unpleasant feeling of dry heat, pains in the limbs and headache are diminished, delirium and restlessness subdued, confusion of mind is cleared, and a beneficent, though brief, euphoria, with not infrequently sleep, is induced. They therefore justly deserve the name of "fever-narcotics" used by Schmiedeberg.

Their *analgesic effect* is also dependent upon their narcotic action. It is of a different form, and much weaker than that of morphine. Antipyretics act especially upon *neuralgia*, *rheumatic pains* and *cephalalgia*, most of all perhaps on the *typical migraine*. Caffeine appears to support the action. In large doses they may also prove efficient in the *shooting pains of tabes*. Among motor neuroses, *chorea* is often favourably influenced, especially by antipyrine, but not *epilepsy*. For *whooping-cough* they are recommended; the paroxysms are said to be relieved and the illness shortened.

What has been said regarding action and therapeutic uses is applicable to all newer antipyretics. The following particulars concerning the separate drugs may be added :—

Antipyrine is a local irritant, causing great smarting on a raw surface, and burning pain when placed in the eye. The vomiting sometimes occurring after internal use must be attributed to irritation of the gastric mucous membrane.

Antipyrine is quickly absorbed, and the greater part of it is excreted unchanged in the urine, combined with glycuronic and sulphuric acids. The urine assumes a dark yellow, almost red colour, which becomes quite red on the addition of ferric chloride.

Like many other good remedies, antipyrine has served as the point of departure for the production of various new compounds. *Salipyrine* (salicylic acid and antipyrine), owing to its constitution, acts more strongly on rheumatic affections than pure antipyrine. *Amidopyrine* (dimethylaminophenyldimethylpyrazolon) acts for a longer period than antipyrine and is suitable for occasional use as an analgesic rather than as an antipyretic. Evidence is accumulating that amidopyrine is one cause of agranulocytosis. When the drug is used for a prolonged period, a leucocyte count should be done occasionally and the proportion of granular cells noted. Idiosyncrasy, fatigue and menstruation appear to be factors favouring the onset of toxic effects from amidopyrine. Several other drugs based upon antipyrine do not appear to have any advantages worth mentioning.

Acetanilide, or *antifebrine*, differs in one important respect from antipyrine, namely, in that, as an aniline derivative, it has a destructive action on the red blood-corpuscles (see p. 223), and may, even in doses of 0·5 gramme 3 or 4 times a day, cause cyanosis. Long use may lead to pronounced anæmia and weakness, and it is therefore now little employed.

Acetanilide is very readily absorbed and is excreted in the urine in various combinations, partly as para-aminophenol combined with sulphuric acid. The urine becomes lævo-rotatory. Acetanilide, too, has been varied in several ways, but not improved.

Phenacetine has a greater narcotic action than the above-mentioned drugs. It produces a pleasant feeling of rest and drowsiness, and may almost be employed as a mild hypnotic. After large doses poisoning may occur, which exhibits the characteristics common to that of all these drugs, viz., somnolence, cyanosis, profuse sweating, rigor and symptoms of collapse.

Phenacetine is excreted in the urine as para-aminophenol combined with sulphuric and glycuronic acids, and as phenetidine.

Among the phenetidine derivatives **Lactophenine,** or lactyl-phenetidine (differing from phenacetine only in the substitution of lactic for acetic acid), deserves attention on account of its conspicuous narcotic action, which makes it a good antipyretic and sedative, especially in typhus fever, where it calms delirium and restlessless, and may induce sleep. Its analgesic action on neuralgia, *e.g.* sciatica, is often very successful. One unpleasant secondary result should be noted, however, namely, that after the employment of large doses for some time, *e.g.* 1 gramme 3 times a day, a febrile but benign jaundice makes its appearance. The icterus is not of the hæmolytic type. This lactophenine jaundice possesses the peculiarity of appearing after a definite incubation-period (10 days), and, like many bacterial diseases, leaves immunity, so that subsequently the same patient can without untoward consequences be treated with equally large or larger doses (Hanssen).

Recent years have brought an overwhelming number of new phenetidine

compounds, which, like lactophenine, differ from phenacetine in that they contain other acid radicals instead of acetyl. The action has, of course, always the same character, as in every case it is due to the liberation in the body of phenetidine or para-aminophenol, but its intensity and rapidity vary somewhat according to the quickness or the slowness with which the liberation takes place. Some of the numerous preparations suggested will be mentioned below. Several more might be included, but will be passed over, as they seem to be rather an outcome of the competition of chemical factories than actual requirements. Nor is there in all probability any special advantage to be expected from future new compounds of a similar nature, for para-aminophenol is already fully represented by phenacetine and lactophenine, both of which possess the property required, namely, a moderate resistance to the decomposing forces of the body.

Preparations and Doses

Phenazonum (B.P.), **Antipyrina** (U.S.P.), colourless, very soluble, tabular cystals, with an unpleasant, bitter, acrid taste. *Dose*, 3—6 decigrms., 5—10 grs. (B.P.); 0·3 grm., 5 grs. (U.S.P.). The doses are varied according to their purpose. For the reduction of temperature 2—4 grms. taken in doses of 1 grm. in the course of 2 or 3 hours, the advantage of dividing the dose being that the temperature falls more gradually than it would do after one large dose; in subcontinuous, not very high, fever (tuberculosis), repeated small doses, *e.g.* 0·3 grm. every other hour; in neuralgia 1—2 grms. per dose, also, but less to be recommended, by hypodermic injection in a solution of 1 in 1, ½—1 mil (painful); for migraine 1 grm. at the beginning of the attack, the effect being better if given with 10 centigrms. caffeine: if without result, the dose may be repeated once or twice at intervals of 1 hour; for children 1 decigrm. for each year of the child's age (for whooping-cough 1—3 times a day); for chorea in older children 1 grm. 2 or 3 times a day. Antipyrine is prescribed for adults in tablets, cachets, or capsules; for children in a solution, with a sweet syrup or honey as a flavouring agent.

Salipyrina (for constitution see p. 232), a white powder with a sweetish, astringent taste, sparingly soluble in water. *Dose*, 1—2 grms., 15—30 grs.

Amidopyrina (B.P., U.S.P.) (for constitution see p. 232), a white crystalline powder, soluble in about 10 parts of water. *Dose*, 0·3—0·6 grm., 5—10 grs. (B.P.); 0·3 grm., 5 grs. (U.S.P.).

Acetanilidum (U.S.P.), antifebrine, colourless crystals with a slightly bitter taste, very insoluble. *Dose*, 12—30 centigrms., 2—5 grs. (B.P.); 0·2 grm., 3 grs. (U.S.P.); for children as many centigrammes as the years of the child's age.

Phenacetinum (B.P.), **Acetophenetidinum** (U.S.P.), colourless, glistening crystals, tasteless and very sparingly soluble in water. *Dose*, 3—6 decigrms., 5—10 grs. (B.P.); 0·3 grm., 5 grs. (U.S.P.); for children ½ decigrm. (nearly 1 gr.) for each year of the child's age.

Lactylphenetidinum, Lactophenine, a white powder with slightly bitter taste, sparingly soluble. *Dose*, 0·5—1 grm., 8—15 grs., 3 times a day, the last-mentioned doses for only a few days at a time.

Other phenetidine compounds are *Phenocoll, Salocoll, Malakine, Citrophen, Apolysine, Kryofine*, all being given in doses of 0·5—1 grm. a few times daily.

Pentnucleotide is a mixture of the sodium salts of pentose nucleotides. Used in the treatment of agranulocytic angina. *Dose*, 10 mils by intra-

muscular injection thrice daily for 3 days and thereafter once daily until improvement.

Addenda. *Dyes*

Methylene Blue, or *Methylthioninæ Chloridum* (B.P., U.S.P.), $C_{16}H_{18}NSCl + 3H_2O$, green, bronzy crystals, forming a deep blue solution in water. Methylene blue is mainly used in a test for renal function. 0·5 mil of a 10 per cent. solution is injected intramuscularly; the dye is excreted by the normal kidney in about 10 minutes and the blue coloured urine can be seen spurting from the ureteric orifices on cystoscopic examination. It has now and then been tried as an analgesic in neuralgia, neuritis, rheumatism, spasmodic migraine and " nervous " headache, and has sometimes proved useful. Its action was assumed to be due to its power of colouring (*i.e.* being taken up by) the nerve tissue, especially the axis-cylinders, in the living organism as in microscopic preparations, and thereby diminishing the feeling of pain. Methylene blue has also been recommended, but little used, for malaria. Injections of a 2 per cent. solution into the urethra in acute gonorrhœa are sometimes recommended. As an analgesic methylene blue is given in pills (dose, 0·1 grm., 1½ grs., up to 0·5 grm., 8 grs., a day). In these doses it is not poisonous, but during its excretion in the urine often causes slight irritation of the bladder. With the use of methylene blue the urine is first coloured green and then a brilliant blue. The colour disappears a few days after the leaving off of the drug. Methylene blue exerts a mild antiseptic effect in the urinary tract and is sometimes of value in chronic infections with *Bacillus coli*.

Indicarminum (B.P.). Indigo carmine. Sodium indigotinsulphonate. A dye used in the same way as methylene blue in testing renal function. Normally the blue colour appears at the ureteric orifice 10 minutes after the intramuscular injection of the dye and after 5 minutes if it is given intravenously. The maximum concentration occurs within one hour. *Doses*, subcutaneously or intramuscularly, 5—10 centigrms., ¾—1½ grs.; intravenous injection, 8—16 milligrms., ⅛—¼ gr.

Phenolsulphonphthaleinum (U.S.P.). Phenol red. Used in testing renal function. Excretion of the dye begins 5—10 minutes after intramuscular or intravenous injection. In two hours 70 per cent. should have appeared in the urine; it is estimated by comparison with solutions of known strength. *Dose*, by intramuscular injection, 6 milligrms., $\frac{1}{10}$ gr.

Iodophthaleinum (B.P.); *Iodophthaleinum Solubile* (U.S.P.). Sodium Tetraiodophenolphthalein. After oral or intravenous administration this substance is concentrated by the healthy gall-bladder which then becomes opaque to X-rays. Thus it is often possible to obtain radiographic confirmation of pathological states of the gall-bladder. *Doses*, 4—6 centigrms. per kg. of body-weight up to 5 grms., ⅓—½ gr. per lb. body-weight up to 75 grs.; by intravenous injection, up to 3 grms. (45 grs.) (B.P.). For each 10 kg. of body-weight, 0·5 grm. (8 grs.) orally; 0·3 grm. (5 grs.) intravenously (U.S.P.).

Fluoresceinum Solubile (B.P., U.S.P.). Disodium salt of fluorescein. 2 per cent. of this salt in water made up with 3 per cent. sodium bicarbonate is used as a diagnostic agent in abrasions of the cornea. The affected area is stained green and the colour disappears after a few hours.

Scarlet Red (*Rubrum Scarlatinum*). It has been observed that subcutaneous injections of oil in which the dye, scarlet red, has been dissolved, produce in rabbits cancerous proliferation of the epithelium. This gave

occasion to the trial on man of this dye or its active constituent, amino-azo-toluol, in order to induce the formation of epithelium. The result was favourable. By the employment of a 4—8 per cent. vaseline ointment, a rapid formation of skin was often successfully attained upon small wounds of various kinds, principally burns, but also ulcus cruris, syphilitic sores, lupus, etc. Malignant new formations do not appear to have been seen. Some caution must be observed in its employment on children, as after its application to large surfaces, symptoms indicating aniline poisoning have been noticed. In order to prevent such consequences, an acetyl group has been substituted in the NH_2 group of the amino-azo-toluol, in accordance with a principle often employed with success. The bodies resulting from this, *Azodermine* and *Pellidol*, seem to be almost non-toxic. Scarlet red is employed as a 2 per cent. vaseline ointment for 24 hours, then an indifferent ointment is used for 2 or 3 days, then once more the scarlet red ointment, and so on.

35. ANTISEPTICS OF THE AROMATIC SERIES

The Carbolic Acid and Salicylic Acid Group

General Characteristics

The simpler benzene compounds have a uniform action upon the living organism, the chief points being that they are *antiseptic* and *antipyretic*, and ultimately paralyse the *central nervous system*.

The first of these properties is the most characteristic. The soluble aromatic compounds are typical **protoplasm poisons,** and even in a very dilute condition hinder the growth of bacteria, and in greater concentration kill all micro-organisms. A good many of them are among the most frequently employed antiseptics and disinfectants. Toxicity to the host and powerful action on bacteria as a rule go together, so that the less poisonous compounds are generally less bactericidal. In exceedingly small quantities they appear to be favourable to the growth of micro-organisms (*e.g.* fermentation of sugar). This apparent paradox has an analogy with the action of other protoplasm poisons which also cause a temporary increase in the activity of the protoplasm before its destruction (*cf.* quinine and sublimate).

In practice a distinction is made between two grades of the action—the *antiseptic*, which consists in the prevention of growth of bacteria as long as the substance in question is present, and the *disinfectant*, by which is meant that the bacteria are killed, so that growth cannot take place after the removal of the drug. The former action, which in the treatment of wounds is generally sufficient, does not, of course, require such strong concentrations as the latter.

What the nature of the action is which the aromatic anti-

septics exert upon micro-organisms is not known. The chemical changes upon which it must be based are less obvious than those of the inorganic antiseptics and disinfectants, which always possess strong chemical affinities, *e.g.* acids, oxidisers, halogens or metallic salts, which destroy the protoplasm by combining with the cell-constituents ; sublimate by combining with albumin ; acids by taking possession of the bases of weaker acids and by forming acid-albuminates ; chlorine by combining with hydrogen, etc. It is a matter of indifference, so to speak, to such antiseptics whether albumin or other substances for which they have an affinity are in the bacteria-bodies or elsewhere, *e.g.* in the cells of the wound-surface : both are acted upon in exactly the same degree, and the destructive action on bacteria runs parallel with that on the tissue on which they grow. The aromatic antiseptics, on the contrary, act apparently more specifically. They, too, injure the cells of the host, or the nutritive substratum, but very frequently less than the bacteria ; they are not so destructive to tissues, and are generally without pronounced chemical affinity, Practically, this difference is an advantage to the aromatic antiseptics, for they retain their activity undisturbed by albumin and other organic substances, with which they do not combine, whereas other antiseptics, such as sublimate, are soon fixed and rendered inert by proteins.

Although the aromatic antiseptics are generally more injurious to micro-organisms than to their host, there is not known among them, nor among other bactericidal compounds, any substance with which a general disinfection of the entire human organism can be attained. No drug can be introduced into the body in such large quantities as to make the concentration sufficient to kill all the micro-organisms that have invaded it without at the same time killing the host : the poisonous action is especially upon the central nervous system. On the other hand, there are a few bodies that are such specific poisons, each for its particular micro-organism, that they succeed in preventing the development of the microbes in a dilution that does no great harm to the organism as a whole, *e.g.* quinine in malaria, arsenic in protozoal diseases, and, in a less pronounced degree, salicylic acid in rheumatic fever, and mercury in syphilis.

Many aromatic compounds lower fever temperature, while having little influence on the temperature of the healthy animal or man unless given in quantities so large as to produce collapse. The question of the cause of their **antipyretic** action has not yet been sufficiently investigated, but it is probably of the same nature as that of antipyrine.

Finally, the **central nervous system** is paralysed, but in a different way from that shown by the methane derivatives. Whereas paralysis of the cerebrum is a family trait common to all the narcotics of the fatty series, the action of the aromatic nerve-

poisons begins with stimulation of the brain and the spinal cord, increased reflex activity, tremor and convulsions. The paralytic symptoms are not evident until a later stage, when, in man especially, partial or complete loss of consciousness may occur; the condition may become one of anæsthesia, which differs, however, from that produced by ether or chloroform, in that sensation is long retained, and voluntary movement is not lost. Death occurs from paralysis of the medulla oblongata and the heart.

Many aromatic compounds show other effects. Those substances which outside the organism behave as powerful reducing drugs—*e.g.* pyrogallol—within it act destructively upon the *red blood-corpuscles* and form methæmoglobin. In the lower phenols and allied compounds, which are highly *corrosive*, the symptoms from stomach and intestine become so pronounced that the poisoning can often scarcely be distinguished from that produced by concentrated acids or corrosive metallic salts. During excretion many such aromatic bodies cause *irritation of the kidneys*.

As regards their **fate in the body** there is a great and most important difference between the aromatic compounds and the methane derivatives. Whereas the bodies of the fatty series generally undergo a more or less complete oxidation to carbonic acid and water, the firmly-constructed benzene ring almost always passes through the organism intact, and is excreted through the kidneys. Even if aromatic bodies could be found that were safe enough to be taken in large quantities, they could never on that account become food-stuffs in the same way as the fats. If an aromatic compound contains side chains belonging to the fatty series they are oxidised, while the ring C_6H_6 remains intact. The oxidation is confined to the formation of hydroxyl and carboxyl compounds, *e.g.* dioxybenzols and aromatic acids. The ultimate fate of the benzol compounds does not therefore exhibit great variation. The phenols are excreted in the urine in combination with glycuronic or sulphuric acid as ether-sulphuric acids, while the aromatic acids are as a rule excreted in combination with glycocoll. The latter synthesis takes place in the kidneys. It is not exactly known where the ether-sulphuric acids are formed. After the urine is passed, partly also before, the phenol sulphates undergo fermentative decomposition; the phenols are liberated and further oxidised to dark-coloured compounds, which give to the urine the well-known smoky appearance (carboluria).

Just as the hydrocarbons of the fatty series have little action in comparison with their hydroxyl compounds, so the alcohols of the aromatic hydrocarbons exert a feeble action compared with the very active phenols, which are remarkable for their strong antiseptic properties and toxicity: the higher members of the

series (polyvalent phenols) are less poisonous than the lower (carbolic acid). The antiseptic action is weakened by the introduction of carboxyl. The aromatic acids are therefore less antiseptic and less poisonous, and some of them are efficient antipyretics. Ortho-hydroxybenzoic acid is particularly noteworthy for its effects in rheumatic fever.

The simpler aromatic compounds thus fall naturally, both chemically and pharmacologically, into 3 groups, namely: (1) hydrocarbons; (2) phenols and allied bodies; and (3) acids. They will be described below in this order.

Aromatic Hydrocarbons

Benzol, or *benzene*, C_6H_6 (not to be confounded with petroleum benzine, which consists of hydrocarbons of the fatty series), is antiseptic and acts as a powerful poison on many of the lower animals. It has long been known that inhalation of concentrated benzol vapour produced in man loss of consciousness and death. Of late years chronic poisoning has also become important, for benzol is used in great quantities in the manufacture of motor and bicycle tyres as a solvent for india-rubber, and may cause serious poisoning in persons who are constantly inhaling the vapour. The symptoms consist in multiple hæmorrhage in the skin, gums and nose, hæmatemesis, and profuse uterine hæmorrhage, which, in acute anæmia, may even end in death. The post-mortem shows extravasation of blood in most of the organs, with extensive fatty degeneration of the vascular endothelium as its cause (Santesson). In such cases of poisoning it was observed that the number of leucocytes decreased greatly, and they might even disappear altogether. This gave rise a few years ago to the treatment of *leucæmia* with benzol. It was found that an improvement—also in the general condition of the patient—could be attained; but the risk of a dangerous continuation of the action was too great. Benzol is also used for *trichinosis*, and externally as an anti-parasitic (*pediculi pubis et capitis*).

Naphthalene, which consists of two combined benzol rings, is formed by the dry distillation of many organic substances, and occurs in great quantities in coal-tar. It, too, is very poisonous to lower animals and insects (moths, mosquitoes, bugs), but not to the higher animals or man, as it is only sparingly absorbed from the intestinal canal, and passes out for the most part unchanged with the fæces, killing both micro-organisms and animal parasites on its way through the intestine. A small part is absorbed and excreted in the urine in the form of oxidised compounds (α- and β-naphthol, naphthoquinone), which are local irritants and may

induce albuminuria, tenesmus, and pain in the region of the kidneys and bladder and in the urethra, the mucous membrane of which becomes swollen and injected. The urine assumes a dark brown colour on standing, and remains sterile for weeks.

Naphthalene is employed as a dry *external antiseptic* in *skin-diseases*, and as an *intestinal disinfectant* (typhoid fever, ascariasis), and is stated to be especially efficient against *oxyuris ;* on account of its slow absorption, it is better able than most internal remedies to reach the habitat of the worm.

Preparations and Doses

Benzenum, benzol, C_6H_6, a clear, colourless, refractive liquid, boiling at 80·5° C. *Dose*, for leucæmia, 2—5 grms., 30—75 grs., daily, mixed with olive oil, in gelatine capsules.

Naphthalinum, naphthalene, $C_{10}H_8$, colourless, shining, laminar crystals, with tarry odour and burning taste. *Dose*, 0·5—3 grms., 8—45 grs., daily ; for oxyuris in children, 6 centigrms., 1 gr. (2 years old), 20 centigrms., 3 grs. (12 years), 3 times a day. For whooping-cough, heat slowly 20 grms. on a plate until it melts and evaporates ; repeat for several evenings in the sickroom.

Phenol (Carbolic Acid)

When hydroxyl is substituted for the hydrogen in the benzol ring, the so-called phenols are formed, the first and most important of which, $C_6H_5.OH$, is often called carbolic acid, although in a chemical sense it is no acid.

Action. Carbolic acid, or phenol, is a **protoplasm poison** which in dilute condition checks the growth of all micro-organisms, and in strong concentration kills them, although it is far less active than some other antiseptics, such as sublimate. It is not equally poisonous to all micro-organisms, its action varying both according to the species of organism (more powerful on protozoa and allied organisms than on bacteria), and still more according to their stage of development, as the actively growing forms are always far more easily affected than spores. Thus the anthrax bacillus quickly succumbs in a $\frac{1}{2}$ per cent. solution, while the spores are still capable of germinating after remaining for 15 days in 1 per cent. phenol, and are killed only after 5 or 6 days in a 5 per cent. solution. The destruction of tubercle bacilli requires 24 hours' action of 5 per cent. phenol. Vaccine lymph to which 1 per cent. of phenol has been added still gives a positive result, while 2 per cent. makes the lymph inert. There are also great differences between the various statements as to its antiseptic capabilities, as the experiments have not always been carried out on the same plan. In the form of vapour phenol has but little effect ; earth containing bacilli which had been exposed to the

vapour for 6 weeks and smelt strongly of carbolic exhibited the most active growth when cultured upon gelatine.

Carbolic acid is **caustic** and produces **local anæsthesia.** When concentrated carbolic acid is applied to the skin, it causes, after a brief period of pain followed by loss of feeling which penetrates to the depth of the skin, the formation of a white crust, which subsequently becomes red and falls off, leaving a pigmented spot. Even a 5 per cent. solution gives a white, tanned appearance to the epidermis, and causes first a slight burning or pricking sensation, and later numbness, the feeling of having a glove on, and diminished sensibility. Still weaker solutions, when applied as a poultice for some time, may cause deep, dry gangrene, as carbolic acid easily penetrates the skin. On wound-surfaces and mucosa the corrosion is greater than on the unbroken skin ; a white precipitate of albumin is formed, and if a mouthful of a concentrated (90 per cent.) phenol solution is swallowed, in a few seconds the prominent folds of the gastric mucous membrane become necrosed as by poisoning with concentrated mineral acids.

The general action, which was only too well known in the early years of antisepsis, when cases of poisoning in consequence of absorption of the carbolic acid from bandages were frequent, affects principally the **central nervous system.** After absorption of medium quantities (1—2 grammes) drowsiness supervenes, sometimes accompanied by delirium, noises in the ears and deafness, general indisposition and vomiting, great languor, slow pulse, temperature sometimes raised, sometimes lowered, by a few tenths of a degree (in cases of fever, more), and often profuse sweating and salivation. Large quantities very quickly bring about collapse, the face becomes pale, the skin clammy with cold sweat, the pulse small and irregular and the respiration laboured, and the temperature falls considerably. Death is due to paralysis of respiration. If pure carbolic acid is taken internally, the "shock" caused by the corrosion of the stomach leads to very rapid collapse and death, even in the course of a few minutes. The smallest lethal dose is stated to be 8—10 grammes, and the amount generally taken by suicides or by accident is 15—30 grammes, but varies within wide limits. Children are very sensitive. It will be seen that in man poisoning with carbolic acid differs from the typical poisoning with aromatic substances, in that convulsions do not (or very seldom) occur, while in animals they form one of the regular symptoms.

With the exception of irritation of the kidneys, there is little effect to be seen on **other organs.** In the body methæmoglobin is not formed, but in the test-glass forms slowly when carbolic acid is added to *blood.* In mammals the *motor nerves and muscles*

do not appear to suffer, while in the frog their irritability is diminished.

Absorption and Excretion. Carbolic acid is absorbed with the greatest ease through unbroken skin, mucous membranes and raw surfaces. The greater part combines unchanged with sulphuric and glycuronic acids, and is excreted as the alkaline salts of the respective acids. A small proportion is oxidised to dihydroxybenzols, principally hydroquinone, which in the urine appears as hydroquinone-sulphuric acid, a very unstable compound which is easily decomposed, and on further oxidation produces substances which give a brownish green or almost black colour to the urine. This may sometimes take place within the body, but sometimes the urine passed is of a pale yellow colour and apparently normal, but after standing becomes dark, beginning at the surface, which is exposed to the oxygen of the atmosphere. Dark urine is often seen simultaneously with the first symptoms of intoxication, but is not constant: the colour, as we have explained, does not depend upon the amount of carbolic acid absorbed, but on the amount oxidised, and therefore makes its appearance far sooner when the carbolic acid is absorbed from an open wound to which oxygen has free access than when the absorption has taken place in the intestine. In the first case urine of a bright green colour may be passed without any poisoning. The glycuronic acid compounds impart a reducing action to the urine, which may on superficial examination give the appearance of sugar.

Therapeutic Uses. Although the antiseptic operation-technique has now been partially superseded by the aseptic, and carbolic acid has given place to other bactericidal substances, it will always be remembered as the drug with which Lister, in 1867, inaugurated the antiseptic method, and with it modern surgery. In the first part of the antiseptic era, carbolic acid reigned alone. The patient, the operator, the instruments and bandages, and even the air of the operating-room, were treated with it or its vapour. Now it is almost discarded by surgeons, because many newer drugs are more efficient, and because it has objectionable effects, such as the troublesome "carbolic eczema." Antiseptics as a whole are employed less now, but carbolic acid still plays an important part with the layman, and is constantly employed in most unpractical ways, which render it useless or even injurious. The favourite carbolic solution poultice is an instance of the latter. As already mentioned, carbolic acid, even in dilute solutions, easily penetrates the skin when evaporation is prevented, and may cause deep, dry necrosis. Its employment on peripherally situated parts is especially open to objection; *a 2 to 3 per cent.*

poultice kept on for a couple of days has often caused gangrene of fingers. When dissolved in fat, carbolic acid is almost useless, and the " carbolic oil " frequently employed, at any rate some years ago, is scarcely more antiseptic than pure oil by itself. An antiseptic can only act by penetrating into the bacteria that are to be made innocuous ; but as carbolic acid is far more easily dissolved in a fixed oil than in the watery secretion from a wound, it remains in the oil without reaching the bacteria. Not only the anthrax spores, but also the far less resistant bacilli, still show every sign of life after being 3 months in a 5 per cent. carbolic oil. On the other hand, the antiseptic action of a carbolic acid solution is augmented by the addition of substances that diminish the solubility of the phenol, *e.g.* sodium chloride, which " salts it out," and thus assists its transfer from the solution to the bacteria.

As an antiseptic, carbolic acid has thus lost most of its importance, but, on the other hand, it is still much used for the *disinfecting* of inanimate objects—rooms, lavatories, drains, all kinds of infected refuse, the excrements of cholera and typhus patients, etc. For the sake of economy, impure preparations or crude products are employed for this purpose, consisting of mixtures of phenols, cresols, etc.

Externally, carbolic acid is employed in *skin-diseases* (pityriasis, sycosis, scabies) as an antiparasitic, and, on account of its local anæsthetic action in concentrated form, for toothache (placed in the decayed tooth). Diluted it is used as a wash for *itching of the skin.* Injections are employed for *tuberculosis in bones and joints*, inhalations for *putrid bronchitis* and *gangrene of the lungs.* By scarification, with subsequent inunction of 5 per cent. carbolic solution, endeavours have been made to circumscribe *erysipelas.* A 20 per cent. solution in glycerin, which prevents corrosion, is employed as a local anæsthetic for the tympanum.

The internal employment of carbolic acid has been almost abandoned. Attempts to disinfect the intestine, *e.g.* in diarrhœa or in typhus fever, fail partly on account of the toxicity of carbolic acid, partly because it is absorbed too quickly. In *diabetes* the amount of sugar decreases, but rises as soon as the drug is left off. Many other aromatic substances exhibit a similar action, probably only because they weaken the appetite or digestion.

Trinitrophenol, or *picric acid,* is an important yellow dye, and being of an explosive character, is much used in the manufacture of explosives. It has the general action of the phenols, somewhat modified by the entrance of the nitro group. In poisoning, the skin and scleræ become yellow, not from the bile colouring matter, but from unchanged picric acid. It has a very toxic action on lower animals, and has been tried for tape-worm and trichina, but is not able to kill the parasites already encysted in the muscles.

Gauze dressings saturated with 1 per cent. trinitrophenol are used for their antiseptic and mildly astringent properties in cases of burns. When the affected area is extensive, however, trinitrophenol is less suitable as the toxic effects of absorption may appear if large quantities are applied to raw surfaces. A more concentrated preparation for local application may be made by dissolving the drug in alcohol (5 per cent. trinitrophenol in 70 per cent. alcohol).

Dinitrophenol. Interest in this derivative of phenol has been revived in recent years. As early as 1885 it was known that this compound administered to dogs increased the metabolic rate. More exact knowledge of its action and possible dangers has emerged since 1933, when it was suggested by Tainter *et al.* that the drug might be used in the treatment of obesity. Doses of 1½ gr. thrice daily produce well marked tachycardia, increased respiratory rate, elevation of temperature and excessive sweating. The blood-pressure, however, is scarcely affected. The metabolic rate is greatly increased up to 100 per cent., and this proceeds almost entirely at the expense of the body fats, the protein and carbohydrate being practically unchanged.

Treatment of obesity with dinitrophenol is undoubtedly effective, but it carries with it the dangers of the toxic effects of the drug, which are serious and by no means uncommon. The complications include pruritus, followed by skin eruptions, cataracts and sometimes blindness, polyneuritis and impairment of special senses, agranulocytosis, etc. In the present state of our knowledge, obesity is best treated by appropriate dietetic measures and, where necessary, the administration of thyroid.

Treatment of Carbolic Acid Poisoning. In cases of poisoning by the mouth, the stomach should be washed out with warm water, or, better still, with 10 per cent. alcohol. If a stomach-tube is not available, brandy is given, as, like oil or glycerin, it prevents or reduces corrosion. This is due to the dissolving action of the alcohol on the carbolic acid, which keeps it from penetrating the tissues in concentrated form. The treatment with alcohol must of course be followed by washing out of the stomach in order to prevent subsequent absorptive action. Syrup of lime is further recommended, the intention being to procure the formation of an insoluble phenolate. If coma has set in, all stimulants and artificial respiration are employed, but generally in vain.

Preparations and Doses

Phenol (B.P., U.S.P.), carbolic acid, C_6H_5OH. Colourless or reddish, deliquescent crystals, soluble in about 15 parts of water, freely soluble in alcohol, in glycerin, and in fixed and volatile oils. *Dose*, 6—20 centigrms., 1—3 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.). Given in the form of pills or mucilaginous solutions, but now very seldom used internally. For disinfection, 5 per cent. on wounds, and for injection, 2 per cent. solution.

Phenol Liquefactum (B.P., U.S.P.), liquefied phenol, is a solution of 1 part water and 4 parts phenol, and forms a colourless or reddish, rather thick fluid, which is more convenient for dispensing than the deliquescent crystals. On the addition of water the phenol is separated in small drops,

and a milky emulsion is obtained, until, when the phenol amounts to 5 or 6 per cent., there is complete solution. *Dose*, 6—18 centimils, 1—3 mins. (B.P.); 0·05 mil, 1 min. (U.S.P.).

Glycerinum Phenolis (B.P.), 16 per cent. of liquefied carbolic acid in glycerin. *Dose*, 0·3—1 mil, 5—15 mins. Used by aurists as a local anæsthetic for the tympanum.

Unguentum Phenolis (B.P.), 3 per cent.; *Unguentum Phenolis* (U.S.P.), 2 per cent. *Suppositorium Phenolis* (B.P.), each containing 0·06 grm., 1 gr., unless otherwise prescribed. *Trochiscus Phenolis* (B.P.), each containing 0·03 grm., ½ gr. The lozenges are tinted pink with carmine.

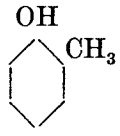
When carbolic acid is dissolved in concentrated sulphuric acid, phenolsulphonic acid is formed. The sodium salt, *Sodii Phenolsulphonas*, colourless crystals, with no odour and a cool, bitter taste, very soluble in water, has been tried as an intestinal disinfectant, but has little effect. *Dose*, 0·25 grm., 4 grs.

Trinitrophenol (B.P., U.S.P.), picric acid, $C_6H_2(OH)(NO_2)_3$. A bright yellow crystalline powder, odourless. Explodes when heated rapidly or when subjected to percussion. Soluble in 90 parts water. More soluble in alcohol. *Dose*, 0·06—0·3 grm., 1—5 grs. (B.P.).

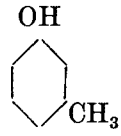
Cresols

Homologous phenols arise by the substitution of methyl, ethyl, etc., for one or more of the hydrogen atoms of the benzol ring.

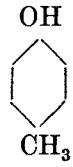
The most important are the cresols, which are methyl compounds and bear the names ortho-cresol, meta-cresol and para-cresol, according to the relative position of OH and CH_3.



Ortho-cresol.



Meta-cresol.



Para-cresol.

By the substitution of methyl for the hydrogen of the benzol nucleus, the antiseptic power of the phenols is increased, this being especially the case with meta-cresol. According to the most recent investigations, ortho-cresol is equal to carbolic acid as regards toxicity, while meta-cresol is rather less poisonous, and para-cresol rather more so. The action of a compound—as will be mentioned again under salicylic acid—is therefore not only dependent on the presence of certain atoms or groups of atoms, but also on their relative position in the molecule. In the quality of their action they are all like carbolic acid, producing the same white scar on unbroken skin, and, when taken internally, the same caustic action in the mouth, throat and stomach. Their

effects after absorption are also the same as those of carbolic acid.

The cresols are used as antiseptics and disinfectants for the same purposes as carbolic acid. For surgical use, the official preparations, which permit of solutions of accurately determined strength, should be chosen, while for the disinfecting of inanimate objects, bacteria-infected fæces, etc., where the concentration is not so much a matter of importance as long as it suffices its purpose, less stable mixtures are used for reasons of economy, *e.g.* the so-called *crude carbolic acid*, which does not quite answer to its name, as it contains mainly cresols and many other products of the dry distillation of coal-tar, *e.g.* naphthalene, and little carbolic acid.

In addition to these there are various preparations in commerce, produced with the object of remedying the cresols' defect in being even less soluble in water than carbolic acid, a defect which detracts from their utility. At first the aim was confined to the production, by various additions, of mixtures that formed a fine emulsion with water. *Creoline* is a preparation of this kind, and was formerly much used, though less now. The easy solubility of cresol has since been attained, principally by the addition of alkaline soap. The commercial antiseptic, *lysol*, is a preparation of this kind ; it gives clear solutions with water, which lather and make the hands slippery, as soap-suds do. Lysol was very popular for a long time, but is now often replaced by the corresponding official preparation, *Liquor Cresolis Saponatus* (B.P., U.S.P.). The term " lysol " is now an official synonym for this preparation (B.P.). *Solveol*, *solutol* and *sapocarbol* are similar preparations intended for wholesale disinfection.

In addition to their defective solubility, crude carbolic acid and crude cresol have further the disadvantage that, owing to their high specific gravity in fluid contents, they fall to the bottom, where they form a heavy layer, which has too little influence on the decomposition that takes place on the surface of the liquid. To remedy this defect, light hydrocarbons are added, thus producing a mixture that floats on the surface like oil. This is the principle of *saprol*, which is also a wholesale disinfectant spreading itself in an unbroken sheet over floating masses, preventing the escape of foul gases, while acting on the matter below, with the co-operation of the ammonia that is always formed in the process of putrefaction, by causing the dissolution of the cresols in the mixture, and their permeation of the entire mass.

It is unnecessary to explain that when preparations such as the above and similar mixtures are advertised as " non-poisonous," this statement is very misleading. Although on an average less poisonous than carbolic acid, they are naturally poisonous in proportion to the amount of cresol and allied bodies they contain ; they are absorbed, like carbolic acid, through the skin, and have often caused very serious poisoning.

Preparations and Doses

Cresol (B.P., U.S.P.), a mixture of the three isomeric cresols, is a yellow or brownish yellow liquid, which becomes darker with keeping ; soluble in 50 parts of water, freely soluble in alcohol, in glycerin and in fixed and volatile oils. *Dose*, 6—18 centimils, 1—3 mins. (B.P.) ; 0·05 mil, 1 min. (U.S.P.). Externally, in a 2 per cent. solution.

Liquor Cresolis Saponatus (B.P., U.S.P.), 50 per cent. of cresol. A brown fluid with a cresol odour ; forms a clear solution in water. Is used in a ¼—2 per cent. solution for washing the surface to be operated on and the hands, and for washing out the vagina, etc. A clear solution cannot be obtained with limestone water, as an insoluble lime soap is precipitated.

Creolinum, a heterogeneous mixture of 10—30 per cent. of cresols with hydrocarbons, pyridine bases from tar, and resinous soap. A dark brown liquid with a tarry odour, which yields a milky emulsion with water. Externally, a 0·5—2 per cent. solution for surgical use, 5—10 per cent. for disinfecting purposes.

Solutol, a brown liquid with alkaline reaction ; *Solveol*, a clear, neutral liquid. The former, in a 3 per cent. solution, is used for the disinfectant washing of rooms, etc., the latter, in a strength of 1—2 per cent., as a surgical antiseptic.

Saprolum, 40 per cent. of cresols, 20 per cent. of light hydrocarbons. A dark brown liquid that floats on the surface of water. Is poured, undiluted, upon putrefying or infected floating masses.

Hycol, Izal, Jeyes' Fluid, Kerol, Monsol, Trikresol, etc., are proprietary antiseptics much more powerful than phenol, but having little or no advantage over cresol.

Thymol

Thymol, "*thyme-camphor*," occurs in the volatile oils of several plants, among them being the common thyme, *Thymus vulgaris*, to which it gives its well-known odour. Synthetic thymol is now official.

Thymol is methyl-isopropyl-phenol, and is far more antiseptic than either phenol or cresol. In a solution of 1 in 10,000 it checks the growth of anthrax bacilli, and in 1 in 4,000 completely arrests it, while the spores are not killed even by a solution of 1 in 3,000.

The action of thymol after absorption resembles that of carbolic acid and cresol, except that thymol does not produce convulsions, but from the commencement has a paralysing effect upon the central nervous system. It is also far less poisonous than the previously-mentioned phenols, probably because it is extremely insoluble and is slowly absorbed. Its local action also is not very marked ; it scarcely affects the unbroken skin, and causes no deep corrosion of mucous membranes, but only a superficial sloughing of the epithelium. In the urine, which it colours green or almost black, thymol is excreted, in combination with sulphuric acid, partly unchanged, partly oxidised to a bivalent phenol (thymol-hydroquinone).

Uses. Thymol, on account of its deodorising and non-poisonous properties, is especially suited as an antiseptic for washing out large cavities with foul-smelling secretion, such as old empyemas. The peculiar flowery scent, which at first is pleasant, after a time becomes disagreeable, and also has the disadvantage of attracting flies. Internally thymol has been tried as a substitute for salicylic acid in acute rheumatism, and as an antipyretic in typhoid fever and pneumonia, but the results have not been encouraging. As an intestinal disinfectant in the diarrhœa of infants it has had better success. The most important use of thymol, however, is in the treatment of hook-worm infection. It has been extensively used for this purpose in India, Ceylon and the Far East, where the disease is a serious menace to public health. (For method employed, see Preparations and Doses, below, and discussion of "Anthelmintics," p. 338.)

Loose iodine compounds have been produced from a very great number of aromatic antiseptics, intended to decompose upon wound-surfaces and combine the action of the iodine with that of the aromatic constituent. Thymol has also contributed to the formation of such a compound in *aristol*, or dithymol-diiodide, which appears to be a very efficient preparation for burns, wounds, syphilitic ulceration, diseases of the ear and nose, etc., but, like most other substitutes, is inferior to iodoform as regards reliability of action.

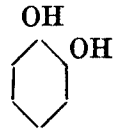
Preparations and Doses

Thymol (B.P., U.S.P.), $C_6H_3.CH_3.C_3H_7.OH$, large, colourless, rhombic prisms, with a pleasant odour, soluble in about 1,100 parts of water, readily soluble in alcohol and in olive oil. *Dose*, 3—12 centigrms., ½—2 grs.; as an anthelmintic, 1—2 grms., 15—30 grs. (B.P.); as an antiseptic, 0·125 grm., 2 grs.; as an anthelmintic, 2 grms. (30 grs.), divided into three doses (U.S.P.). For hook-worm, large doses are recommended, *e.g.* 2 grms. (for a child of 5 years, 0·5 grm.), divided into three portions, taken at intervals of 1 hour. Two hours after the last portion, a strong saline purgative is given for the purpose of clearing out the intestine and preventing absorption. Treatment is most effective when the patient fasts for about 12 hours beforehand, *i.e.* from the previous evening. During this time it is advisable to clear the bowel with a dose of magnesium sulphate, thus exposing the worms to the action of the anthelmintic. In particular, alcohol, oils and fats are forbidden as they dissolve thymol and so facilitate its absorption (see also p. 338). The cure is repeated once a week until its purpose is attained. Externally, for poultices and the washing out of cavities, etc., or as a mouth-wash, the saturated aqueous solution is used.

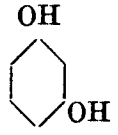
Thymolis Iodidum (U.S.P.), aristol, a reddish brown powder, with a faint aromatic odour; insoluble in water, soluble in ether and in fixed and volatile oils. Is used pure as a dusting powder, as a 10 per cent. ointment or a 10 per cent. solution in collodion or olive oil.

Bivalent Phenols

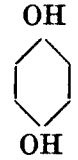
The bivalent phenols, the dioxybenzols, occur, like the cresols, in three isomeric forms, ortho, meta and para compounds.



Pyrocatechin (ortho).



Resorcin (meta).



Hydroquinone (para).

These all resemble carbolic acid as regards the quality of their action, but the different position of the hydroxyl group occasions a quantitative difference, resorcin being less poisonous than the other two. They are all excreted in the urine, in combination with sulphuric and glycuronic acids, in part unchanged, in part oxidised to green or black compounds. Their affinity for oxygen makes them highly reducing drugs, especially in alkaline solutions.

Of the three bivalent phenols, resorcin is the only official drug. Pyrocatechin is of therapeutic importance only inasmuch as its methyl ether is a constituent of creosote ; and hydroquinone is also only indirectly employed, as it is formed by the decomposition of arbutin.

The antiseptic action of **resorcin** is as strong as, or even stronger than, that of carbolic acid, but it is less caustic and less poisonous. The action is brief, however, and is also accompanied by profuse sweating, and frequently by intoxication, delirium, drowsiness, and fibrillary muscular twitching ; altogether, such unmistakable signs of collapse may occur that its employment as an antipyretic was soon abandoned. As an antiseptic, resorcin is still given for vomiting occasioned by fermentation of the contents of the stomach, *e.g.* in *dilatatio ventriculi* and in *summer diarrhœa* in adults and children, and is also recommended for the *vomiting of pregnancy*. Its most frequent use is external in *skin-diseases*, such as acne, psoriasis, eczema, lupus and erysipelas. When highly concentrated it has a slow and painless corrosive or solvent action on the epidermis ; when diluted it acts only as an antiseptic (*gonorrhœa*).

Arctostaphylos uva ursi (not official) contains the glucoside *arbutin*—which on decomposing yields glucose, hydroquinone and methyl-hydroquinone—the bitter *ericolin*, also a glucoside, the camphoraceous *urson*, and finally about 30 per cent. of *tannic* and *gallic acids*. A decoction of the leaves is slightly diuretic, enables

the urine to withstand putrefaction for a long time, and is employed in *catarrhal conditions of the urinary passages*, especially in *cystitis* with foul-smelling, cloudy and alkaline urine. It has not yet been determined which of the constituents is the most important. Some of the activity is probably to be ascribed to the arbutin, which itself is slightly antiseptic, and may also give off hydroquinone, at any rate in alkaline urine containing an abundance of bacteria. The tannic acid was originally considered to be the most important, but probably wrongly, as it is excreted in the urine as gallic acid, which has no astringent properties (see chapter on Astringents).

Arbutin and tannic acid are also found in the cowberry plant, *Vaccinium vitis-idœa*, the leaves of which are one of the many ineffective popular remedies for rheumatism.

Preparations and Doses

Resorcinol (B.P., U.S.P.), $C_6H_4(OH)_2$, colourless or pale yellow prisms, easily soluble in all the ordinary solvents. *Dose*, 6—30 centigrms., 1—5 grs. (B.P.); 0·125 grm., 2 grs. (U.S.P.). In diarrhœa, in a ½—1 per cent. solution, for adults 1 tablespoonful, for children 1 teaspoonful, every 2 hours. Externally, in a 5—50 per cent. ointment or paste, according to the strength of the skin-solvent action desired. For acute eczema, a 1 per cent. poultice. For injection in gonorrhœa, ½—1 per cent., for irrigation of the bladder, 1—5 per cent. solution.

Uvœ Ursi Folia (not official), the leaves of the bearberry, *Arctostaphylos uva ursi* (*Ericaceœ*), a creeping bush growing in most parts of Europe, in the north of Asia, and in America. The leaves are obovate or lanceolate, and leathery, 2 cm. long and 1 cm. broad. *Dose*, 2 grms., 30 grs. Is often prescribed as a 10 per cent. decoction, 1 tablespoonful 4—6 times a day.

Infusum Uvœ Ursi, 5 per cent. *Dose*, 15—30 mils, ½—1 fl. oz.

Trivalent Phenols

The only trivalent phenol employed is *pyrogallol*, often called pyrogallic acid on account of the acid reaction that takes place in an aqueous solution when it has been exposed to the air for some time.

Its most important property is its affinity for oxygen. Even in an ordinary temperature it reduces salts of silver to metallic silver, and in gas-analysis serves as an absorbent of oxygen. Within the body, too, its reducing properties are so strongly marked that they almost entirely cover the action of the benzol nucleus, and make pyrogallol behave mainly as a blood-poison which destroys the red blood-cells so that the hæmaglobin passes into the plasma and is changed into methæmoglobin. The blood assumes a chocolate-brown colour, hæmoglobinuria and methæmoglobinuria appear, and acute nephritis with albuminuria, the renal tubules sometimes becoming so filled with fragments of

epithelium and blood-corpuscles that the secretion of urine is stopped. The most important clinical symptoms are diarrhœa and vomiting, jaundice, rigors and fibrillary muscular twitchings ; and the poisoning terminates in anuria and the well-known characteristic features of uræmia.

Pyrogallol is easily absorbed through the skin, and is excreted in part unchanged in combination with sulphuric acid, in part is converted into unknown products which by themselves colour the urine a deep green, and in combination with hæmoglobin almost black.

On raw surfaces and mucous membranes pyrogallol acts as a mild caustic, on unbroken skin only as a slight irritant, but stains the skin black by its oxidation.

Pyrogallol is used principally for *psoriasis*, in which it is better adapted for application to the face than chrysarobin, though less active ; it is also less irritant than chrysarobin, and the discoloration of the skin disappears more quickly. It is also used for *lupus*—where it acts more corrosively upon the diseased tissue than on healthy granulations—and for various *parasitic skin-diseases*, such as *favus*, *herpes tonsurans* and *eczema marginatum*. In *ozæna* and *offensive-smelling ulceration* (cancer), pyrogallol acts as a deodoriser. On account of its toxicity and easy absorption, it must be employed in such a way that the total amount used does not exceed 5 grammes in 24 hours ; the troublesome erythema that may follow its use forbids the application of strong ointments or solutions over large areas of the skin at one time.

Preparations and Doses

Pyrogallol (U.S.P.), pyrogallic acid, $C_6H_3(OH)_3$. Very light, colourless, glistening laminæ and needles, readily soluble in water and in alcohol. *Dose*, for psoriasis and lupus, a 5—10 per cent. ointment ; for parasitic skin-diseases, a 1—2 per cent. alcoholic solution ; for ozœna and foul-smelling sores, a 3 per cent. aqueous solution.

Chrysarobin

Chrysarobin is a mixture of several derivatives of anthracene, $C_{14}H_{10}$, a hydrocarbon occurring in coal-tar. It is the active constituent of the remarkable Goa powder, which is found as a yellowish brown or ochre-coloured substance in large cavities in the trunk of *Andira Araroba*, a Brazilian tree belonging to the *Leguminosæ* order.

Both chemically and therapeutically chrysarobin resembles pyrogallol. It very readily takes up oxygen, especially when alkalies are present, and is converted into chrysophanic acid. It is an irritant to the skin and still more to the mucous membranes,

and produces erythema and, more rarely, a pustular eruption accompanied by fever. In the eye it causes great inflammation, which may lead to a dimming of the cornea. It is readily absorbed from the skin and is excreted in the urine, partly as chrysophanic acid, recognisable by the red colouring of the urine (similar to that with the use of rhubarb) on the addition of potash or ammonia, partly as more or less unknown substances, which may cause irritation of the kidneys and albuminuria. Internally even a few centigrammes produce vomiting and diarrhœa, while large doses cause pain in the kidneys and hæmaturia.

Therapeutic Uses. Chrysarobin is the most certain and quickly-acting remedy for *psoriasis*, but is no more capable than any other locally-applied drug of preventing a return of this disease. With daily inunction of chrysarobin ointment, the scale-formation very soon begins to decrease and the efflorescence becomes less prominent, while, at the same time, the surrounding healthy skin becomes the seat of a diffuse inflammation, which may extend far beyond the region under treatment. At last the parts originally affected by psoriasis present the appearance of smooth, perfectly white patches standing out in strong contrast to the surrounding inflamed skin, which is first red and then brown or brownish purple in hue. Chrysarobin, like pyrogallol, is also efficient in various *parasitic skin-diseases* such as *herpes tonsurans*, *eczema marginatum* and *pityriasis versicolor*. Besides staining the skin and nails, it has the disadvantage of leaving brownish purple stains on linen ; the stains can, however, be removed by chlorinated lime or benzol. Out of regard for the eyes it should not be used, or used only with the greatest caution, on the face or the head, nor should it be applied over large surfaces at one time.

Preparations and Doses

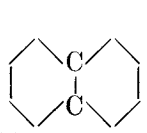
Chrysarobinum (B.P., U.S.P.), a yellow, light, crystalline powder, almost insoluble in water, produced by the purifying of crude Goa powder (*araroba*). Is prescribed as a 10—25 per cent. ointment, or the weaker official ointments, in collodion (10 per cent.) or gelatine (5—15 per cent.).

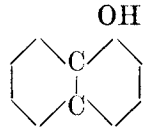
Unguentum Chrysarobini (B.P.), 4 per cent. ; (U.S.P.) 6 per cent.

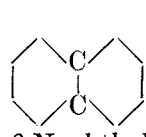
Naphthol

Naphthol is derived from the hydrocarbon naphthalene, just as carbolic acid is from benzol, by the substitution of hydroxyl for a hydrogen atom ; but whereas there can be only one carbolic acid, as OH can be placed in only one way in benzol, there are two

naphthols, as OH may stand either close to, or separated from, the carbon atoms connecting the two benzol rings.


Naphthalene.


α-Naphthol.


β-Naphthol.

β-naphthol, often called simply "naphthol," has been introduced into medicine and included in the pharmacopœias.

The **action** of naphthol is that usual in all members of the phenol series. Its vapour and dilute solutions act as irritants upon the mucous membranes, strong solutions also on unbroken skin, and after prolonged use cause superficial corrosion and necrosis. Its bactericidal action is more powerful than that of carbolic acid. After absorption it produces, in most animals, first strong convulsions, then paralysis and unconsciousness, diarrhœa, and finally death from asphyxia while there is still heart-action. It is important to remember in practice that naphthol is very easily absorbed through the skin, and that during its excretion through the kidneys it is more irritating than the other aromatic antiseptics, and causes far more quickly than they acute nephritis with albuminuria, hæmaturia, reduced flow of urine and uræmic symptoms. In man, serious kidney trouble may be caused by doses that have no toxic action otherwise.

Therapeutic Uses. β-naphthol was introduced into dermal medicine as an active and clean substitute for tar, and possesses similar actions on the skin. It is used for chronic dry *eczema*, in slight cases of *psoriasis*, for *acne* and *parasitic skin-diseases* such as *scabies*, *favus*, *herpes tonsurans* and *eczema marginatum*, and it relieves (as a local anæsthetic) pruritus ; according to Kaposi it is equally effectual for *prurigo* and for *excessive sweating of the hands and feet*. It is a deodoriser in *ozœna*.

Naphthol is employed internally as a gastro-intestinal disinfectant, especially in *typhoid fever* and *dysentery*, and in large doses in the treatment of *ankylostomiasis*. On account of its action on the kidneys, naphthol in strong solutions or ointment should be applied only to small areas of the skin at a time, and the urine must now and then be examined for albumin. Naphthol is contra-indicated in renal diseases.

Various compounds of naphthol have recently been produced and tried for various purposes. *Salinaphthol* (betol) and *benzonaphthol* are compounds that are not changed in, and do not irritate, the stomach, but are split up in the intestine into naphthol, and respectively salicylic and benzoic acid ; they are intestinal disinfectants, the second, moreover,

being used for rheumatic fever. *Epicarine*, a condensation-product of naphthol and cresotinic acid, may be characterised as a more mildly acting, less poisonous naphthol, which rarely causes irritation of the kidneys. It produces a superficial corrosion of the epidermis, and is used especially for scabies and also for seborrhœa capitis with falling hair, chilblains, pruritus and prurigo.

Preparations and Doses

Beta-naphthol (B.P., U.S.P.), colourless glistening crystals with a phenol odour, almost insoluble in water, easily soluble in alcohol and in fixed oils. *Dose*, 2—6 decigrms., 3—10 grs. (B.P.); 0·25 grm., 4 grs. (U.S.P.). For tape-worm, 1—2 grms., 15—30 grs., in the course of an hour, followed by a purgative. Externally, a 1—10 per cent. ointment or solution; for scabies, naphthol 15, soft soap 50, vaseline 100; for itching, a 2—5 per cent. solution in alcohol or olive oil; for sweating of hands or feet, 2 per cent. alcoholic solution.

Salinaphthol, betol, salicylic-acid-naphthol ester, colourless laminæ, almost odourless, insoluble in water. *Dose*, 0·50 grm., 8 grs., a few times a day.

Benzonaphthol, benzoic-acid-naphthol ester, white microscopic crystals, almost insoluble in water. *Dose*, as of the preceding.

Epicarine, naphthol-cresotinic acid, a yellowish pink powder, soluble in alcohol and in ether. Externally, a 10—20 per cent. ointment or solution.

Creosote

Creosote is obtained by the distillation of beech-tar. It is not a simple chemical compound, but a mixture of the various tar-products which boil at about 220° C. Its most important constituents are *guaiacol*, $C_6H_4{<}^{OH}_{OCH_3}$, the methyl ester of pyrocatechin, and the homologous phenol, *creosol*, $C_6H_3(CH_3){<}^{OH}_{OCH_3}$, the methyl ester of homopyrocatechin.

As regards both local and general action, creosote differs only slightly from carbolic acid. It is, if anything, more antiseptic, but is less caustic and less poisonous. A further difference mentioned is that the violent convulsions that characterise carbolic acid poisoning in animals are here less marked than the central paralysis. Creosote is absorbed very easily both from the skin and the mucous membranes. After subcutaneous creosote injections, both in man and in animals, the breath has an aromatic odour. It is, however, only a very small, scarcely determinable amount that is excreted through the lungs; the greater part leaves the body through the kidneys, appearing in the usual combination with sulphuric acid; further oxidation products give a dark colour to the urine.

Therapeutic Uses. Creosote is employed for various purposes,

very much as carbolic acid, but it is mainly interesting on account of its employment in *tuberculosis of the lungs*. Only a few years after creosote had been produced from beech-tar by Reichenbach (1830), and had received its name, which describes it as the flesh-preserving constituent of smoke, it was prescribed by French physicians for chronic catarrh of the bronchi, especially in phthisis. For a long time half forgotten, it was taken up again in 1887 on Sommerbrodt's warm recommendation, and for some years was an indispensable tuberculosis remedy ; but it has now once more declined in favour.

Opinions differ as to the results of the creosote treatment. Most observers who have had wide experience in the matter are of opinion that the patient's appetite, and with it his nutrition and body-weight, are favourably affected, and that fever and night sweats are often diminished, but cannot consider it proved that creosote has any influence upon the state of the lung. The earlier description of cures due to creosote treatment is now regarded with scepticism, as the knowledge gained in recent years has shown how much can be attained by dietetic-hygienic treatment without drugs, and that tuberculosis is much more common and more frequently cured spontaneously than was formerly supposed.

Various theories have been held as to its *mode of action*. It is certain that creosote is not able to kill the tubercle bacilli in the lung or elsewhere ; and it is very doubtful whether it can hinder their development, as its phenol-like constituents are very soon converted in the body into ethereal sulphuric acids, which have little or no antiseptic action. Many authors attribute the good effect that a creosote treatment undeniably may have upon nutrition and general condition to the stimulating action that it has in common with bitters upon the appetite, and they further assert that by its antiseptic properties it protects the intestinal canal from secondary infection. Instead of creosote, its principal constituent, *guaiacol*, is sometimes employed ; it is less caustic, but otherwise appears to act in the same way.

Creosote and guaiacol can only be employed in *chronic* phthisis. They must be given in large doses and during a period of several months, or even years, with occasional rests. This prolonged treatment may be difficult to carry out, partly because the smell and the taste of both preparations become nauseous, partly because they are caustic liquids, and may, instead of improving digestion, produce gastric irritation. In order to overcome these disadvantages, an expedient may be resorted to which of late has been used with great success with drugs that have unpleasant or deleterious gastric action, namely, the employment of compounds that are insoluble and only give off their active constituent under

the influence of alkali in the intestine. Upon this principle are based numerous modern preparations of creosote and guaiacol. It is true that in this way the supposed beneficial gastric action must be renounced ; but, on the other hand, far larger doses can be administered than of the free creosote or guaiacol, because the liberation of the active substance in the intestine takes place so slowly that only small quantities reach the blood at a time, and these are rendered innocuous by conversion into ether-sulphuric acids. There is now a large choice of such compounds, all of which possess the property of passing through the stomach unchanged, but being decomposed in the intestine into creosote or guaiacol and their respective acids. As regards facility of absorption, it is probably immaterial which of these compounds is chosen, and it is therefore as well to keep to the official preparations, the carbonates of creosote and guaiacol.

Creosote and allied preparations are also employed in *ordinary* and *putrid bronchitis* and sometimes in *pneumonia*.

Preparations and Doses

Creosotum (B.P., U.S.P.), a colourless or pale yellow, oily liquid, with an odour of smoke and a burning taste. *Dose*, 12—60 centimils, 2—10 mins. (B.P.) ; 0·25 mil, 4 mins. (U.S.P.). Is always given diluted, for instance, with mucilages, or in wine, or as pills or capsules containing 5 centigrms. (about 1 gr.) creosote with cod-liver oil or olive oil. The first doses should be small, *e.g.* 1 min. or 5 centigrms. 3 times a day after meals, and gradually increased, *e.g.* 1—2 grms. (about 15—30 mins.) each day. "The right dose is the largest that the patient can tolerate." When giving large doses, the patient's general condition and his urine must be carefully observed.

Creosoti Carbonas (U.S.P.), a mixture of the carbonates of the constituents of creosote. A yellowish, rather thick liquid, with a slight taste and odour of creosote. *Dose*, 1 grm., 15 grs. ; 2 grms. 3 times a day may be given.

Calcii Creosotas (U.S.P.), a mixture of the calcium compounds of the various constituents of creosote. A dark brown powder, phenolic odour and taste. *Dose*, 0·5 grm., 8 grs.

Guaiacol (B.P., U.S.P.), colourless crystals when chemically pure, melting at about 30° C. The ordinary preparation is a colourless liquid, with less disagreeable odour than creosote. *Dose*, 30—60 centimils, 5—10 mins. (B.P.) ; 0·5 mil, 8 mins. (U.S.P.). Is given in the same way as creosote.

Guaiacol Carbonas (B.P.C.), a white, crystalline powder, inodorous and almost tasteless, insoluble in water. *Dose*, 3—10 decigrms., 5—15 grs. The dose may be increased to 6 grms. a day.

There are also many other preparations which, like the carbonates, are found by substituting acyl groups for OH. As far as their absorptive action is concerned, it is immaterial which is chosen. The following are briefly mentioned :—

Thiocol, potassium guaiacol sulphonate, a white powder. *Dose*, 2—5 grms. a day. *Sirolin*, a solution of thiocol in orange syrup. *Dose*, 1 teaspoonful 3 or 4 times a day. A good medicine for children.

Tar and Ichthyol

Tar is the thick brown or black liquid obtained by the dry distillation of the wood of conifers and deciduous trees, of coal, animal refuse (horn, hide, hoofs, bone), or of geological formations, strata and shales, which contain the carboniferous remains of former animal and vegetable life. As a reult of the method of production, the various kinds of tar contain a great number of products formed by heating, varying according to the material from which they originate.

Wood-tar

The various kinds of this tar obtained by dry distillation all have an acid reaction, as, in addition to phenols, aromatic hydrocarbons, and resinous bodies, they contain a percentage of the lower fatty acids, principally acetic acid. Beech-tar contains more creosote than does pine-tar, but in other respects both composition and action are in the main more or less alike in all the vegetable tars. Applied to the skin undiluted they cause inflammation. The surface becomes injected, with shallow corrosion, and an œdematous infiltration, which raises the epidermis in vesicles, appears; this is caused by the acids and phenols of the tar. Continued application results in a deeper, pustular inflammation of the follicles, the openings of which become black like blackheads (tar-acne). The irritation of the skin may be attended by great itching, but, on the other hand, the slight local anæsthetic property of the phenols also makes tar a very efficient remedy for allaying itching. Internally, tar is highly irritant to the mucous membranes, and large doses cause very severe vomiting, abdominal pain, diarrhœa and collapse. The aromatic constituents are easily absorbed through the skin and mucous membranes, and by incautious employment over large surfaces may produce acute nephritis with albuminous dark green urine, followed by the same nervous symptoms as in carbolic acid or creosote poisoning. Some tar-constituents, probably resinous acids and terpenes, are also excreted in the bronchial secretion and in the sweat, which acquires a peculiar aromatic odour.

Therapeutic Uses. The various kinds of wood-tar are employed for *skin-diseases*, but have now to a great extent been replaced by naphthol, resorcin and similar substances, which are more convenient and cleaner. The indications for tar (parasitic diseases, especially scabies, chronic dry eczema, itching, etc.) are the same as for the above-mentioned pure substances. In the

treatment of wounds tar has been replaced by newer remedies. In several countries the internal use of tar is popular for *chronic bronchial catarrh* with profuse, purulent secretion, and *cystitis*, in which diseases it is the action of the resinous acids and terpenes in decreasing and disinfecting the secretion that asserts itself. Tar-vapour (tar poured into a saucer and heated until there is a strong odour in the room) is sometimes employed for *putrid bronchitis* and *gangrene of the lungs*. Tar is popularly considered to be a good anthelmintic, and is often taken in doses that are far too large.

Coal-tar

Coal-tar, which plays so important a part in organic chemistry as the inexhaustible mine of aromatic compounds, is now and then employed as a cheap disinfectant. It contains large quantities of carbolic acid and naphthalene, and numerous aniline, quinoline and pyridine bases, which give it an alkaline reaction and render it more toxic than wood-tar.

Animal-tar

Another species of tar is animal-tar, which is obtained by the dry distillation of bone, horn, hoofs, scraps of hide, etc. As there is an abundance of nitrogen in the original material, the distillate contains, besides phenols and hydrocarbons, numerous nitrogenous bases such as aniline, pyridine and quinoline. It is therefore more poisonous than ordinary tar, and has an alkaline reaction. It was employed formerly for asthma (pyridine action) and as an anthelmintic.

Ichthyol

Ichthyol is an oily tar with a disagreeable odour, and is obtained by distillation of a bituminous shale found in Seefeld, in the Tyrol, containing the fossil remains of fish. It was long held in esteem as a popular remedy for many diseases, and is remarkable from the fact that it contains 10 per cent. of sulphur. By treatment of the crude products of distillation with concentrated sulphuric acid, they are partially converted into a sulphurous acid, ichthyol sulphonic acid, the ammonium salt of which is the *ichthyol* ("fish-oil," ἰχθύς = fish) now used in medicine. The purpose of the preparation is to make the sulphurous tar-constituents soluble in water, which in their original form they are not.

Ichthyol is antiseptic, but weaker than carbolic acid. On unbroken skin it causes only slight irritation, and, it is said, vaso-constriction ; taken internally in large doses it produces gastro-intestinal irritation (diarrhœa), but without being very poisonous. Its action after absorption is not very marked and is little understood.

The value of ichthyol as a drug is much disputed. In many quarters it was enthusiastically recommended for a number of diseases of the most varied nature (renal disease, intestinal complaints, rheumatism, tuberculosis, scarlet fever), but it has now only a limited employment in gynæcological practice as an antiseptic and absorbent in *uterine catarrh* and *inflammation of the tubes*, and in *skin-diseases* such as *acne*, *running and itching eczema*, *intertrigo*, *cutaneous ulceration*, *burns*, etc. In *erysipelas*, ichthyol seems both to allay the pain and to prevent the spread of the infection. Its employment internally has not yielded any convincing results, and it is rendered difficult by the troublesome eructation with disagreeable taste and smell that it causes in most patients. It has been sought to remove this disadvantage by the production of insoluble compounds with albumin (*ichthalbine*) or formaldehyde (*ichthoform*), by which the ichthyol is only set free when it reaches the intestine.

The active constituents in ichthyol are probably sulphurous hydrocarbons. Attempts have been made to produce similar bodies artificially by first treating various originally non-sulphurous products of distillation and oils with sulphur at a high temperature, and then converting them into sulphonic acids. *Thiol* and *tumenol* are two such rivals of ichthyol, the first produced from the " gas-oil " obtained from brown coal-tar, the second from a mineral oil contained, like ichthyol, in bituminous rock. The old, well-known household remedy, Haarlem oil (composed of sulphur, linseed oil and crude oil of turpentine), was a forerunner of ichthyol, and a remedy for all ills, external and internal.

Preparations and Doses

Pix Liquida (B.P.), **Pix Pini** (U.S.P.), tar, is obtained by the distillation of the wood of several species of *Pinus*. It is a dark brown, oily liquid, with acid reaction and empyreumatic odour. *Dose*, 0·12—0·6 grm., 2—10 grs. (B.P.). Is prescribed for internal use as pills, capsules or pastilles ; externally as a 25—50 per cent. ointment, soap or alcoholic solution. When tar is used for inhalation, a little chalk or ash should be added to it, in order to fix the volatile fatty acids, of which the vapour, by its irritation, causes coughing.

Unguentum Picis Pini (U.S.P.), 50 per cent.

Syrupus Picis Pini (U.S.P.), 0·5 per cent. *Dose*, 4 mils, 1 fl. dr.

Oleum Picis Pini (U.S.P.), a volatile oil distilled from tar, containing

the more volatile constituents of tar, phenols and acetic acid. *Dose*, 0·2 mil, 3 mins.; externally, diluted with 20 parts of water, as an antiseptic.

Oleum Cadinum (B.P.), *Pix Juniperi Empyreumaticum*, juniper-tar oil, a dark, reddish brown, oily liquid, obtained by the dry distillation of the wood of *Juniperus oxycedrus*, growing in the countries surrounding the Mediterranean. Is employed externally in the same way as ordinary tar, as are also birch-tar (*Oleum Betulæ Empyreumaticum*) and beech-tar (*Oleum Fagi Empyreumaticum*).

Pix Carbonis Præparata (B.P.), commercial coal-tar, heated to 50° C. to expel the ammonia.

Liquor Picis Carbonis (B.P.), a 20 per cent. solution of the preceding preparation in an alcoholic solution of quillaia. A mild tar preparation.

Ichthammol (B.P.), *Ichthyol*, ammonium-sulpho-ichthyolate, a clear, dark brown, thick liquid, with a disagreeable odour, soluble in water. Externally, either pure or as a 10—30 per cent. solution or ointment for skin-diseases and the massage of parts affected with rheumatism. For diseases of women a 10 per cent. glycerin solution on a tampon. In gonorrhœa, 1 per cent. injections. *Dose*, internally, 5—15 drops a few times a day in wine or fruit juice; official dose, 3—6 decigrms., 5—10 grs.

Ichthalbin, ichthyol-albumin, a greyish brown powder, without taste and odour. *Dose*, 1—2 grms. 3 times a day.

Ichthoform, ichthyol-formaldehyde, a grey, insoluble powder. *Dose*, 1 grm. a few times a day for diarrhœa.

Benzoic and Cinnamic Acids

Benzoic Acid, C_6H_5COOH, has a wide distribution in the vegetable kingdom in various balsams, resins and volatile oils, and also occurs in combination with glycocoll as hippuric acid in the urine of man and herbivorous animals.

Like the other aromatic acids, benzoic acid is far less poisonous than the phenols, but more antiseptic and in large doses antipyretic. Small doses have no appreciable effect on the healthy individual, and even 10—15 grammes, in Schreiber's experiments on himself, produced only heaviness in the head, gastro-intestinal irritation, profuse sweating, constant pricking in the throat, and evacuation of mucus. According to Rost, the continued daily administration of benzoic acid to animals produces peculiar symptoms, namely, epileptiform convulsions at varying intervals of hours or days, the condition in the intervals being apparently quite normal, thus resembling the epilepsy of man. Continued use leads to death from central paralysis. Benzoic acid is not allowed to circulate unchanged in the blood-stream, but in the tissues (especially the kidneys) combines with glycocoll to form hippuric acid. This in turn is converted into alkaline hippurates which are eliminated in the urine. Thus the body is protected from the effects of a potential poison by the process of "protective synthesis" (*cf.* Stokvis's interesting observation that in renal disease benzoic acid is excreted for the most part unchanged). In

consequence of the antiseptic action in the intestine, the amount of ethereal sulphuric acids and of indican in the urine diminishes, while the excretion of uric acid is not changed.

For the *therapeutic employment* of benzoic acid and its salts, several indications were formerly laid down which have now been discarded, *e.g.* uræmia and arthritis urica ; and some 30 years ago sodium benzoate enjoyed a brief reputation as a remedy for tuberculosis of the lungs. It is employed now as an *expectorant*, especially in *bronchitis* with profuse thin secretion in children and old or feeble persons. Benzoic acid seems in such cases efficacious in promoting expectoration, perhaps by causing irritation in the throat which brings on coughing. The tendency, mentioned above, for the benzoates to deplete the alkali reserve is the explanation of their use as urinary acidifiers. Thus they have been used with some success as urinary antiseptics in conjunction with hexamine. It is of interest to note that benzoic acid has a definite though feeble action in rheumatic fever. The effect is increased remarkably by the introduction of a hydroxyl group in the ortho position (see p. 262).

Cinnamic Acid ($C_6H_5.CH.CH.COOH$), the frequent companion of benzoic acid in the vegetable kingdom, attracted attention some years ago in Landerer's tuberculosis cure. This original treatment consisted in intravenous injections of sodium cinnamate, which were to produce an inflammatory reaction round the tuberculous foci, leading to the formation of fibrous tissue, and finally to calcification—thus an imitation of the spontaneous cure. The results, however, were very doubtful, and the treatment is now very seldom practised.

Benzoic and cinnamic acids, partly in free condition, partly in the form of various esters, are the most important constituents of *benzoin* and of the balsams mentioned below, which also contain volatile oils and other aromatic constituents.

Balsam of Peru, with its odour of vanilla, contains 50—60 per cent. of benzoate and cinnamate of benzyl, resin, and about 10 per cent. of free cinnamic acid. It acts very powerfully on *Acarus scabiei*, destroying the eggs in the space of half an hour. Balsam of Peru differs from tar, naphthol, etc., in not being very irritant to the skin, nor very poisonous, but, like all aromatic substances, must be used with a certain amount of caution to avoid irritation of the kidneys. It is also used as a mild irritant and antiseptic for *indolent granulations*, *tuberculous ulceration*, *eczema* and other *skin-diseases* attended by *itching*. After absorption, it reduces the bronchial secretion and increases the amount of urine.

Storax, which consists mainly of a mixture of various esters of

cinnamic acid, and resin, is also a very efficacious antiparasitic (scabies, pediculi pubis).

Preparations and Doses

Acidum Benzoicum (B.P., U.S.P.), colourless or yellowish crystalline needles or plates, with a pleasant odour when prepared from benzoin, odourless when prepared synthetically, and a bitter, acrid taste; slightly soluble in water, freely in alcohol. *Dose*, 3—10 decigrms., 5—15 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). A constituent of paregoric, mentioned under "Opium."

Ammonii Benzoas (U.S.P.), a white powder or crystals, with a bitter taste, readily soluble in water. *Dose*, 3—10 decigrms., 5—15 grs. (B.P.); 1 grm., 15 grs. (U.S.P.).

Sodii Benzoas (B.P., U.S.P.), white crystals or an amorphous powder with a sweet taste, easily soluble in water. *Dose*, 3—20 decigrms., 5—30 grs. (B.P.); 1 grm., 15 grs. (U.S.P.).

Benzoinum (B.P., U.S.P.), a resin obtained from the incised stem of *Styrax Benzoin* (*Styraceæ*), a tree growing in Siam and Sumatra. White grains of almost pure benzoic acid, imbedded in a greyish brown or greyish red substance. The best Siam benzoin often consists almost exclusively of these grains. Used as a preservative of fat (benzoated lard), preventing it for a long time from becoming rancid.

Tinctura Benzoini (U.S.P.). *Dose*, 1 mil, 15 mins. Externally, for painting excoriations, indolent granulations, sore nipples, etc.

Tinctura Benzoini Composita (B.P., U.S.P.), Friar's balsam, Turlington's balsam, also contains storax, balsam of Tolu, and aloes. *Dose*, 2—4 mils, ½—1 fl. dr. (B.P.); 2 mils, 30 mins. (U.S.P.); internally, as an expectorant, externally, on wounds, mixed with equal parts of water and glycerin as a lotion for chapped hands.

Balsamum Peruvianum (B.P., U.S.P.), balsam of Peru, a dark brown, viscid balsam with an odour of vanilla, obtained from *Myroxylon Pereiræ* (B.P.), or *Toluifera Pereiræ* (U.S.P.), order *Leguminosæ*, growing in San Salvador. *Dose*, 3—10 decimils, 5—15 mins. (B.P.); externally, on indolent sores, tuberculous sores, fistulas, etc., undiluted; for scabies, 2—3 grms. rubbed in 4—6 times in the course of a day, after a bath, 12—15 grms. in all; after 2 days a cleansing bath.

Balsamum Tolutanum (B.P., U.S.P.), balsam of Tolu, a reddish brown, semi-solid mass with an agreeable odour, obtained by incision of the stem of *Myroxylon Toluiferum* (*Toluifera Balsamum*, U.S.P.), belonging to the order *Leguminosæ*, and a native of Columbia. *Dose*, 3—10 decigrms., 5—15 grs.

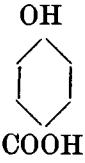
Syrupus Tolutanus (B.P.), *Syrupus Balsami Tolutani* (U.S.P.). *Dose*, 2—8 mils, ½—2 fl. dr. (B.P.); 15 mils, 4 fl. drs. (U.S.P.). The British preparation is the more concentrated.

Tinctura Tolutana (B.P.), 10 per cent., *Tinctura Balsami Tolutani* (U.S.P.), 20 per cent. *Dose*, 2—4 mils, ½—1 fl. dr. (B.P.); 2 mils, 30 mins. (U.S.P.).

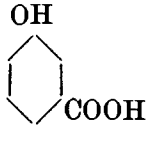
Styrax (B.P., U.S.P.), a viscid balsam obtained from *Liquidambar orientale* (*Hamamelidaceæ*), Asia Minor. Is used externally, like balsam of Peru, as a cure for scabies, mixed with sufficient olive oil to make it thin enough for inunction, *e.g.* storax 20 grms., olive oil 10 grms., rubbed in in 2 portions. *Dose*, 0·6—2 grms., 10—30 grs. (B.P.); 1 grm., 15 grs. (U.S.P.).

Salicylic Acid

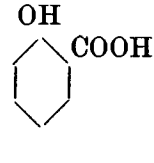
Hydroxybenzoic acids are benzol in which one atom of hydrogen is replaced by hydroxyl, and another by carboxyl. There are 3 such acids answering to the 3 different relative positions that these may occupy :—



Para-hydroxybenzoic acid.



Meta-hydroxybenzoic acid.



Ortho-hydroxy-benzoic acid (Salicylic acid).

Two of these, the para and meta compounds, are substances with little activity, while the third, ortho-hydroxybenzoic acid, in which OH and COOH are neighbours, is very active, and one of the most indispensable of the newer drugs. It was first obtained from the bark of species of *Salix*, whence its name of *salicylic* acid. The great difference between the three hydroxybenzoic acids makes itself apparent in many ways. The para and meta acids are only feebly antiseptic, and have little toxicity (Stockman). The para acid also lacks the action of salicylic acid upon the excretion of uric acid (Denis).

Action. Free salicylic acid is a powerful **antiseptic**. Like many other aromatic compounds and like quinine, it arrests the movements of protozoa, living vegetable protoplasm and the white blood-corpuscles ; it prevents alcoholic fermentation of sugar, the acetic acid fermentation of beer, and the souring of milk ; in short, it checks the development of all kinds of micro-organisms. Its antiseptic power is about equal to that of carbolic acid, but the latter, owing to its volatility, is better able to make its way into tissue cells ; salicylic acid, on the other hand, preserves substances exposed to the air for a longer time than the more quickly evaporating carbolic acid. The activity of salicylic acid is weakened when alkali phosphates and carbonates are present (*e.g.* in meat, fish, and other articles of food), as they fix the acid ; for the alkali salts, like sodium salicylate, although not, as formerly supposed, inert, are far less antiseptic than the free acid.

Applied to unbroken **skin,** salicylic acid slowly and painlessly removes epithelium ; applied as a solid or in strong solutions to mucous membranes, it gives a whitish colour to the epithelium, with superficial corrosion, while dilute solutions, like the salicylates taken by the mouth, show no other local action than a

slight irritation of the gastric mucous membrane (unpleasant sensations in the epigastrium, nausea, and sometimes, though rarely, vomiting).

Salicylic acid and sodium salicylate behave exactly alike after **absorption,** as the free acid is converted into the sodium salt. They are not highly poisonous : doses of 2 grammes of sodium salicylate produce no perceptible effect on the healthy person ; 4—5 grammes occasion heat and heaviness in the head, a hot skin, sweating, very slight, if any, fall of temperature, often indistinct vision, and the very constant symptom of noises in the ears and deafness. These secondary effects closely resemble those of quinine, especially when skin-eruptions (erythema, urticaria, pemphigus) are present, but eruptions are less frequent with salicylic acid than with quinine. The anomalies of hearing are associated with congestion of the ear, the rashes with the dilatation of the cutaneous vessels. It is only on the administration of far larger quantities that action on the **central nervous system** produces severe poisoning, with delirium followed by sleepiness, great fall of temperature, laboured slow respiration, cardiac weakness and finally asphyxial convulsions and death from respiratory paralysis. In enfeebled patients even 4 or 5 grammes may produce collapse symptoms of serious appearance. The lethal dose seems to be very large, perhaps about 20—25 grammes ; but in many cases of reputed death from salicylic poisoning the real cause of death is doubtful.

In fever patients salicylic acid and sodium salicylate lower the **temperature** quickly and considerably, the fall often beginning after 30—40 minutes, and amounting to 3° or more. In all probability the action, like that of antipyrine, is due to loss of heat through the dilated cutaneous vessels. The thermolytic fulness of blood in the skin also occurs in healthy persons, but is there presumably counterbalanced by increased thermogenesis, which prevents cooling of the body (*cf.* what has been said under " Antipyrine " about the regulation of heat in febrile and normal conditions).

In both animals and man the effect of salicylic acid, even in the ordinary small doses, upon **metabolism** is an increase of 10 to 12 per cent. in the amount of nitrogen in the urine and also in the amount of sulphur. The quantity of uric acid is even more increased (30—45 or even 100 per cent.) ; but it is not at present known whether this is endogenous or whether it is due to increased permeability of the kidneys for uric acid.

The **peripheral nerves and muscles** do not seem to be affected by salicylic acid. The frequent pulse which small doses produce in animals may possibly be due to direct influence upon the heart.

Both salicylic acid and its salts have a *slight diuretic* action, probably by stimulation of the renal epithelium. After large doses a severe, but generally brief, attack of acute nephritis, in which the urine contains blood and albumin, is occasionally seen.

The so-called cholagogues are a group of drugs the action of which is not clearly defined. A number of drugs, particularly alkaline salts and various laxatives, such as rhubarb, aloes and calomel, have long been credited with promoting the **secretion of bile.** More recent and comprehensive investigations (400—500 animal experiments, Stadelmann, 1896) show, however, that none of the old cholagogues, in animals at any rate (dogs with biliary fistula), have any such influence. The only drugs that undoubtedly increase the secretion of bile are the bile salts, of which the action is powerful, and several aromatic substances, *e.g.* sodium benzoate, thymol, menthol and sodium salicylate in medium doses, and perhaps also a few soaps. In man Pfaff found from a case of biliary fistula that sodium salicylate increased the amount, and still more the solids, of the bile.

Abortion has repeatedly been observed during treatment with salicylic acid, but it is not certain whether this was due to the drug or to the disease for which the drug was given. It is well known that febrile diseases are among the causes of abortion and miscarriage. Salicylic acid is also considered liable to increase the tendency to hæmorrhage in disease (typhoid fever).

Absorption and Excretion. Salicylic acid, both in solution and as ointment, is very rapidly absorbed through the unbroken skin and through mucous membranes. The excretion, which takes place through the kidneys, soon begins ; an hour after administration by the mouth the urine is coloured a deep violet by ferric chloride. Excretion is concluded in about 72 hours. In healthy subjects Hanzlik found about 75 per cent. of the amount given in the urine. The fate of the remainder is not known ; in dogs a certain amount is oxidised, probably to dihydroxybenzoic acid (Angelico). After very large doses, small quantities are also excreted in the saliva, the sweat and other secretions.

Therapeutic Uses. Salicylic acid is the sovereign remedy for *rheumatic fever.* The action in the typical fever is so certain that obstinate cases inspire doubt as to the correctness of the diagnosis. If the treatment is begun early, the rule is that the inflammation in the joints is lessened, the pain diminished, and the temperature lowered after 1 or 2 days, or even after a few hours, and that the disease assumes a milder character and is of shorter duration than with any other treatment. The action as a whole seems to indicate that salicylic acid is a specific poison to the still unknown

micro-organisms that are undoubtedly the cause of the disease. The action is the same whether sodium salicylate be employed or salicylic acid, which is converted into the sodium salt in the blood ; and the former is generally chosen as being less irritant to the stomach. As free salicylic acid is a powerful antiseptic, while the sodium salt, although not quite inert, is, at any rate, a much weaker protoplasm poison, the action upon a disease such as rheumatic fever would be best understood if one were to imagine the salicylic acid as once more liberated in the body. It has been assumed that the increased carbonic acid tension in the blood and in the inflamed tissues would effect this. The investigations of Hanzlik and his co-workers, however, give no support to such a theory. In the synovial fluid of individuals suffering from rheumatic fever and receiving full therapeutic doses of the sodium salt, they found, on an average, 0·018 per cent. of the salicylate, but could not demonstrate free acid. The exact nature of the action is thus not yet experimentally explained. The salicylic treatment has no influence on the frequency of the heart complications.

Remarks on the Dosing. Rheumatic fever is a disease that in many cases is not entirely cured. It often happens that, sooner or later after apparent recovery, relapses occur in the form of febrile or afebrile attacks of pain, swelling, etc., in one or several joints. These may recur during months or years, and leave the impression that the body is not freed from the virus. In other diseases with analogous conditions, *e.g.* syphilis and malaria, endeavours are made to exterminate the disease-bearing parasite by the most intense treatment possible. On the same principle, in rheumatic fever, the largest possible doses of salicylates should be given ; it is well to begin with 8—10 grammes of sodium salicylate a day, either in 2 or 3 large doses or preferably, according to the more general opinion, smaller doses every 1 or 2 hours, the doses diminishing later on as the symptoms disappear. As a rule the large doses are tolerated for only a few days, and may cause inconvenience ; but one advantage is that salicylic acid poisoning, though unpleasant enough, is seldom—provided the kidneys are sound—of a serious character. Again, still bearing in mind the analogy with syphilis, it would not be rational to consider the patient off one's hands as soon as the acute disease appears to be cured, but a " chronic intermittent treatment " should be continued in the form of a few days' salicylic cure at intervals of some weeks for, say, a year. This would probably reduce the number of patients who now suffer chronically from the consequences of a past attack of rheumatic fever. It should be added, however, that the presence

of renal disease necessitates caution, partly because salicylic acid is not altogether without action on the renal epithelium, partly because it is probably not excreted as quickly as it would be under normal conditions. On the other hand, the hæmorrhagic *nephritis* which may occur in undoubted rheumatic fever, which may be associated with relatively slight arthritic symptoms, seems to be benefited by salicylic acid. *Angina tonsillaris*, attended with suspicious tenderness and pains in joints, should be immediately treated with salicylic acid.

The typical rheumatic fever is thus the true field for the salicylic acid treatment. *Atypical subacute rheumatism*, which begins mildly, is attended with less fever and runs a slow course, is somewhat benefited by the treatment, as is also *chronic rheumatism* without fever or with only slight, irregular rises of temperature ; but neither of these conditions benefits from salicylate treatment to nearly the same extent as rheumatic fever. The reports regarding its value in *gonorrhœal rheumatism* and *epididymitis* are contradictory, but the pain is at any rate sometimes relieved. In acute attacks of *gout*, sodium salicylate is one of the best remedies, but it is doubtful whether it does more than lessen the pain.

Intravenous injections of sodium salicylate are recommended as a treatment that may give instantaneous relief in, and often cure, rheumatic affections that do not react to the ordinary treatment, *e.g.* the *recurrent rheumatic fever* which may go on for months, appearing now in one joint, now in another ; *monarticular rheumatism ; lumbago*, and *afebrile rheumatic affections* generally. In rheumatic fever the swelling and pain disappear immediately after such injections, but very soon return.

Salicylic acid was much used as an *antipyretic* from 1876 until the discovery of antipyrine and allied drugs, when it was replaced by those remedies, which have fewer unpleasant secondary effects. Antipyrine, acetanilide, and phenacetine also, as a rule, act with greater certainty in *neuralgia* and *cephalalgia*.

Sodium salicylate is believed to promote the absorption of fluid in *serous pleurisy*. It is one of the remedies employed for *gall-stones* and *biliary colic*. It is not probable that the increased secretion of bile that it produces can expel firmly-fixed concretions, but it is possible that it may have a favourable action on the microbial catarrh of the mucous membrane, which is supposed to be the most frequent cause of gall-stones.

Externally, salicylic acid (but not sodium salicylate) is employed in the manufacture of antiseptic dressings (salicylic wool) ; dissolved in alcohol, or as an ointment, it is useful in *itching skin-diseases* such as urticaria ; as a dusting powder it may be used to prevent sweating, and as a plaster to soften and remove epithelium

(corn-plaster). As a *preservative for articles of food* salicylic acid is objectionable, and is forbidden by law in many countries.

Other Salicylic Compounds

The frequent secondary effects of sodium salicylate—noises in the ears, profuse sweating, etc.—and its nauseous taste, which often makes its employment difficult, have prompted many attempts to produce salicylic compounds that are without these disadvantages; but only a few of them have attained any practical importance.

Phenyl salicylate, or **Salol,** is an ester of salicylic acid (60 per cent.) and phenol (40 per cent.); it was produced by Nencki in 1886 and is the first representative of a principle subsequently much employed in the synthesis of drugs (see, for instance, creosote carbonate). This consists in depriving substances which in a free state act deleteriously upon the gastric mucous membrane of their immediate action by administering them in the form of compounds that are insoluble and therefore inactive in acid liquids, but are decomposed by alkalies and liberated in the intestine. Salol passes unchanged through the stomach, but is split up by the alkaline juices and the intestinal bacteria in the small intestine into salicylic and carbolic acids, which are absorbed separately and excreted through the kidneys. In *rheumatic fever* salol acts rather less strongly than sodium salicylate, and must be given in smaller doses, as one of its constituents is the poisonous phenol. The symptoms that have been observed after large doses are a combination of those of carbolic acid and salicylic acid poisoning. The reason why poisoning is not caused even by the ordinary doses of 1 or 2 grammes, in which the amount of phenol far exceeds that given of free phenol, is that the decomposition in the intestine takes place gradually, so that the phenol does not reach the blood all at once, but little by little, and is there rendered innocuous by union with sulphuric acid. Salol is further employed as an *intestinal disinfectant*, but as such is not very efficient, for both its constituents are quickly absorbed as soon as the connection between them is dissolved. On the other hand, it is a good *disinfectant for the urinary passages*, especially in *chronic cystitis*, in which it appears to make turbid urine smelling of ammonia clearer and diminishes the bacteria. After prolonged use of salol, the formation of intestinal concretions, "salol stones," has been observed, the evacuation of which may occasion severe attacks of colic. *Externally*, salol is used as an antiseptic, being decomposed by the bacteria in wounds. It

is used in pharmacy to coat pills which are not to be dissolved in the stomach.

Another compound that has acquired importance is **acetylsalicylic acid** (aspirin), which is probably absorbed principally in the intestine, where it is split up into salicylic and acetic acids. Some is absorbed as sodium acetyl salicylate. Acetylsalicylic acid differs clinically from the parent substance in its greater antipyretic and analgesic properties and the rarer occurrence of unpleasant secondary effects. It has therefore justly acquired an extensive employment in *febrile diseases, neuralgia, cephalalgia* and *pain of various kinds.* In rheumatic fever the treatment with large doses of sodium salicylate is the best.

Both in rheumatic fever and in other rheumatic affections, the local treatment with a salicylic acid ointment is often recommended as relieving the pain more quickly than by the internal treatment alone. A still more rapid action is attained with the volatile *methyl salicylate*, or with *oil of Gaultheria* (oil of wintergreen), a volatile oil extracted from the North American ericaceous plant, *Gaultheria procumbens*, the principal constituent of this oil being the above-mentioned ester. The value of methyl salicylate applied to a painful joint depends almost entirely upon counter-irritation. It is true that the drug is rapidly absorbed through the skin, but the amounts are too small to exert any systemic effect. The penetrating odour is a disadvantage when methyl salicylate is applied externally.

Salicylic acid is in reality an ancient medical remedy. The now discarded drug, *Salicis cortex*, the bark of various kinds of willow, was known in the early ages, and was once a rival of cinchona bark. It contains the glucoside salicin, which, on decomposing, gives off saligenin (salicylic alcohol), this, by oxidation, being converted into salicylic acid. When the anti-rheumatic properties of the acid were discovered, both salicin and saligenin were tried, but it appeared that they were to some extent excreted unchanged, and were generally of weak action. Small quantities of methyl salicylate are found in the wild pansy, *Viola tricolor*, growing in all parts of Europe, and formerly used as a " blood-purifier " ; salicylic acid occurs in the common meadow-sweet, *Spiræa ulmaria*, which grows beside streams and damp ditches.

Preparations and Doses

Salicinum (B.P.), salicin, consists of colourless, silky, crystalline needles with a very bitter taste, soluble in 28 parts of water. *Dose*, 0·3—1 grm., 5—15 grs.

Acidum Salicylicum (B.P., U.S.P.), salicylic acid, $C_6H_4.OH.COOH$, colourless needle-like crystals with a sweetish, afterwards acid, acrid taste, almost insoluble in water, very soluble in alcohol. Is now seldom employed internally. *Dose*, 3—6 decigrms., 5—10 grs. (B.P.) ; externally as a 10 per cent. ointment ; for epithelial corns, a 20 per cent. salicyl collodion

or plaster; to check sweating of the feet, a powder mixed with talc (1 in 30) to be shaken into the stocking.

Unguentum Acidi Salicylici (B.P.), 2 per cent.

Sodii Salicylas (B.P., U.S.P.), sodium salicylate, $C_6H_4.OH.COONa$, colourless scales or tabular crystals with a disagreeable, sweetish-salt taste, very soluble in water. Even very dilute solutions give a violet colour with ferric chloride. *Dose*, 6—20 decigrms., 10—30 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). In rheumatic fever, 8—10 grms. daily for the first few days in solution or capsules, either divided into doses of 1 grm. every hour, or in 2 doses of 4 or 5 grms., the doses afterwards diminishing. The first way of administration is generally employed; if the second is preferred, a dose of 1 grm. should be given beforehand to test the tolerance. If there are cardialgic pains, bicarbonate of soda should be given at the same time to prevent the appearance of the gastric-irritant free salicylic acid in the acid gastric juice. If an unconquerable aversion forbids internal use, the drug is given as an enema, or another preparation is employed, *e.g.* acetylsalicylic acid. As an antipyretic, 3—8 grms. in 2 doses. Daily dose for children, from 2 to 4 years, 0·5—1 grm.; from 5 to 10 years, 1—2 grms.; from 11 to 15 years, 2·5—3 grms. Intravenously, sodium salicylate, 8·75, caffeine 1·25, aq. ad 50, 2 mils 1—3 times a day.

Ammonii Salicylas (U.S.P.) possesses no advantages over the sodium salt. *Dose*, 1 grm., 15 grs.

Salol (B.P.C.), *Phenylis Salicylas* (U.S.P.), phenyl salicylate, $C_6H_4.OH.COOC_6H_5$, a white crystalline powder with slightly aromatic taste, almost insoluble in water, readily soluble in alcohol or ether. *Dose*, 0·3 grm., 5 grs. (U.S.P.); for rheumatic fever, 0·5—2 grms. per dose, 4—6 grms. a day; for pyelitis or cystitis, 1 grm. 3 or 4 times a day; for diarrhœa in children, doses of 0·1 grm. for children of 1 year; externally as a 5 per cent. ointment, or dissolved in oil.

Acidum Acetylsalicylicum (B.P., U.S.P.), acetylsalicylic acid, aspirin, $C_6H_4.OCH_3CO.COOH$, colourless crystals with slightly acid taste, almost insoluble in water, readily soluble in alcohol or ether. *Dose*, 3—10 decigrms., 5—15 grs. (B.P.); 0·3 grm., 5 grs. (U.S.P.).

Methyl Salicylas (B.P.), *Methylis Salicylas* (U.S.P.), methyl salicylate, the methyl ester of salicylic acid, $C_6H_4.OH.COOCH_3$, colourless or yellowish oily liquid, with a characteristic aromatic odour. *Dose*, 3—10 decimils, 5—15 mins. (B.P.); 0·75 mil, 12 mins. (U.S.P.); externally, for inunction, pure or diluted with 1—2 parts of olive oil.

Calcium Aspirin, calcium acetylsalicylic acid, has been advocated in recent years, especially for the treatment of chorea. Its superiority over ordinary aspirin has not yet been established, but its solubility is sometimes an advantage. *Dose*, about 10 grs.

Extractum Fellis Bovini (B.P., U.S.P.), extract of Ox Bile. Contains the bile salts and pigments free from mucus. A dark yellowish-green plastic substance. Bitter, disagreeable taste. Soluble in water. *Dose*, 0·3—1 grm., 5—15 grs. (B.P.); 0·4 grm., 6 grs. (U.S.P.). For use as a cholagogue, see p. 264.

Other Aromatic Acids

Cinchophenum, phenyl-quinoline-carboxylic acid, ($C_6H_5.C_9H_5N.COOH$), introduced into medicine under the name of

atophan, is a new drug with peculiar action. It causes, even with a purine-free diet, an immense increase in the amount of uric acid excreted. Whether this is due to an increased production (metabolic action), or only to an increased excretion (renal action), is a much-disputed question. The latter view is favoured because the amount of uric acid in the blood is diminished and the excretion of phosphoric acid does not at the same time increase as might be expected if an increased break-down of the nucloproteins, the source of the endogenous uric acid, were the cause. The action begins very quickly, but is of short duration. When the drug is stopped, the amount of uric acid diminishes in the course of 6—8 hours to below the normal, and then gradually increases to the normal quantity.

The chief employment of atophan is in the treatment of *acute attacks of gout*. If given as soon as the pain begins, the attack is often arrested in the course of a few hours. This cannot, however, be ascribed solely to the excretion of uric acid, for several allied compounds have a similar, though not quite so good, effect in acute attacks of rheumatism, although they do not increase the excretion of uric acid. The chief reason probably is that atophan, like other quinoline derivatives, is analgesic and antipyretic, and inhibits inflammation (oil of mustard dropped into the eye of a rabbit previously treated with atophan does not produce the usual inflammation). Atophan is accordingly a good remedy in *rheumatic fever*, *gonorrhœal affections of the joints*, and *neuralgia*. One secondary effect that must be remembered is the precipitation of uric acid and urates in the urine, caused by the great excretion ; the urine may be thick even when evacuated, or may throw down an abundant sediment only when cooled. Atophan is therefore contra-indicated in patients with a tendency to the formation of calculi in the urinary passages ; and it is always advisable, during its employment, to provide, by the drinking of water, for an abundant flow of urine, and to give half a teaspoonful of bicarbonate of soda several times a day. The latter remedy also prevents the otherwise often-occurring cardialgia.

Preparations and Doses

Cinchophenum (B.P.), phenyl-quinoline-carboxylic acid, atophan, quinophan, colourless crystals or a white powder with a bitter taste, insoluble in water. *Dose*, 0·3—1 grm., 5—15 grs. ; for gout 1 grm. 3 or 4 times a day until 10 grms. have been taken ; if necessary, the treatment may be repeated after an interval of a few days. For rheumatism 2—4 grms. daily, and when improvement begins, reduced doses for a few days.

Neocinchophenum (U.S.P.), novatophan, an ethyl-methyl ester of atophan ; a yellowish, insoluble powder, given in doses similar to those

of atophan. Its action on the uric acid excretion is somewhat weaker, but it is advisable to use at the same time bicarbonate of soda or an alkaline mineral water. *Dose*, 0·5 grm., 8 grs.

Quinic Acid, hexahydro-tetraoxybenzoic acid, which is converted in the body into benzoic acid and excreted as hippurates, has been tried in various combinations (urosin, sidonal, chinotropin) for gout. Average *dose*, about 5 grms. daily. Opinions differ regarding their usefulness.

36. FORMALDEHYDE

Formaldehyde (formic aldehyde) is a colourless gas, very irritating to the eyes and nose. When dissolved in water (*formaline*), it serves as a disinfectant.

Like all aldehydes, formaldehyde reacts very readily, combining with, or changing, a great many organic substances. It causes coagulation of blood and of albumin, and "tans" the skin, making it dry and brittle like old leather. A rabbit's ear, painted repeatedly with formaline, becomes completely mummified and can at last be broken off. A compound of this nature also affects, of course, the substances of which the bacterial bodies consist, and is therefore a very efficient disinfectant. Formaldehyde kills anthrax bacilli in a dilution of 1 in 20,000 and anthrax spores (which resist 5 per cent. carbolic acid for five days) in a dilution of 1 in 1,000 in the course of one hour. Even when dry, that is to say, in their most resistant condition, the spores are killed by exposure for a few hours to formaldehyde vapour. For higher animals formaldehyde has comparatively little toxicity. The lethal dose for a rabbit is about 0·25 gramme. In the few fatal cases of poisoning in man hitherto described, considerable quantities of the commercial 35—40 per cent. solution have been drunk. In these the usual symptoms of corrosion of the gastric mucous membrane appear—great pain, vomiting and diarrhœa (the evacuations being mingled with blood), loss of consciousness, weak irregular pulse, shallow respiration, anuria, and death during coma.

Concerning the fate of formaldehyde in the body it is known that to some extent it is oxidised and found in the urine as formic acid. After the internal employment of formaldehyde preparations the urine takes some time to become putrid, and it may be assumed therefore that some is excreted unchanged.

Uses. Much diluted, formaldehyde is recommended for *purulent eye affections* and *lesions of the cornea ;* in stronger concentration for lavage in *vaginal catarrh* and *endometritis*, and for injections in *local tuberculosis* and *abscesses*. By washing with strong solutions the skin is slightly tanned, and troublesome *secretions of sweat* may be reduced. It cannot be used in phthisis,

however, as the pungent odour brings on coughing. Its irritating properties forbid its use as an ordinary antiseptic for sores, but it is an admirable *disinfectant for inanimate objects.* Formaldehyde has the advantage of being able to spread everywhere like gas, and to penetrate clothing, etc. It may be used in many cases in which chlorine cannot be used (because it destroys colours), and is also serviceable in the disinfection of things that would be injured by dry or moist heat, *e.g.* books and furs. It is not very reliable for thick or bulky objects such as bed-clothes. Rooms are disinfected by being sprayed with a formaldehyde solution (8 c.c. per c.m.), after which the room should remain closed for at least 12 hours. Bacteria-cultures placed in such an atmosphere are found to be dead. Books, clothing, brushes, etc., are allowed to lie for 24 hours in a tightly-closed receptacle with towels dipped in formaline. Like other aldehydes, formaldehyde is very prone to polymerisation, and forms paraformaldehyde, a solid white substance that on being heated again gives off formaldehyde, and is used in a special apparatus for the disinfecting of rooms. A very practical form of its employment is represented by mixtures of formaldehyde and metallic peroxides or permanganate. Upon the addition of water a very great development of heat occurs, which causes the escape of a dense vapour of water and formaldehyde. For a room with cubic contents of 80 metres, about 1 lb. of potassium permanganate is mixed with 1 quart of 40 per cent. formaldehyde in a 2-gallon pail, which is placed in a large tin of cold water.

Formaldehyde has become an indispensable preservative in scientific collections and zoological and anatomical laboratories, as its hardening properties preserve the form of the preparations, and most of their colour. Bacteria-cultures can be fixed by formaldehyde and preserved in unchanged condition for demonstration.

In cases of *formaldehyde poisoning*, the stomach should be washed out and treated with very dilute ammonia or ammonium salts, as these form the non-poisonous hexamethylene-tetramine.

As a preservative for articles of food, formaldehyde must be condemned, as it causes changes in the protein.

Many preparations are known which produce formaldehyde, the most important being *Hexamethylene-tetramine* or *urotropine.* The urine passed after the use of this substance keeps sterile a little longer than ordinary urine, and has the power of dissolving urate calculi. Both these properties are supposed to be due to the liberation in the urine of formaldehyde, which counteracts putrefaction and forms with uric acid di-formaldehyde-uric acid, which is soluble in 300—400 parts of water, while sodium urate is

only dissolved in 1,130 parts, and free uric acid in 38,000 parts of water. Upon these grounds hexamethylene-tetramine is recommended for cystitis and bacteriuria, and as a remedy for gout and for lithiasis ; it is certainly useful to disinfect the urine, but its value in gout is doubtful. Urine containing urotropine yields a sediment with Esbach's reagent (picric acid), resembling the sediment of albumin, and may give rise to diagnostic errors.

After internal use urotropine may be demonstrated almost all over the body, *e.g.* in the cerebro-spinal fluid, in bronchial secretion, in pleuritic effusion, in the eye, etc. It has therefore been tried for a great many diseases, and among others has been recommended for *meningitis* and *poliomyelitis*. On the other hand, it has been urged that urotropine itself is indifferent to bacteria, and is only antiseptic in that it gives off formaldehyde. Urotropine, therefore, can only act where there is an acid reaction, as in the gastric juice and in the urine. In all other liquids and organs, where the reaction is alkaline, no effect on inflammation or infection can be expected, and not on cystitis unless the urine has an acid reaction.

The employment of alkalies simultaneously with urotropine is of course irrational.

Acriflavine is a very effective antiseptic, being 800 times more powerful than phenol and about 20 times more so than corrosive sublimate. It acts slowly, but its antiseptic value is actually enhanced by the presence of serum, and in therapeutic concentrations it does not damage the tissues. Repeated application to wounds, however, tends to delay healing. It is mainly employed as an external antiseptic and for the irrigation of mucous membranes. When administered intravenously it is excreted in the urine and has therefore been used for infections of the urinary tract. Acriflavine inhibits the growth of *B. coli* in alkaline but not in acid urine (see also Preparations and Doses). In meningitis, pneumonia and puerperal fever acriflavine appears to be without effect. Acriflavine stains the tissues bright yellow. To remove stains from the skin the part should be washed with soap and water and then swabbed with 3 per cent. hydrochloric acid in 95 per cent. alcohol.

Among the most effective urinary antiseptics is β-hydroxybutyric acid, which is excreted by the kidney in the state of acidosis. Infections of the urinary tract have therefore been treated by inducing ketosis on a suitable diet in which the weight of fat is four times that of the protein and carbohydrate. It is difficult, however, to tolerate such a diet (*ketogenic diet*) for more than a week, and substances analogous to β-oxybutyric acid were therefore tried by oral administration. Thus **Mandelic Acid** in the form

of ammonium mandelate was found to be a valuable remedy in urinary infections, especially those due to *B. coli*. About 20 grains of this salt flavoured with liquid extract of liquorice and aromatics is given four times daily. Treatment is most successful when the urine is kept strongly acid, and for this purpose 15 grains of calcium or ammonium chloride may conveniently be added to the mixture.

Preparations and Doses

Liquor Formaldehydi (B.P., U.S.P.), formaline, an aqueous solution containing 37 per cent. of formaldehyde, H.CHO. A clear liquid with a pungent odour and a caustic taste. *Dose*, in the eye, 2 drops in 100 c.c. water; on mucous membranes, ½—1 per cent. solution; as an external wash, a 10 per cent. solution; for injection in local tuberculosis, 1—5 in 100 of glycerin. The disagreeable odour after disinfection may be easily removed by the aid of ammonia.

Hexamina (B.P.), **Methenamina** (U.S.P.), hexamethylene-tetramine, urotropine, $(CH_2)_6N_4$, a condensation product of ammonia and formaldehyde. Colourless crystals, very soluble in water, inodorous, taste at first sweetish, afterwards bitter. *Dose*, 6—20 decigrms., 10—30 grs. (B.P.); 0·3 grm., 5 grs. (U.S.P.), up to 6 grms. a day. Infants at the breast are said to tolerate doses of 0·75—1 grm. a day for a long time, but it is advisable to begin with smaller doses.

Caprokol is a proprietary preparation of hexyl-resorcinol, $C_6H_3(OH)_2(CH_2)_5CH_3$. It has the advantage of acting in both acid and alkaline urine, is non-toxic and non-irritating. Caprokol is of value in urinary infections due to staphylococci and, to a lesser extent, in *B. coli* infections. *Dose*, 0·12—0·6 grm., 2—10 grs. A 25 per cent. solution is made in olive oil and the preparation administered in gelatine capsules.

Brilliant Green (not official). Tetra-ethyl-diamino-triphenyl-carbinol. Solutions, about 0·1 per cent. strength in normal saline, are used as an external antiseptic. Damaged tissue stains more deeply than normal.

Acriflavina (B.P., U.S.P.), a mixture of 2:8 diamino-10-methyl-acridinium chloride and 2:8 diaminoacridine. *Acriflavinæ Hydrochloridum* (U.S.P.), the hydrochlorides of these. Both are brownish-red powders freely soluble in water, but only the latter is soluble in alcohol. As an antiseptic lotion for wounds 0·1 per cent. solution in water or normal saline. The same strength can be used for irrigation of the urethra in gonorrhœa. Weekly intravenous injections of 0·3 per cent. solution in normal saline have been used with favourable results in the treatment of gonorrhœa. *Dose*, 0·03—0·1 grm., ½—1½ grs. (B.P.).

II.—ORGANIC SUBSTANCES ACTING LOCALLY

I. MUCILAGINOUS DRUGS

THE mucilages, or demulcents, are amorphous, colloid substances which have the property of forming, with water, thick solutions or rather pseudo-solutions, as they do not really dissolve but take up the water and thus form viscid fluids, which, when cold, are often gelatinous. The action of these drugs, which have been employed from the earliest ages, but up to the present have received but scant attention, has recently been elucidated by Schmiedeberg and Tappeiner.

Owing to the inert nature and the thick viscid consistency of the solutions, demulcents act upon mucosa and raw surfaces as a poultice; they protect from mechanical irritation, and to a certain extent surround and envelop all kinds of irritating substances, and thus prevent them from coming into contact with the tissue. These drugs therefore tend to diminish local reflexes.

Demulcents weaken most *impressions of taste*, and having a wide natural distribution, are of importance to the flavour of many beverages and articles of food. A solution of sugar, for instance, in water is sweeter than a solution of similar concentration in mucilage. The impression of acidity is still more weakened. Raspberries contain relatively less sugar and more acid than red currants, but taste sweeter because they are rich in mucilage, which conceals the taste of the acids, while red currents contain little mucilage. *Impressions of temperature* are likewise moderated, especially the feeling of cold, cold water tasting far cooler than milk of the same temperature. It is the same with the *feeling of pain*. If one of the hind feet of a decapitated frog is placed in $\frac{1}{10}$ per cent. hydrochloric acid, the animal draws up its leg after a few seconds; if a small percentage of gum is added the foot is sometimes not raised until $\frac{1}{2}$ to $1\frac{1}{2}$ minutes have passed, sometimes not at all. The great pain that a 5—6 per cent. saline solution produces in an open wound is only slightly felt if the solution is prepared with a mucilaginous liquid instead of water alone. The *inflammatory reaction* to irritating substances is diminished as well as the pain. If a ligatured living convolution of the intestine is filled with water to which a few drops of oil of mustard have been added, the mucous membrane in the course of

an hour becomes inflamed, swollen and injected, and the intestine filled with a highly albuminous inflammatory exudation ; but when 10 per cent. of mucilage has previously been added, the effect is limited to slight redness of the mucous membrane. Most colloid bodies are not only taken up very slowly themselves, but they also hinder the *absorption* of both water and solid substances, such as salt and sugar, whence the familiar experience that beverages containing an abundance of colloids, *e.g.* the dark, strong beers, " lie heavy on the stomach."

Therapeutic Uses. Demulcents are employed as *flavouring agents*, especially for acid and acrid substances ; to *envelop* local irritants of too great strength ; and in *cases of poisoning* with caustic substances such as alkalies and acids. In pharmacy mucilaginous liquids are employed for suspending in water insoluble substances finely diffused (emulsions). In *catarrhal conditions of the alimentary canal*, mucilages act as a softening, protecting covering that guards the mucous membrane both against the mechanical irritation caused by the continual movement of the contents of the intestine and against the chemical irritation of digestive fluids and ferments. They are thus analgesic and weaken reflex peristalsis, and may thus effect a cure (*e.g.* salep in diarrhœa). An inflamed mucous membrane also defends itself spontaneously by increased secretion of mucus, and thus the employment of mucilage is an imitation of the natural healing-process. That *catarrh of the larynx* is relieved by mucilaginous solutions is accounted for by the fact that in being swallowed they touch the epiglottis and thence trickle down into the larynx. It is improbable that from the intestinal canal demulcents can reach the urinary passages ; as they are nevertheless said to act beneficially in irritable conditions of the latter—*e.g.* in cystitis—the action can only be due to the dilution of the urine by the water in which they are given.

Demulcents delay absorption ; this property is utilised when active substances that alone or in aqueous solution would be absorbed too quickly are required to reach the lower portions of the intestinal canal. Many laxatives are far less efficient when given pure than when taken in the form of crude drugs where they are accompanied by colloid substances which retard their absorption. This is also of importance for the action of anthelmintics.

Iceland moss, Cetraria Islandica, which was formerly used in Scandinavian countries as an article of food, consists to a great extent (about 40 per cent.) of the dextrine-like carbohydrate *lichenin*, which when boiled with dilute acids yields dextrose, and with hot water produces a mucilaginous liquid, which on cooling

stiffens into a jelly. This jelly, under the name of *Gelatina lichenis islandici*, was formerly often used as an article of food in wasting diseases, especially pulmonary tuberculosis. Iceland moss also contains a considerable quantity of carbohydrates that are modifications of cellulose, the so-called *semi-cellulose*, which by interaction with dilute acids yields two other kinds of sugar besides dextrose, namely, mannose and galactose.

The demulcents serving for the above indications are derived from the vegetable kingdom. Glue, or **gelatine**, is of animal origin, and is employed in pharmacy in the manufacture of various kinds of glycerin demulcents, which have acquired practical importance in cutaneous affections, both as coverings and as vehicles for various substances acting on the skin. One employment of gelatine that is new in Europe, but has been known in China, according to Miura, for about 1,800 years and in Japan for at least 1,000, is as a hæmostatic. Subcutaneous injections of gelatine are often employed for *hæmorrhages* of all kinds, *e.g.* from the lungs, kidneys and uterus, hæmatemesis, typhoid and other intestinal hæmorrhages, and also for hæmophilia, purpura hæmorrhagica, and for profuse hæmorrhages generally that recur frequently and are inaccessible to surgical treatment. The effect is so often good that their efficacy can hardly be denied, even when due consideration is paid to the fact that most hæmorrhages ultimately cease spontaneously by producing cardiac weakness. Gelatine has also been tried to a considerable extent internally for hæmatemesis, hæmorrhoids, lung and kidney hæmorrhage, etc., apparently with good effect. In what way the bleeding is arrested is not exactly known. It is ascribed by some to the calcium contained in the gelatine (about 6 per cent.). Determination of the rate of coagulation of the blood before and after subcutaneous injection of gelatine has not given convincing results; but, on the other hand, it has been found by animal experiments that blood that has been deprived of its coagulating power by the injection of peptone or of hirudin (a substance demonstrated by Jacobj and secreted in the buccal parts of the leech, which serves to keep fluid the blood sucked up, and is the cause of the often obstinate bleeding after the application of leeches) regains that power after subcutaneous injections of gelatine.

In the employment of gelatine on man, special attention should be paid to the purity of the preparation. Tetanus has several times been known to occur after gelatine injections, and it appears that the ordinary gelatine of commerce very frequently contains tetanus spores, which are furnished with the most favourable conditions for development when injected with the gelatine.

Preparations and Doses

Amylum (B.P., U.S.P.), starch, a white powder or irregular pieces, insoluble in cold water, but forming with hot water a mucilaginous liquid. As an enema to allay irritation, 1 teaspoonful to a cup of boiling water (the starch mixed first with a little cold water to prevent the formation of lumps). Internally as an antidote to poisoning with iodine, which forms, with starch, the well-known blue compound.

Glycerinum Amylis (B.P.), *Glyceritum Amylis* (U.S.P.), is used as an ointment for chapped hands, etc.

Acacia (B.P., U.S.P.), gum acacia, gum arabic, the gummy exudation from African species of *Acacia* (*Leguminosæ*). Colourless or yellowish glassy pieces, which are dissolved in water to form a sticky mucilage. Is used in the form of *Mucilago Acaciæ* (B.P., U.S.P.) in the preparation of emulsions. *Dose*, 4—16 mils, 1—4 fl. drs. (B.P.). *Syrupus Acaciæ* (N.F.). A useful flavouring-agent for saline preparations, including urea.

Tragacantha (B.P., U.S.P.) is a gummy exudation from Asiatic species of *Astragalus* (*Leguminosæ*), and differs from gum acacia in not dissolving, but merely swelling up into a jelly in water. Is used in the preparation of pastilles.

Mucilago Tragacanthæ (B.P., U.S.P.). *Dose*, 4—16 mils, 1—4 fl. drs. *Pulvis Tragacanthæ Compositus* (B.P.), also contains gum acacia, starch and sugar. *Dose*, 6—40 decigrms., 10—60 grs.

Althæa (U.S.P.), marsh-mallow root, the sweet-tasting, mucilaginous root of *Althæa officinalis* (*Malvaceæ*), Central Europe. Is used as an excipient for pills.

Linum (B.P., U.S.P.), linseed, flax-seed, the seeds of *Linum usitatissimum* (*Linaceæ*), cultivated all over the world. The testa contains much mucilage, and the kernel a fixed oil. *Linum Contusum* (B.P.), crushed linseed, linseed meal, used in making poultices. An infusion (10 per cent.) is an old household remedy for acute catarrh of the mucous membrane, especially in the urinary passages.

Ulmus, the inner bark of *Ulmus fulva*, Slippery Elm, a popular remedy for application to bruises and ulcers.

Chondrus, Irish moss, carragheen, the dried plants, *Chondrus crispus* and *Gigartina mamillosa*, North Atlantic algæ. They swell up in water, forming a jelly with a fresh sea-odour, but an insipid taste. Were formerly used as an invalid food, but this is of little value, as it consists mainly of water. In man, only a small proportion of the carbohydrates (semi-cellulose) it contains is digested.

Cetraria Islandica, Iceland moss, a species of lichen found throughout the north frigid zone, was formerly employed in the same way as carragheen, but is now discarded. It contains a bitter acid, which must first be removed by soaking in a potash solution.

Gelatinum (B.P., U.S.P.), almost colourless, translucent sheets or shreds. *For hæmorrhage, locally*, a 5—10 per cent. solution, or *subcutaneously*, a 2 per cent. solution, heated to the temperature of the body, of which 50—100—200 c.c. is injected at the seat of the hæmorrhage. The gelatine must be sterilised, and the injection given under the strictest aseptic conditions. *Internally*, 2 tablespoonfuls or more of a 10 per cent. solution, 3 times a day. The bottle must be slightly warmed before each administration, until the contents are liquefied. As an *enema*, 50—100 c.c. of a 10 per cent. solution.

Coccus (B.P., U.S.P.), Cochineal. The dried female insect. A colouring agent. *Tinctura Cocci* (B.P.). *Dose*, 0·3—1 mil, 5—15 mins.

2. SWEETENING AGENTS

Sweet substances (*saccharines*) are used in medicine as flavouring agents, in the endeavour to cover the nauseous taste that many drugs have with the agreeable taste of the sugar.

For this purpose either the ordinary cane-sugar is used or various preparations which contain, in addition to sugar, fruit acids and mucilaginous or aromatic constituents, which also serve to improve the flavour. In substance, sugar is antiseptic, and is an old remedy for wounds. Concentrated solutions are also preservative (medicinal syrups, preserves), while dilute solutions form a good nutritive basis for micro-organisms.

Dextrose, as a flavouring agent, is less useful than cane-sugar, as it is not so sweet. *Lactose* is more difficult to dissolve, and still less sweet ; it is not hygroscopic and is therefore suitable as an excipient for medicines that attract moisture (powders, vegetable extracts).

Several kinds of sugar, *e.g.* cane-sugar, grape-sugar and sugar of milk, which are all dextro-rotatory, are valuable articles of food that are completely burnt up in the body to carbonic acid and water. Only when taken in exceedingly large quantities are they partly excreted by the normal organism in the urine. In diabetes these sugars do not undergo combustion. The behaviour of *lævo-rotatory fruit-sugar* (lævulose) in the diabetic organism has been repeatedly investigated since Külz, in 1873, found that even considerable quantities of lævulose in some cases of slight diabetes did not cause glycosuria. The hope thus aroused of finding in lævulose a carbohydrate of which sufferers from diabetes could make use has not, however, been fulfilled. It seems to be assimilated a little better than other sugars, but not so much more easily as to offer any advantage worth mentioning. In diabetes, as a rule, the greater part of the lævulose given is excreted in the urine as glucose, some appears unchanged, and only a very little undergoes combustion. In the experimental pancreatic diabetes, according to Minkowski, lævulose behaves in the same manner.

As far as can be judged from the knowledge at present possessed of the behaviour of the sugars with 5 carbon atoms (the *pentoses*) in the human body, they will not prove to be any more useful. They are utilised less completely in man and animals which live on a mixed diet than in the herbivora, and are excreted to some extent unchanged ; in diabetics the assimilation is still worse, and the excretion is partly in the form of glucose.

A few synthetically produced aromatic compounds, which are not chemically related to sugar, but have an intensely sweet taste, have recently been taken into use. Of these the best known

is *saccharine*, the anhydride of orthosulphamido-benzoic acid $C_6H_4<\overset{CO}{\underset{SO_2}{}}>NH$, which is about 300 times as sweet as cane-sugar, as its taste is still perceptible in a dilution of 1 in 100,000, while that of cane-sugar disappears in a dilution of 1 in 300. The taste of saccharine, however, is not wholly identical with that of cane-sugar, and it is rejected by sugar-eating insects. Ants will pick the sugar out of a mixture of sugar and saccharine and leave the latter. Saccharine is slightly antiseptic; it weakens the effect of ptyalin on starch, but does not prevent the digestion of albumin. Saccharine is easily absorbed, and is excreted unchanged in the urine. As it does not seem to be poisonous, even with prolonged use, it can safely be used by diabetic patients as a sweetening agent instead of the restricted cane-sugar. It may also take the place of sugar in strict obesity cure. It has been recommended, but is seldom used, as an intestinal antiseptic and in cystitis. Saccharine combines with alkalies to form salts that are readily soluble and also have a sweet taste.

Preparations and Doses

Dextrosum (B.P., U.S.P.), obtained from starch by hydrolysis. A white crystalline or granular powder with a sweet taste. Soluble in less than 1 part of water.

Sucrosum (B.P., U.S.P.), Sucrose, $C_{12}H_{22}O_{11}$, white, hard, dry crystals, or a white crystalline powder, soluble in half its weight of water. When heated to 160° C., sugar turns into a hard, glassy mass (sweets); at 200° C. it loses water and is transformed into the pungent caramel, which is used for the colouring of beers and liqueurs. *Caramose*, dextrose-caramel, was formerly used in preference to dextrose to reduce the acidosis in diabetes. As a trial, 50 grms. a day. Sugar is employed as *Syrupus* (B.P., U.S.P.), or as other official syrups—*S. Aromaticus*, *S. Aurantii*, *S. Limonis*, etc.—which have the aromatic taste of the drugs in question.

Lactosum (B.P., U.S.P.), sugar of milk, lactose, $C_{12}H_{22}O_{11} + H_2O$, hard, white crystals, soluble in 7 parts of water. Large quantities have a slight aperient action. For infants, 30 grms. to a litre of milk-food.

Glucosum Liquidum (B.P., U.S.P.), glucose, a viscous syrup consisting principally of dextrose and dextrine, and obtained by the hydrolysis of starch.

Saccharinum (U.S.P.), Ortho-sulpho-benzimide, saccharine, a white, crystalline powder, soluble in 400 parts of water. To a cup of coffee or tea, 3—6 centigrms., ½—1 gr. Saccharine forms with alkalies readily soluble salts, of which the sodium salt, also called "soluble saccharine," *Saccharinum Solubile* (B.P., U.S.P.), is the one most frequently used. *Doses*, the same as those of saccharine.

Glycyrrhizæ Radix (B.P.), *Glycyrrhiza* (U.S.P.), liquorice root, the yellow inside of the root of *Glycyrrhiza glabra* (*Leguminosæ*), a plant growing wild and cultivated in Southern and Eastern Europe. Taste mucilaginous and very sweet, followed by a slight stinging. The peculiar sweet taste is due to the glucoside glycyrrhizin. The root also contains sugar, starch and gum.

Extractum Glycyrrhizæ (B.P., U.S.P.), a dark brown extract, used as a flavouring agent, and held in high esteem by laymen as an expectorant and demulcent for coughs and bronchial catarrh. Is often used with ammonium chloride as a lozenge, or as "liquorice mixture" or "brown mixture," with somewhat varying constitution, a favourite preparation in many countries. The *Mistura Opii et Glycyrrhizæ Composita* of the U.S.P. contains small quantities of tartar emetic, opium, camphor and spirit of nitrous ether. *Dose*, 4 mils, 1 fl. dr., several times a day.

Extractum Glycyrrhizæ Liquidum (B.P.). *Dose*, 2—4 mils, ½—1 fl. dr. *Fluidextractum Glycyrrhizæ* (U.S.P.). *Dose*, 2 mils, 30 mins. Is used as an addition to mixtures.

Mel Depuratum (B.P.), *Mel* (U.S.P.), honey, the product of the industry of bees (1 kilogrm. of honey is the result of the visits of bees to 663,000 clover-flowers), in its natural state is a yellow or yellowish brown syrup, which is principally a solution of dextrose and lævulose. It originates in the honey-bags of the bees by inversion of the nectar, and contains small quantities of volatile oils, which belong to the various flowers. On standing, honey often becomes thick with crystallised dextrose, the lævulose remaining in solution. It is employed to flavour various preparations, and in large doses has a slight aperient action.

3. FATS

Fats are to the skin what mucilages are to the mucosa. They act as a covering and protection from irritation, and promote the healing of excoriations, fissures, and abrasions. Most kinds of fat are easily absorbed by the skin, and make it pliable and soft and, by preventing the evaporation of the water, also moist. They restrict the secretion of sweat, and when rubbed upon large areas of the body, produce a compensating increase in the flow of urine.

Aqueous solutions of drugs are not absorbed through the unbroken skin, because the epidermis, being permeated by the secretion from the sebaceous glands, is impervious to water; substances dissolved in oil not only penetrate to the deeper layers of the skin, but are also abundantly absorbed. Aqueous solutions can only penetrate after the fat of the skin has been removed by thorough washing with fat-solvents, such as alcohol and ether. On the other hand, watery solutions are far more readily absorbed by mucous membranes than are oily solutions. The fats are suitable as vehicles for antiseptics for wounds only when the antiseptic in question is more readily, or as readily, soluble in water or in the secretion from the wound as in oil, for otherwise it would remain in the oil without coming into contact with the micro-organisms (*cf.* Carbolic Acid, p. 242).

The fats are very important foods, which are saponified and absorbed in the small intestine. In large doses they induce peristalsis, lubricate the intestine, and act as purgatives.

The **ordinary emollients,** lard, suet, olive oil, linseed oil, etc., consist principally of esters of glycerin with stearic, palmitic and oleic or linoleic acids. All these are only capable of being kept for a limited time; if kept long they become rancid, *i.e.* they acquire an acid reaction and an unpleasant odour of free volatile fatty acids which act as irritants on raw surfaces. Of late a new kind of fat that is free from these disadvantages has been extensively employed, namely, purified **wool-fat,** *adeps lanae,* which differs chemically from lard, suet, etc., in that the acids are not combined with glycerin, but with cholesterin and isocholesterin, isomeric alcohols with the formula $C_{26}H_{44}O$. Wool-fat is remarkable for two valuable properties, namely, that it does not become rancid, and that it can take up an equal weight, or even more, of water, and can thus serve as a vehicle for aqueous medicinal solutions.

Soft paraffin, or petrolate, commonly called vaseline, is obtained from crude petroleum after the volatile hydrocarbons that are used for technical and illuminating purposes are distilled off. It consists of a mixture of higher paraffins, and is thus quite different chemically from the fats, but has the same therapeutic uses. It follows from its chemical constitution that vaseline also does not become rancid. After prolonged rubbing into the skin of animals, vaseline is absorbed and deposited in the body, especially in the muscles, where it remains for a long time unchanged; it is only after the lapse of months that in part it undergoes combustion and in part is excreted through the intestine. **Liquid paraffin,** an oily liquid, has of late become a popular aperient. It acts mechanically by softening the fæces and lubricating the intestinal walls. It occasionally causes nausea.

Glycerin, the only normal trivalent alcohol at present known, also belongs therapeutically to the fatty substances. Like them, it softens the skin, but owing to its affinity for water, it produces irritation and smarting for a short time on places where the skin is broken. Glycerin has a slightly antiseptic action, probably by depriving the micro-organisms of water. It is easily absorbed, and small quantities of it are completely oxidised to water and carbonic acid. Larger quantities undergo only partial combustion in the body, while the rest is excreted unchanged in the urine. Large doses, taken internally, have a laxative effect. Injected into the rectum, even small doses are irritant, and elicit vigorous peristaltic movements, which are transmitted far up through the large intestine and result in evacuation of the bowels. To man glycerin does not seem to be poisonous, even in considerable quantities, *e.g.* 100 grammes in the course of a day. Still larger doses (in proportion to the body-weight) in animals cause

acceleration of the pulse and respiration, an intoxication resembling that of acute alcohol poisoning, a rise of temperature, tremor, convulsions, and death from paralysis of the respiration. Subcutaneous injection causes also hæmoglobinuria and nephritis.

Therapeutic Uses. Fats are employed as *emollients* and *protectives* in *abrasions, surface-ulcerations, burns*, etc., either alone or as ointments and liniments containing antiseptic or astringent substances. In many *cutaneous affections* they serve to soften hard crusts, and are used as vehicles for substances that are intended to penetrate to the deeper layers of the skin. Drugs intended for absorption, *e.g.* mercury, are seldom applied in the form of ointment. Those emollients which are able to take up large quantities of water, especially wool-fat, have a cooling effect owing to the evaporation of the water.

The selection of the kind of fat to be used for an ointment is not a matter of indifference. If the object is to replace lacking sebum, or make the skin pliant, the fat chosen should be liquid, or one that has a low melting-point, *e.g.* ordinary lard, vaseline, or olive oil, which can easily be worked in. For protective ointments that have to remain for some time on the site of application, substances that do not melt so easily are more suitable ; such ointments are prepared with suet, wax or spermaceti, of which the melting-point is far above the temperature of the skin.

Internally, fixed oils are employed for the same purposes as externally, together with mucilage in the form of emulsions. In *biliary colic*, the pain is sometimes found to cease suddenly after large doses of *olive oil*. According to recent investigations, the oil has no influence upon the secretion of bile, but on its passage through the duodenum may, perhaps, make its way into the biliary duct, lessen the great irritation of the mucous membrane, and lubricate the walls so that a firmly-wedged gall-stone is more easily dislodged.

Glycerin, like the fixed oils, is employed as a remedy for *abrasions* (" chapped hands "). Internally it has been tried as a nutritive agent for diabetic patients, but as only small quantities undergo combustion, and large quantities readily cause diarrhœa, its nutritive value is not great. Sometimes in diabetes the amount of sugar is found to decrease, while acetonuria becomes worse. Very large doses of glycerin are effective against *trichinæ*, but, of course, only as long as the worms are still in the intestine and have not yet migrated to the muscles ; the trichinæ shrink up and die even in glycerin that is diluted with 3—4 parts of water. In *constipation* due to inertia of the large intestine, glycerin as small enemata or in suppositories is an efficient aperient but is not

suitable for constant use during a very long period as the irritability of the intestinal mucous membrane is gradually weakened and the effect becomes uncertain. Placed in the cervix uteri glycerin causes uterine contractions, and is therefore employed for hæmorrhages, and as a preliminary to *abortion* and an ecbolic in uterine inertia.

Glycerin is employed in pharmacy as a solvent for salts, *e.g.* borax, and is added to the mass of most pills in order that the pills may remain soft and easily soluble. Glycerin is used for the preservation of vaccine as a preventive of putrefaction without being strongly antiseptic.

Preparations

Animal Fats

Adeps (B.P., U.S.P.), lard, the purified internal fat of the hog, a soft, white, unguinous substance, melting at about the temperature of the body. *Adeps Benzoinatus* (B.P., U.S.P.), lard combined with benzoin. Has a pleasant odour, and keeps better.

Sevum Præparatum (B.P., U.S.P.), prepared suet, the purified internal fat from the abdomen of the sheep. Contains more stearin, and has therefore a higher melting-point (about 47° C.) than lard.

Adeps Lanæ Hydrosus (B.P., U.S.P.), hydrous wool-fat, lanolin, contains 25—30 per cent. of water. Is sticky, and is therefore not suitable alone for ointments that are to be rubbed into the skin. The proper consistency is obtained by mixture with equal parts of lard or about 20 per cent. of olive oil. *Adeps Lanæ* (B.P., U.S.P.), wool-fat without water. Melts between 30° and 42° C.

Cera Flava and *Cera Alba* (B.P., U.S.P.), yellow and white wax, the latter obtained by bleaching the yellow wax. At an ordinary temperature wax is hard, and does not melt until about 63° C. Employed in the making of plasters and stiff ointments.

Cetaceum, spermaceti, from a liquid, yellow oil found in two large cavities in the front of the huge head of the cosmopolitan sperm-whale (*Physeter macrocephalus*), as also in numerous small sacs in its blubber and muscle. When the animal is dead, the spermaceti crystallises out of this oil in large, glistening lamellæ (from one animal as much as 3,000 kilogrms.), which melt at 40—45° C.

Vegetable Fats

Oleum Olivæ (B.P., U.S.P.), olive oil, obtained from the ripe fruit of *Olea Europœa* (*Oleaceæ*), Southern Europe. Very often adulterated with other oils, especially cotton-seed oil. Used externally as a constituent of liniments and ointments; internally for biliary colic, 100—200 grms. to be taken in the course of a few hours; the addition of ½ grm. of menthol makes the oil less nauseous. For the dispersion of accumulations of hard fæcal masses, ½ litre as an enema. The dose of this and similar bland oils mentioned below is 15—30 mils, 4—8 fl. drs.

Oleum Amygdalæ (B.P.), *Oleum Amygdalæ Expressum* (U.S.P.), almond oil, expressed from the kernels of *Prunus Amygdalus* (*Rosaceæ*), Southern Europe. Is remarkable for its pleasant flavour, and is employed in the manufacture of fine soaps. It is also a convenient vehicle in which to administer certain volatile oils, *e.g.* oil of turpentine, oil of chenopodium, etc. *Emulsio Amygdalæ* is prepared from sweet almonds, and is given by the tablespoonful as an emollient in intestinal diseases. Unlike mucilaginous substances, oily emulsions have a slightly aperient action. "Almond-bread," formerly recommended as a substitute for the ordinary bread for diabetics, contains much fat and albumin, but no starch.

Oleum Lini (B.P., U.S.P.), linseed oil, obtained from *Linum usitatissimum* (*Linaceæ*), a textile plant, cultivated almost all over the world. For external use only.

Oleum Gossypii Seminis (B.P.), *Oleum Gossypii* (U.S.P.), cotton-seed oil, from cultivated species of *Gossypium* (*Malvaceæ*), specially adapted for external use on account of its cheapness.

Oleum Arachis (B.P.), earth-nut oil, ground-nut oil, pea-nut oil, is obtained from the seed of *Arachis hypogæa* (*Leguminosæ*), a native of tropical America. Is used in hot countries as a substitute for olive oil. This also applies to—

Oleum Sesami (B.P.), sesame oil, obtained from *Sesamum Indicum* (*Pedaliaceæ*), a plant cultivated in many countries.

Oleum Maydis (U.S.P.), corn oil, a fixed oil used as a vehicle.

Oleum Theobromatis (B.P., U.S.P.), a white, solid fat, expressed from the seeds of *Theobroma cacao* (*Sterculiaceæ*), a native of tropical America. Melts between 30° and 35° C., and is used as a basis for suppositories.

Lycopodium (U.S.P.), the spores of club moss, *Lycopodium clavatum* (*Lycopodiaceæ*), a creeping plant found in most quarters of the globe. A pale yellow, very mobile powder, containing about 50 per cent. of fat. Is used as a dusting-powder for abrasions, etc., especially in young children.

Glycerinum (B.P., U.S.P.), glycerin, $C_3H_5(OH)_3$, a viscid, oily, colourless liquid with a sweet taste. May be mixed with water or with alcohol in any proportions. *Dose*, 4—8 mils, 1—2 fl. drs. (B.P.); 4 mils, 1 fl. dr. (U.S.P.); internally, for trichinæ, by the tablespoonful, 100—150 grms. in the course of the day; as a laxative, 2—8 grms. as an enema or in suppositories.

Suppositoria Glycerini (B.P., U.S.P.).

Glycerins (B.P.), *Glycerites* (U.S.P.), are solutions of drugs in glycerin.

Acidum Oleicum (B.P.), a brownish-yellow, oily liquid; odour usually faintly rancid. Insoluble in water, soluble in alcohol, chloroform and ether. It is a solvent for making oleates. *Dose*, 0·3—1 mil, 5—15 mins.

Mineral Fats

Paraffinum Liquidum (B.P.), **Petrolatum Liquidum** (U.S.P.), liquid paraffin, a colourless, transparent, viscous liquid, with neither taste nor odour. *Dose*, 8—30 mils, 2—8 fl. drs. (B.P.); 15 mils, 4 fl. drs. (U.S.P.). Is also used in ointments for the suspension of insoluble substances (*e.g.* calomel) to be injected subcutaneously or intramuscularly.

Emulsum Petrolati Liquidi (U.S.P.), contains liquid paraffin, acacia, syrup, vanillin, alcohol and distilled water. An agreeable preparation of liquid paraffin for use as an intestinal lubricant. *Dose*, 30 mils, 1 fl. oz.

Paraffinum Chlorinatum (U.S.P.), an amber coloured oily liquid,

miscible with fatty solvents but insoluble in water and in alcohol. It is used as a vehicle for di-chloramine-T (8 per cent.). The preparation is rendered less viscous for use as a spray when mixed with 10 per cent. of carbon tetrachloride.

Paraffinum Molle Album, Paraffinum Molle Flavum (B.P.), **Petrolatum, Petrolatum Album** (U.S.P.), soft paraffin, vaseline, a white or yellowish unctuous mass, which liquefies a few degrees above the temperature of the blood. The white preparation is obtained from the yellow soft paraffin by bleaching. Much used as a basis for ointments.

Paraffinum Durum (B.P.), *Paraffinum* (U.S.P.), hard paraffin, a colourless or white, more or less translucent, crystalline mass, which melts between 50° and 60° C.

Ambrine is a paraffin preparation for application to burns.

Compound Ointment-bases and Cerates

Typical ointment melts at the temperature of the body; the cerates are stiffer.

Unguentum Simplex (B.P.), Simple Ointment. Contains wool fat, hard paraffin, white soft paraffin or yellow soft paraffin. *Unguentum* (U.S.P.), simple ointment, the basis of many other ointments, is a mixture of lard and white wax. *Unguentum Paraffini* (B.P.), a mixture of soft and hard paraffins and beeswax.

Unguentum Aquosum (B.P.), Hydrous Ointment. This is a cold cream containing distilled water, borax, white beeswax, white soft paraffin and olive oil. *Unguentum Aquæ Rosæ* (U.S.P.), cold cream, has a pleasant, cooling effect, as it contains about 20 per cent. of water.

Ceratum (U.S.P.), simple cerate, white wax and benzoated lard.

Addendum

In the absence of a more suitable place, *Collodion* is inserted here. *Collodium Flexile* (B.P.), *Collodium* (U.S.P.), is a syrupy solution of pyroxylin (soluble gun-cotton, consisting chiefly of cellulose tetranitrate) in alcohol and ether. When painted on the skin, the volatile solvents evaporate, leaving a transparent film which contracts and exerts a slight pressure, but cracks easily. This may be prevented by the addition of a little castor oil (*Collodium Flexile*, B.P., U.S.P.). Collodion may also serve as a vehicle for drugs, *e.g.* cantharidin (*Liquor Epispasticus*, B.P.), iodoform or sublimate.

4. VOLATILE OILS

General Characteristics

Volatile or ethereal oils are widely diffused through the vegetable kingdom, either in the form of small, refractile drops occurring in the cellular fluid, or collected in large receptacles, the so-called oil-glands. They may be found in all parts of the plant, but most frequently in flowers and fruit, and occur more especially in certain orders, *e.g.* the *Labiatæ*, *Cruciferæ*, *Umbelliferæ*, *Auran-*

tiaceæ, *Myrtaceæ*, *Lauraceæ* and *Coniferæ*. In cryptogams they are of rare occurrence, but are found in ferns. The volatile oils are colourless or pale yellow, less frequently green or blue, often somewhat viscid liquids; they are seldom solid at ordinary temperatures, and nearly always possess a pleasant aromatic odour, which becomes stronger when the oil is diluted with a light volatile liquid, *e.g.* alcohol. Some, however, have an unpleasant or offensive odour (valerian, asafetida); a few have a penetrating carrion-smell, which tempts blow-flies to deposit their eggs upon such plants (species of *Aristolochia*). Although the boiling-point of most of them is high, they are volatile both at ordinary temperatures and in steam, and are generally prepared by distillation with water.

Although the volatile oils outwardly have many properties in common, they differ greatly as regards their *chemical constitution*, and often consist of very complex mixtures of a large number of aromatic compounds. Certain constituents are characteristic, however, and are seldom absent. Almost all volatile oils contain, for instance, *terpenes*, volatile hydrocarbons with formula C_5H_8 or some multiple of this, occurring in many isomeric forms that differ from one another as regards boiling-point and other physical properties. Few oils consist exclusively of these hydrocarbons; many oxidised aromatic compounds are generally found dissolved in the terpenes, such as phenols, ketones, acids, alcohols, solid camphors (*e.g.* ordinary camphor, menthol, thymol, borneol), all being important from the fact that it is generally these constituents that give to the oils their characteristic aroma. Some volatile oils have quite a different constitution. The oils of bulbous, cruciferous and umbelliferous plants, for instance, contain sulphur, the oil of bitter almonds consists of benzaldehyde, and gaultheria oil is almost a pure methyl ester of salicylic acid. A few occur in incomplete form in the plants as glucosides, out of which the volatile oil only makes its appearance on decomposition (oil of mustard, oil of bitter almonds).

Action. From the varied chemical structure of the volatile oils it follows naturally that they also differ from one another pharmacologically. All those, however, which consist principally of terpenes and camphors have many features of their action in common. They are all more or less **antiseptic,** a property which is mainly due to phenols and terpenes, which, on account of their volatility, easily penetrate protoplasm and micro-organisms.

Locally, the volatile oils have an *irritant* action, make the skin hot and hyperæmic, and may, if sufficient time be given them, cause severe inflammation with pain, serous exudation and vesica-

tion. Those that act most strongly in this respect are the most volatile, consisting of terpenes only (oil of turpentine), and, still more, certain oils that contain sulphur, *e.g.* oil of mustard.

Upon *mucous membranes* the local action is especially marked. Even when greatly diluted, the volatile oils have a sharp, burning taste—followed by cold when they contain an abundance of camphors—and cause increased salivation. It is probable that even their taste and smell, like the taste and smell of appetising food, which, according to Pawlow's well-known experiments, make not only the mouth, but also the stomach, "water," are sufficient to start by reflex action the secretion of gastric juice. Daily experience teaches that aromatic and pungent substances sharpen the appetite, and, according to Brandl's experiments, accelerate the movements of the stomach and the absorption of dissolved substances, *e.g.* sugar, salts, peptones and various drugs, so that the stomach is more quickly unloaded. These effects explain the instinctive use of condiments at heavy meals. On the other hand, the chemical part of the digestion is not assisted, for, like antiseptic substances, the volatile oils not only counteract all kinds of abnormal fermentation, but also appear to retard somewhat the pepsin action.

Upon the intestine, too, the volatile oils have an antiseptic action, and are often employed for diarrhœa. As in the stomach, the absorption of the dissolved contents is accelerated. Volatile oils have long been extensively used as carminatives. It has been shown by various investigators that they increase the tone and the amplitude of the peristaltic contractions in isolated pieces of intestine. The action is due to slight irritation of the mucous membrane, and does not take place when the sensory nerve-endings are paralysed by cocaine (Plant).

When large doses are given internally, the action on the mucous membrane increases to great irritation of the entire gastro-intestinal tract, with the usual consequent symptoms—pain, vomiting and diarrhœa. The hyperæmia may spread to the peritoneum and to all neighbouring parts, among others, in women, to the sexual organs, where the congestion may find expression in hæmorrhage and abortion. This applies especially to the poisonous oil of *Juniperus Sabina*, which has played a great part as a popular abortifacient.

Specific Action. The volatile oils are absorbed easily and are all poisonous, but no general effects are noticed after the small doses generally employed in medicine. When inhaled for some time they cause drowsiness, headache and indisposition, symptoms that are well known in persons remaining in newly-painted rooms (turpentine) or rooms filled with strongly-scented flowers. The

more serious cases of poisoning are different with each separate oil. As a rule it may be said that the terpenes have a paralysing action on the central nervous system, while camphor generally first has the opposite effect. It is therefore usual to see first symptoms of excitation, among them being convulsions that may take the form of an epileptic attack, and afterwards symptoms of depression which end in respiratory paralysis.

The manner in which the volatile oils are **excreted** is of practical interest, as many of them are employed for the sole purpose of acting upon the organs through which they leave the body. They are perhaps to a small extent excreted through the glands of the skin. Several of them, *e.g. Olea Pimpinellæ*, *Anisi* and *Thymi*, are excreted through the lungs, impart to the air expired their peculiar odour, and probably act antiseptically on the bronchi. The principal excretion, however, both of the terpenes and of the other constituents, takes place in the urine, where they appear either unchanged, in the form of new, little-known compounds, or combined with glycuronic acid ; in the last case the urine reduces Fehling's solution, which has given rise to the erroneous assumption that volatile oils produce glycosuria. In large doses they increase the amount of urine, and in inordinately large doses they cause deleterious irritation of the kidneys.

The number of volatile oils and aromatic vegetable drugs included in the pharmacopœias is great, and they are employed in all kinds of ways. Some of them, namely, those that are used for their stimulation of the skin, those that occur together with, or contain, bitter principles, and certain kinds of camphor that have a special action, are mentioned in other chapters. The remainder may be divided according to their medicinal uses into the three following groups : (*a*) aromatic volatile oils used principally as perfuming and flavouring agents ; (*b*) malodorous volatile oils used as nerve-remedies ; and (*c*) volatile oils used as genito-urinary disinfectants.

(*a*) Aromatic Volatile Oils used principally as Perfuming and Flavouring Agents

A very few of the drugs and oils that are employed to give an attractive taste and odour to medicines would be sufficient, but all the pharmacopœias have included far more than are required, partly in order to satisfy various tastes and fancies, and partly from a desire not to do away with many time-honoured drugs. Many are also retained because, although they have long since disappeared from the physician's prescriptions, they have

still continued to live for generations in popular medicines. Several drugs called *spices* are included among the perfuming and flavouring agents, and, owing to their much more frequent use as condiments than as medicines, are of greater interest to the housewife than to the doctor. These, too, however, are sometimes employed in medicine to stimulate the appetite, as stimulants in gastro-intestinal atony, and as antiseptics in gastric fermentation and diarrhœa. As they are all local irritants, their employment is restricted to cases in which there is no great irritation or inflammation of mucous membrane. Those oils which are excreted through the lungs are also employed as expectorants and as disinfectants of the bronchial secretion.

The volatile oils are used in various forms.

In olden days there were none but the *crude drugs*, several of which are still favourite household remedies in the form of home-made infusions or "teas," which are generally drunk hot and in large quantities as diaphoretics; for instance, for colds. It is doubtful whether the volatile oil has any share in the diaphoretic action, but it imparts an aromatic taste to the water without which the latter would be nauseous, and would not be drunk in sufficient quantity. Among the drugs thus used are elder and chamomile flowers, peppermint, spearmint, anise, fennel, caraway, etc., the selection varying with the flora of the country.

The *volatile oils* are seldom used alone, but generally in various compound preparations and as additions to insipid solutions or mixtures. One drop to 100 c.c. is sufficient.

The volatile oils are almost insoluble in water, but on being shaken up with water, or on distillation of the drug with water, a sufficient quantity of the oil is taken up to impart an aromatic flavour to the water. The *aromatic waters* may be employed in solutions or mixtures instead of ordinary distilled water.

Aromatic tinctures are made by extraction of the drugs with alcohol.

Aromatic spirits are prepared by dissolving the oil in alcohol, sometimes with the addition of the crude drug. They are not miscible with water, but are employed in alcoholic or oily liquids.

The *average dose* of volatile oil is 2 minims; of aromatic tinctures, 2—4 mils, ½—1 fl. dr.; of aromatic spirits, 3—20 decimils, 5—30 minims; of aromatic syrups, 2—8 mils, ½—2 fl. dr. Doses differing from these are given below under the respective preparations.

Oleum Rosæ (B.P.C., U.S.P.), the most fragrant and the most frequently adulterated of all the volatile oils, is manufactured in Turkey and Bulgaria, and now also in other countries, from the fresh flowers of various kinds of

rose (*R. centifolia, R. Damascena*). At an ordinary temperature it is a semi-solid, crystalline mass. Among the preparations is *Aqua Rosæ* (B.P.C., U.S.P.). *Unguentum Aquæ Rosæ* (B.P.C., U.S.P.), cold cream, is mentioned in the preceding chapter.

Various species of *Citrus* (*Rutaceæ*), natives of Asia and cultivated in all countries where the climate is suitable, contain much-employed volatile oils in the external yellow layer of the pericarp of their fruit. Some species contain bitters, and will be mentioned in a subsequent chapter.

Limonis Cortex (B.P., U.S.P.), lemon peel, the outer rind of the fruit of *Citrus medica*, var. *Limonum*.

Oleum Limonis (B.P., U.S.P.), is obtained, by expression, from the fresh lemon peel. *Syrupus Limonis* (B.P.). *Tinctura Limonis* (B.P.).

Aurantii Dulcis Cortex (U.S.P.), sweet-orange peel, from *Citrus aurantium Sinensis*.

Oleum Aurantii (U.S.P.), orange oil. *Spiritus Aurantii Compositus* (U.S.P.), composed of oils of orange, lemon, coriander and anise. *Elixir Aromaticum* (U.S.P.), simple elixir, *Syrupus Aurantii* (B.P.), syrup of orange.

Aqua Aurantii Florum (U.S.P.), orange-flower water, the saturated aqueous distillate from the fresh flowers of *Citrus aurantium amara* (diluted with water). *Syrupus Aurantii Floris* (U.S.P.).

The *Labiatæ* are remarkable for the abundance of their fragrant species. The following, which all come from the South of Europe, are official :—

Mentha Piperita, peppermint, and *Mentha Viridis*, spearmint (U.S.P.), the dried leaves and tops of the respective flowering plants.

Oleum Menthæ Piperitæ (B.P., U.S.P.), peppermint oil, has first a pungent taste, then a sensation of cold, and contains the well-known member of the camphor-group, menthol (p. 150). *Aqua* and *Spiritus Menthæ Piperitæ* (B.P., U.S.P.) are much used as flavouring agents, and the corresponding preparations of *Mentha Viridis* (U.S.P.) are similarly employed.

Oleum Lavandulæ (B.P., U.S.P.), oil of lavender, obtained from *Lavandula vera*, is much used in the manufacture of perfumes. *Spiritus Lavandulæ* (B.P., U.S.P.) ; *Tinctura Lavandulæ Composita* (B.P., U.S.P.).

Oleum Thymi, obtained from *Thymus vulgaris*, has the odour of thymol (p. 246), which separates on cooling. In several countries, *Extractum Thymi Saccharatum* (not official), a fluid extract to which sugar has been added, is used as a frequently efficacious remedy for acute bronchitis and laryngitis. It is also recommended for whooping-cough. Is given by the tablespoonful. A similar commercial preparation is much advertised under the name of *Pertussin*.

The formerly much-valued *Rosmarinus Officinalis*, rosemary, is now principally known as a popular remedy. The oil, *Oleum Rosmarini* (B.P., U.S.P.), is a strong skin-irritant. *Spiritus Rosmarini* (B.P.) is used externally as a rubifacient.

The following plants are among the *Umbelliferæ*, anise being a native of Egypt and Asia Minor, the remainder belonging to Europe :—

Carum (B.P., U.S.P.), the fruit of *Carum carvi* (caraway), much used in many countries as a spice, and in bread, cheese and spirit. *Dose*, 0·6—2 grms., 10—30 grs.

Oleum Cari (B.P.).

Fœniculum (B.P., U.S.P.), the fruit of *Fœniculum vulgare* (fennel). *Dose*, 0·3—0·6 grm., 5—10 grs. (B.P.).

Oleum Fœniculi (U.S.P.) has a mild, sweet taste. *Aqua Fœniculi* (B.P., U.S.P.), a good flavouring agent for children's medicines.

Coriandrum (B.P., U.S.P.), the fruit of *Coriandrum sativum*. *Dose*, 0·3—1 grm., 5—15 grs. (B.P.). *Oleum Coriandri* (B.P., U.S.P.).

Anisi Fructus (B.P.C.), anise, the fruit of *Pimpinella anisum*, one of the oldest of spices and drugs.

Oleum Anisi (B.P., U.S.P.). Ninety per cent. of this oil consists of anise camphor, or anethol, $C_6H_4<^{OCH_3}_{C_3H_5}$, which is solid in ordinary temperatures. Anise has long been famed for its efficiency in bronchitis, and is a constituent of *Tinctura Opii Camphorata* (B.P., U.S.P.). The U.S.P. includes the *Aqua* and *Spiritus Anisi*.

Anethum (B.P.), obtained from *Peucedanum graveolens* dill. *Oleum*, *Aqua Anethi* and *Aqua Anethi Concentrata* (B.P.).

The following ancient drugs are used for catarrh of the respiratory tract :—

Myrrha (B.P., U.S.P.), myrrh, obtained from one or more species of *Commiphora* (*Rutaceæ*), natives of Arabia and East Africa. From the bark of these trees there exudes a white sap, a mixture of gum, resin and a little of a volatile oil, which hardens in the air into yellowish or reddish brown tears or masses. *Dose*, 3—10 decigrms., 5—15 grs. (B.P.) ; 0·5 grm., 8 grs. (U.S.P.). Is used as a stimulant and expectorant in acute and chronic bronchitis, *e.g.* in the form of the well-known *Mistura Ferri Composita* (B.P.C.), Griffith's mixture, of which the principal constituents are myrrh and ferrous carbonate. *Dose*, 15—30 mils, ½—1 fl. oz.

Tinctura Myrrhæ (B.P., U.S.P.) is used for painting the mouth in chronic gingivitis and with aphthous ulcers. From ½ to 1 teaspoonful in a tumbler of water makes a good mouth-wash. *Dose*, 2—4 mils, 30—60 mins. (B.P.) ; 2 mils, 30 mins. (U.S.P.).

The once famed, but no longer official, *Olibanum*, is also obtained from trees belonging to the natural order *Burseraceæ*, and like myrrh was known to the ancients, who used it as incense.

From the *Myrtaceæ* we have the well-known *clove*, which has long been employed both as a spice and a drug. The principal constituent of the volatile oil is a phenol, *eugenol*, $C_6H_3C_3H_5OCH_3OH$ (related to guaiacol in creosote), which gives it its strong odour and burning taste, and to the oil of cloves its local anæsthetic action. The same order contains *Eucalyptus globulus*, a gigantic tree, a native of Australia, which is used in

combating the endemic malaria prevalent in so many unhealthy marshy regions in the South of Europe, such as the Roman Campagna. By the extraordinarily rapid growth of these trees and their great consumption of water, the wet soil that harbours the parasite-bearing mosquito is dried up. The most important constituent of oil of eucalyptus is *eucalyptol* (or cineol), which is also the chief constituent of cajuput oil. The *Lauraceæ* is another order that is rich in volatile oils, the most important of these being ordinary camphor. The aromatic oil of cinnamon bark and sassafras, are also official ; but the latter, which was formerly supposed to be a " blood-purifier," and was employed with the same indications as guaiacum wood and sarsaparilla root, is now fast falling into disuse.

Caryophyllum (B.P., U.S.P.), clove, the dried flower-buds of *Caryophyllus aromaticus*, a tree growing wild in the Moluccas and cultivated in many tropical countries. *Dose*, 0·12—0·3 grm., 2—5 grs. (B.P.) ; 0·25 grm., 4 grs. (U.S.P.). The volatile oil is found in large quantities (18 per cent.) in numerous cavities that are visible when slightly magnified and from which it exudes on gentle pressure. *Infusum Caryophylli Concentratum* (B.P.). *Dose*, 2—4 mils, 30—60 mins., and *Infusum Caryophylli Recens* (B.P.). *Dose*, 15—30 mils, ½—1 fl. oz.

Cinnamomum (B.P., U.S.P.), the dried inner bark of the shoots of coppiced trees of *Cinnamomum zeylanicum* (B.P.) or *Cinnamomum Loureirii* (U.S.P.). *Dose*, 0·3—1·2 grms., 5—20 grs. (B.P.). Oil of cinnamon and the distilled and concentrated waters are official preparations in the B.P. Cinnamon water and spirit of cinnamon are official in the U.S.P. The doses correspond with those of similar aromatic preparations above. Cinnamon is an excellent flavouring-agent in mixtures containing salicylate of soda.

Oleum Caryophylli (B.P., U.S.P.), oil of cloves, is a thick yellow oil, which becomes darker with age and is heavier than water. Is employed alone or mixed with equal parts of chloroform or carbolic acid, on cotton wool, as a local anæsthetic in hollow teeth. *Eugenol* should be substituted for the oil.

Oleum Eucalypti (B.P., U.S.P.), oil of eucalyptus. *Dose*, internally, for bronchitis, 10—20 drops at a time on sugar or in capsules ; for inhalation, ½ a teaspoonful in a cupful of boiling water and the vapour inhaled. Oil of eucalyptus, and cajuput oil, *Oleum Cajuputi* (B.P.), obtained from *Melaleuca leucadendron* (*Myrtaceæ*), growing in the Moluccas, should be replaced by *Eucalyptol* (*Cineol*) which is now official (B.P., U.S.P.).

Eucalyptol (B.P., U.S.P.), $C_{10}H_{18}O$. A colourless liquid with a camphoraceous odour and a pungent cooling taste. Local stimulant and antiseptic. A useful constituent of inhalations and oily sprays. *Dose*, 0·06—0·2 mil, 1—3 mins. (B.P.) ; 0·3 mil, 5 mins. (U.S.P.).

Sassafras, the bark of *S. variifolium*, North America. *Oleum Sassafras* (U.S.P.).

Several of the *Zingiberaceæ* contain oils and resinous substances with an exceedingly sharp, burning taste. The species of this order are remarkable chemically from the fact that they contain

so much manganese that they yield a green ash. The following are official :—

Cardomomum (B.P.), *Cardamomi Semina* (U.S.P.), cardamom seeds, from *Elettaria cardamomum*, East Indies. Small brown seeds contained in straw-coloured capsules. *Dose*, 0·6—2 grms., 10—30 grs. (B.P.). *Tinctura Cardamomi Composita* (B.P., U.S.P.).

Zingiber (B.P., U.S.P.), ginger, the rhizome of *Zingiber officinale*, a native of the East Indies, cultivated also in Jamaica; a highly-valued spice. *Dose*, 0·3—1 grm., 5—15 grs. (B.P.); 0·6 grm., 10 grs. (U.S.P.). *Syrupus Zingiberis* (B.P.). *Fluidextractum Zingiberis* (U.S.P.). *Dose*, 0·06 mil, 10 mins. *Tinctura Zingiberis Mitis* (B.P.). *Dose*, 2—4 mils, 30—60 mins. *Tinctura Zingiberis Fortis* (B.P.). *Dose*, 3—6 decimils, 5—10 mins.

Myristica (B.P., U.S.P.), nutmeg, has a still more sharp, hot taste than these *Zingiberaceæ*. The nutmeg is the kernel of the seed of *M. fragrans* (*Myristicaceæ*), the Moluccas. *Dose*, 0·3—0·6 grm., 5—10 grs. *Oleum Myristicæ* (B.P., U.S.P.) was once famed as an abortifacient and was therefore the cause of poisoning. Used rarely, in doses of 2 drops, as a digestive. *Spiritus Myristicæ* (B.P.).

A number of other aromatic drugs are only rarely prescribed by physicians, but still play a part as popular and household remedies. They have been almost entirely deleted from the pharmacopœias. Some of these are as follows :—

Anthemidis Flores, from *Anthemis nobilis* (*Compositæ*), Western Europe; *Matricaria*, the flowers of *M. chamomilla*, a common weed of Central Europe and Russian Asia. Both these drugs are called chamomile, and are employed in the form of "tea" as a household remedy, internally as a diaphoretic and carminative, especially in meteorism and abdominal pain in little children; externally as a poultice. Both species contain a blue oil, *Oleum Anthemidis*.

Sambuci Flores (not official), elder-flowers, from *Sambucus nigra* (*Caprifoliaceæ*), Central and Southern Europe. A dessertspoonful to a teacupful of boiling water makes the popular "elder tea," used especially as a sudorific at the commencement of a cold; three or four cupfuls are drunk hot, and the sweating is promoted by warm coverings. The fragrant flowers of the lime, *Tiliæ Flores*, are also employed for this purpose.

(*b*) Malodorous Volatile Oils used as Nerve Remedies

Several malodorous drugs, of which *asafetida* and *valerian* are the most important, have long enjoyed a reputation for their soothing properties in conditions of nervous excitement, especially those of a "hysterical" nature. There is some difference of opinion as to the value of these drugs; a few observers consider the action not to be specific, but a consequence of the unusual and unpleasant odour (*cf.* the similar employment of animal substances with disagreeable odour, *e.g.*, castor), and quote, as an instance of the influence of smell, the behaviour of cats with regard to valerian.

Asafetida contains, besides gum and resin, several sulphur compounds, among these being a sulphide, $C_{11}H_{20}S_2$, to which it owes its disagreeable odour. Regarding its effects, it is sometimes stated that in addition to unpleasant symptoms from the alimentary canal, asafetida causes heaviness and pains in the head, and increased sexual desire, and sometimes that even very large doses have no particular effect. Trousseau took, for instance, ½ ounce (about 16 grammes) with no other result than that all secretions had acquired the odour of the drug, so that for two days he lived in a horrible atmosphere. Asafetida is now and then employed to control convulsions in hysteria. It is slightly aperient, and, like other drugs containing volatile oils, is credited with digestive powers ; it is little used on account of the nausea caused by the smell, and the malodorous flatus expelled. Tastes differ greatly, however ; for valerian was formerly used as a scent on handkerchiefs, and in Iran asafetida is a favourite condiment in daily use, supposed to counteract the inertia of the intestine caused by the very general custom in that country of taking daily a few centigrammes of opium.

Valerian is also an old remedy for hysteria and was, moreover, employed for many centuries for epilepsy, until the bromine preparations threw it, with other old epileptic remedies, into the shade. A sedative influence in ordinary nervousness is ascribed to valerian, and it is frequently given with bromide of potassium ; but these conditions yield so readily to suggestion that it is not possible to judge with certainty of the effects. It has been found by animal experiments that the volatile oil, which occurs in quantities of ½ to 1 per cent. and is supposed to represent in all essentials the action of the plant, in small doses causes excitement and heightened blood-pressure, while large doses paralyse the central nervous system, lower the blood-pressure, and so reduce the reflex irritability that even strychnine convulsions can be suppressed ; the latter result is only attained by enormous quantities. The volatile oil of valerian contains borneol—which differs in action from ordinary camphor in that it paralyses and diminishes reflexes—and esters of this camphor—with formic, acetic and valerianic acids. According to Kionka's investigations, several such synthetically produced compounds exhibit, like the amide of valerianic acid, effects similar to those of the rhizome, and they are now suggested as substitutes for the variable drug.

Preparations and Doses

Asafetida (B.P.), *Asafœtida* (U.S.P.), the gum-resin obtained by incision into the root of species of *Ferula* (*Umbelliferæ*), plants indigenous to Iran

and adjacent countries. Contains 3—9 per cent. of volatile oil, has a bitter, acrid taste, and a garlic-like and, as the name implies, very disagreeable odour. *Dose*, 3—10 decigrms., 5—15 grs. (B.P.); 0·4 grm., 6 grs. (U.S.P.). When the taste or the offensive eructations occasion difficulties, may be given as an enema in doses of 2—4 grms.

Tinctura Asafetidæ (B.P.). *Dose*, 2—4 mils, ½—1 fl. dr.

Pilula Aloes et Asafetidæ (B.P.), 30 per cent. of aloes, 30 per cent. of asafetida. Has a laxative action. *Dose*, 25—50 centigrms., 4—8 grs.

Emulsum Asafœtidæ (U.S.P.), 4 per cent. *Dose*, 15 mils, 4 fl. dr.

Valeriana (B.P., U.S.P.), the rhizome of *V. officinalis* (*Valerianaceæ*), closely wound round with numerous slender rootlets. A native of Europe and Siberia. *Dose*, 0·3—1 grm., 5—15 grs. (B.P.). 0·75 grm., 12 grs. (U.S.P.). Is often prescribed as a 10 per cent. infusion, 1 tablespoonful to be taken a few times daily.

Tinctura Valerianæ (U.S.P.), 20 per cent. *Dose*, 4 mils, 1 fl. dr.

Tinctura Valerianæ Ammoniata (B.P.). *Dose*, 2—4 mils, ½—1 fl. dr.

Sumbul, musk root, the rhizome and root of *Ferula Sumbul* (*Umbelliferæ*), has a bitter taste and a strong musk-like odour. Is used as a sedative with the same indications as valerian.

(c) Volatile Oils used as Genito-urinary Disinfectants

Copaiba, cubebs and **oil of sandalwood** are the most important of a class of drugs containing essential oils that are rich in volatile and easily-absorbed terpenes and terpene alcohols; they are excreted in part through the lungs, but principally through the kidneys in combination with glycuronic acid. These compounds render the urine antiseptic, so that it can stand for some time without acquiring an offensive odour; and when at last it becomes infected, the growth consists principally of mould-fungi, while bacteria are comparatively few in number. Copaiba and cubebs also contain resinous acids, but opinions differ as to their share in the action; they are more locally irritant, and are considered by some to be as important as the terpenes. They are also excreted to some extent in the bronchi, where they are supposed to act by diminishing the secretion and as antiseptics. When nitric acid is added to the urine, they are precipitated in a white layer which may resemble albumin. Diagnostic errors may be avoided by adding alcohol, which dissolves resin but not albumen. The reducing action of the urine after the use of these drugs is due to the glycuronic acid compounds.

Large doses of copaiba, etc., produce great irritation of the urinary passages, pain in the kidneys, albuminuria, painful micturition, and retention. If the mucous membrane is already inflamed, these symptoms make their appearance all the sooner.

Other secondary effects due to the irritant properties are unpleasant gastric and intestinal symptoms, such as cardialgia, disagreeable-tasting eructations, and diarrhœa. Oil of sandalwood

has the advantage of disturbing the digestion least. Various skin-eruptions (roseola, urticaria, pemphigus) also occur, and are ascribed to the excretion of irritating constituents through the skin.

Therapeutic Uses. Copaiba and allied drugs are employed for bacterial inflammation of the urinary passages, principally in *gonorrhœal urethritis* and *cystitis*. They are prescribed in gonorrhœa only when the worst inflammatory symptoms are over and the disease has entered upon its sub-acute or chronic stage. An attempt to begin at once with " balsams " often increases the symptoms of irritation. The importance of these drugs lies in the circumstance that the whole mucous membrane is being incessantly bathed in a weakly antiseptic urine. The antiseptics introduced from without (injection) are, indeed, generally stronger, but they are more quickly washed out again.

Other species of the genus *Piper* are also employed for gonorrhœa, viz., *P. angustifolium*, whose leaves, *Matico Folia*, are used principally in France, and *P. methysticum* (kava), the rhizome of which contains two kinds of resin which have local anæsthetic properties, and are famed for their analgesic action in urethritis.

Several other volatile oils and drugs have a slightly irritant action upon the renal epithelium, thus producing an increased flow of urine, and they are sometimes employed for this purpose. Since the discovery of the diuretic purine derivatives, caffeine, theobromine, etc., the employment of volatile oils has been greatly restricted. Among the more important are *oil of turpentine*, which is more generally used for other purposes and will be mentioned under skin-irritants, *oil of juniper*, in which the action of the terpenes is supported by organic alkali salts, and *oil of parsley*, which is obtained from the fruit of the common culinary parsley.

Preparations and Doses

Copaiba (B.P., U.S.P.), a yellow to golden brown, viscid oleo-resin with disagreeable taste, obtained by incision in the trunk of South American species of *Copaifera* (*Leguminosæ*). Contains 40—60 per cent. of volatile oil, and several amorphous and crystalline resins. *Dose*, 0·6—2 mils, 10—30 mins. (B.P.); 1 mil, 15 mins. (U.S.P.). Is given best in gelatine capsules or as pills.

Oleum Copaibæ (B.P.C.), the oil distilled from copaiba, and thus containing no resins. *Dose*, 3—12 decimils, 5—20 mins.

Cubeba (B.P.C.), almost black, reticulated, wrinkled fruit of *Piper Cubeba* (*Piperaceæ*), a climbing bush, indigenous to Java, Sumatra and Borneo. *Dose*, 2—4 grms., 20—60 grs. Prescribed as powders.

Oleum Cubebæ (B.P.C.). *Dose*, 3—12 decimils, 5—20 mins. Given in gelatine capsules or on sugar.

Matico (not official), the thick, reticulate-veined leaves of *P. longifolium*, South America. *Dose*, 0·5—2 grms., 8—30 grs. as powders 3 or 4 times a day, or as a 10 per cent. infusion by the tablespoonful.

Oleum Santali Australiensis (B.P.), **Oleum Santali** (U.S.P.), a yellow oil with a disagreeable taste, but, when greatly diluted, an odour almost like that of roses. Obtained by distillation from the wood of *Santalum album* (*Santalaceæ*), East Indies. Contains two terpene alcohols, santalol and santalal, 90 per cent. in all. *Dose*, 3—10 decimils, 5—15 mins. (B.P.); 0·5 mil, 8 mins. (U.S.P.). Given as drops upon pieces of sugar, or in gelatine capsules.

The following are non-official: *Santyl*, a salicylic acid ester of santalol; *Salosantal*, a salol solution in oil of sandalwood; *Gonosan*, a kava resin solution in oil of sandalwood. These are all oily liquids, and are taken in doses of 20—30 mins. 3 times a day.

Buchu (B.P.), the leaves of *Barosma betulina*, of the order *Rutaceæ*, South Africa. The leaves are stiff and denticulated, and are furnished with oil-glands. *Dose*, 1—2 grms., 15—30 grs.

Infusum Buchu Recens (B.P.). *Dose*, 30—60 mils, 1—2 fl. oz. *Infusum Buchu Concentratum* (B.P.). *Dose*, 4—8 mils, 1—2 fl. dr.

Tinctura Buchu (B.P.). *Dose*, 2—4 mils, ½—1 fl. dr.

Oleum Juniperi (B.P., U.S.P.), distilled from the ripe fruit of *Juniperus communis* (*Pinaceæ*), a shrub that is distributed throughout the north temperate zone in Europe, Asia and America. The round, almost black berries also contain a considerable amount of sugar. By fermenting and subsequent distilling, gin is produced. *Dose*, 3—18 centimils, ½—3 mins. (B.P.); 0·2 mil, 3 mins. (U.S.P.).

Spiritus Juniperi (B.P.C.), 10 per cent. *Dose*, 3—12 decimils, 5—20 mins. Used alone or as an addition to diuretic mixtures.

Petroselinum, parsley seed, the fruit of *P. sativum* (*Umbelliferæ*), a native of the Mediterranean region, and a widely-distributed garden herb. A favourite diuretic with laymen is 1 teaspoonful to a breakfastcupful of hot water.

5. BITTERS

By *bitters* is understood, in medicine, various vegetable substances which have no marked property except those of tasting bitter and of having, in the ordinary small doses, no absorptive action. They are often non-nitrogenous, beautifully crystallising substances, and several are easy to produce in pure condition; but little is known of their constitution. They are probably of very varied nature. Some are glucosides or alkaloids.

Action. The custom of employing bitter vegetable substances for stimulating the appetite and promoting digestion is very old and long-established in all parts of the world; but the knowledge of their mode of action is imperfect, and the results of the numerous attempts to explain it are extremely conflicting. It is only recently that the ancient custom has found an explanation in animal experiments, though of a different kind from that expected.

Gastric Secretion. All bitters produce increased secretion of saliva, and the original view was that upon reaching the stomach they would act in the same way. According to Moorhead's experiments with dogs (1915), however, this does not appear to be the case. In order to resemble the cases that are met with in practice, the animals were first, by repeated blood-letting, reduced to a cachectic condition, of which some of the evidences were general weakness, want of appetite, and impaired gastric functions. In this condition the result of the administration of bitters was a considerable increase in the amount of gastric juice, and in its total acidity and contents of free hydrochloric acid. To obtain this result it was sufficient, however, for the bitter to come in contact with the mucous membrane of the mouth. If this were evaded by introducing the bitter by stomach-tube directly into the stomach, there was no effect. It would thus appear to be the bitter taste that determines the action and, by some reflex path, arouses the activity of the gastric glands. This is in accordance with earlier experiments by Pawlow, who demonstrated the great significance of taste-impressions upon dogs with œsophageal fistulæ ; food placed in the mouth of the experiment-animal produced abundant gastric secretion, although none of the food reached the stomach, as it passed out through the fistula. In healthy animals, Moorhead saw no effect upon the amount or character of the gastric juice, no matter how the bitter was administered. Thus the normal function at its best could not be improved, an experience that often repeats itself (digitalis and camphor have no effect upon the sound heart, nor antipyrine upon the normal temperature).

Investigations of the **motor conditions of the stomach** have given varying results. In dogs, according to Heubner, small doses answering to those employed in medicine seem to hasten its evacuation. Jodlbauer found a good effect upon secretion and absorption in the **small intestine.**

The counting of the **blood-corpuscles** in both normal and anæmic persons before and after the taking of small doses of various bitters shows a corresponding increase both of white and red corpuscles. In animals, too, Pohl found a large increase in the number of white blood-corpuscles, perhaps a greater emigration of leucocytes from the lymphoid tissue of the intestine, indicating a cellular transfer of nutrition.

In small doses, as already mentioned, bitters have no noticeable specific effect. Nothing can be said of the general effect of large doses, as these substances, being exceedingly heterogeneous bodies, with only their bitter taste in common, act, after absorption, each in its own way.

Therapeutic Uses. The most important field for the activity of bitters, as shown both by experiments and by clinical experience, is that of *dyspeptic disorders*, which diminish the secretory activity of the stomach and produce the numerous characteristic morbid symptoms—want of appetite, oppression and eructation after meals, irregular evacuations, hypochondriacal frame of mind, etc. As *convalescence after weakening illnesses* and *anæmia* are often the cause of unsatisfactory gastric functions, bitters are frequently used in such conditions. By improving the digestion, they may indirectly remedy the anæmia, etc., and for that purpose are often given with iron medicines, choice being made of such as contain little or no tannic acid. Although bitters, unlike volatile oils, are not local irritants (*i.e.*, do not induce hyperæmia and inflammation), they appear, in acute inflammation of mucous membrane, to do harm rather than good, and are then to be avoided.

Lay opinion all the world over ascribes a febrifuge action to bitters, a supposition which entirely lacks foundation.

The bitters may be divided into three groups, namely, *simple bitters*, of which bitter principles are the active constituents; *astringent bitters*, which also contain tannin; and *aromatic bitters*, in which the bitter principle is accompanied by a volatile oil.

The most important members of the first group are **Gentian, Quassia** and **Calumba.** The first of these, which is the most frequently employed of all the bitters, contains, in addition to a considerable amount of sugar, the very bitter glucoside, *gentiopicrin*. *Quassia* is poisonous to many insects, and is employed as an insecticide in agriculture. Very large doses have been found to produce faintness and confusion of mind in man. *Calumba* contains mucilaginous substances, starch and no less than three bitter alkaloids that are allied to the alkaloid *berberine*, which is also found in many other plants, *e.g.* the common barberry (*Berberis vulgaris*), *Hydrastis Canadensis*, and *Podophyllum peltatum*. By these constituents the root acts both as a bitter and as a mucilage, in the latter character with a constipating effect on diarrhœa.

Cascarilla contains a large amount of resin (15 per cent.), volatile oil, the crystalline bitter *cascarillin*, and *tannic acid*. Its action is, therefore, somewhat astringent, and it is employed for diarrhœa, generally together with opium. In over-large doses it produces nausea and vomiting. Like many allied drugs, cascarilla bark is also a discarded fever remedy.

The most important of the aromatic bitters, though not medically so, is the **hop,** which gives to beer its refreshing bitter taste. The aroma of the hop arises from a volatile oil, occurring

in small quantities in the glands of the bracts, its bitter taste from crystalline bitters. The hop was formerly credited with a sedative effect, especially on the genital organs in man, and given in cases of frequent emission, painful erections, etc., but with doubtful benefit. Experiments with enormous doses (30 grammes) on healthy subjects had no effect. The soporific property of beer must be ascribed to its alcohol.

Absinth (vermouth, wormwood) is obtained from the flowering tops and leaves of *Artemisia absinthium*, belonging to the order *Compositæ*, and contains a green volatile oil and the bitter *absinthin*, its chief importance being that it is an ingredient in the well-known absinth liqueur. In animals small quantities of the volatile oil produce slight muscular twitchings, and large doses convulsions of an epileptic character, the oil being thus responsible for the epileptic attacks which complicate the chronic alcoholism of habitual absinth-drinkers. The manufacture of the liqueur is now prohibited in Belgium, Holland, France and Switzerland, and its importation into the United States. Medicinally, absinth was formerly frequently employed as an emmenagogue, a febrifuge and an anthelmintic, an evidence of the last-named use being found in the name "vermouth" (vermis = worm); but it is now little used.

A drug that may be mentioned here, though not containing any real bitter, is *Coto*, the bark of an unknown Bolivian tree. The active constituent is the crystalline, pungent cotoin, which in small doses lowers the tone of the intestine and weakens the movements, and in large doses produces complete relaxation of the entire intestinal musculature. In South America, coto-bark is an ancient intestinal astringent, and also, according to recent European experience, deserves attention as a peculiar remedy that is sometimes very efficacious in chronic diarrhœa.

A recent therapeutic ally of the bitters is a synthetically-produced quinoline derivative, phenyl-dihydroxy-quinoline, introduced into medicine by Penzoldt under the name of *Orexine*. It is said to act in many cases of anorexia by causing a feeling of hunger. This action is probably due to irritation of the gastric mucous membrane. Orexine is contra-indicated in nephritis, gastric ulcer and fever. For the vomiting of pregnancy it should be given a trial, as it sometimes quickly causes the vomiting to cease.

Preparations and Doses

Gentiana (B.P., U.S.P.), the rhizome and root of *G. lutea* (*Gentianaceæ*), Switzerland. Long, almost cylindrical pieces up to 3 cm. in thickness, and of a reddish brown colour. *Dose*, 0·6—2 grms., 10—30 grs. (B.P.); 1 grm. (U.S.P.).

Extractum Gentianæ (B.P.), a soft extract, much used as an excipient for pills. *Dose*, 12—50 centigrms., 2—8 grs.

Tinctura Gentianæ Composita (B.P., U.S.P.), containing gentian, bitter orange peel, and cardamom. *Dose*, 2—4 mils, ½—1 fl. dr. (B.P.); 4 mils,

1 fl. dr. (U.S.P.), or 1 teaspoonful in a wineglassful of water ½ hour before meals as an appetiser.

Infusum Gentianæ Compositum Recens (B.P.), containing gentian, bitter orange peel, and lemon peel. *Dose,* 15—30 mils, ½—1 fl. oz. *Infusum Gentianæ Compositum Concentratum* (B.P.). *Dose,* 2—4 mils, ½—1 fl. dr.

Quassia (B.P., U.S.P.), yellowish white chips or raspings of the wood of *Picræna* (*Picrasma*) *excelsa* (Jamaica quassia). *Dose,* 0·12—0·5 grm., 2—8 grs.

Infusum Quassiæ Recens (B.P.). *Dose,* 15—30 mils, ½—1 fl. dr. *Infusum Quassiæ Concentratum* (B.P.). *Dose,* 2—4 mils, ½—1 fl. dr.

Tinctura Quassiæ (B.P., N.F.). *Dose,* 2—4 mils, ½—1 fl. dr. (B.P.); 2 mils, 30 mins. (N.F.).

Calumba (B.P.), calumba root, circular or oval yellow slices of the root of *Jateorrhiza calumba, Menispermaceæ,* growing in the coast regions of South-East Africa. *Dose,* 0·6—2 grms., 10—30 grs.

Tinctura Calumbæ (B.P.). *Dose,* 2—4 mils, ½—1 fl. dr.

Infusum Calumbæ Recens (B.P.). *Dose,* 15—30 mils, ½—1 fl. oz. *Infusum Calumbæ Concentratum* (B.P.). *Dose,* 2—4 mils, ½—1 fl. dr.

Taraxaci Radix (B.P.C.), dandelion root, the root of *Taraxacum officinale* (*Compositæ*), one of the most widely distributed of plants; in transverse section showing concentric rings, and yielding a milky juice in the spring. Contains a crystalline bitter substance. It is prescribed in the form of a tincture (2—4 mils) or an infusion (15—30 mils). Similar constituents are found in the nearly-related *Cichorium Intybus,* which yields the well-known coffee-substitute, chicory.

Like many other plants containing bitter, pungent substances, the dandelion, when young (*herba recens cum radice*) was used as one of the so-called spring cures so popular in former days. The juice of the fresh plants was expressed, mixed with water, and drunk early in the morning on an empty stomach during a walk—really a practical treatment of dyspepsia and chronic obstruction (*plethora abdominalis*), the effect being due partly to the bitter, aromatic herbs, and partly to the early rising and exercise it imposed upon the patient.

Cascarilla (B.P.C.), small, externally pale grey pieces of the bark of *Croton eluteria* (*Euphorbiaceæ*), a native of the West Indies. Prescribed as—

Tinctura Cascarillæ. Dose, 2—4 mils, ½—1 fl. dr.

Infusum Cascarillæ. Dose, 15—30 mils, ½—1 fl. oz.

Several species of *Citrus* contain, besides volatile oils (see the preceding chapter), the bitter glucoside hesperidin. The following preparations are official:—

Aurantii Cortex Recens and *Siccatus* (B.P.), *Aurantii Amari Cortex* (U.S.P.), orange peel from a bitter variety of *Citrus aurantium.*

Tinctura Aurantii (B.P.), *Tinctura Aurantii Amari* (U.S.P.). *Dose,* 2—4 mils, ½—1 fl. dr. (B.P.); 4 mils, 1 fl. dr. (U.S.P.). *Infusum Aurantii Recens* (B.P.). *Dose,* 15—30 mils, ½—1 fl. oz. *Infusum Aurantii Concentratum* (B.P.). *Dose,* 2—4 mils, ½—1 fl. dr.

Coto Cortex, heavy, almost flat pieces of reddish brown bark with an odour resembling that of camphor. Either the pulverised bark is given—0·5—1 grm., 8—15 grs. for adults, 0·12—0·25 grm., 2—4 grs. for children—or *Tinctura Coto,* 15—30 mins. for adults, 5—10 mins. for children, about 4 times a day. *Cotoin,* yellow crystals, sparingly soluble in water, has also been tried in doses of 5—8 milligrms., $\frac{1}{1\frac{1}{2}}$—⅛ gr., every other hour.

Orexinum Tannicum, orexine tannate, a yellow, tasteless powder,

insoluble in water. *Dose*, 0·3 grm., 5 grs., up to three times a day, 1 hour before meals.

The above-mentioned drugs are sufficient for all medical requirements, but all the pharmacopœias, as in the case of the volatile oils, have, besides, a number of superfluous drugs, partly a reminiscence of the fancy of bygone days that an intensely bitter taste indicated great activity in other directions too. The names of a few of these easily dispensed with drugs are here given. The South American *Condurango Bark*, about the year 1870, became famed for its power of healing cancer of the stomach, and is still official in several European pharmacopœias, but has shown that it only acts like other bitters. *Berberis* contains the alkaloid berberine, which is also found in Hydrastis and several other plants. *Serpentaria* (B.P., U.S.P.), snake-root, contains a bitter substance and an alkaloid. *Dose*, 0·05—0·1 grm., ¾—1½ grs. (B.P.). *Angostura Bark*, the bark of *Galipea officinalis* (*Rutaceæ*), Venezuela, contains bitters and a volatile oil, and is used in the manufacture of a well-known stomachic and popular anti-dyspeptic, Angostura bitters.

6. SKIN-IRRITANTS

By the term "skin-irritants" is understood such drugs as produce irritation and inflammation of the skin, and thereby act upon diseases in more deeply-seated organs, or more rarely in the skin itself. They possess both local and remote action.

The **local action** may be of very varied character and pass through every stage, from slight hyperæmia to deep suppurative inflammation. How far the action goes depends upon various circumstances, such as the chemical properties of the drug, the concentration in which it is employed, the time given it to act, and the sensitiveness of the skin. The rapidity with which the effect begins is mainly determined by the volatility of the drug; if its vapour easily penetrates the skin, the symptoms may appear almost immediately, although a few substances, even when volatile, only act after a long incubation-period.

The regular development is as follows: The first change that occurs is great injection of the skin, heat and a feeling of pricking and itching; more rarely, intense, burning pain is felt, the intensity being generally proportional to the rapidity of the action. The rapidly-acting volatile substances may even in the course of a few minutes produce almost intolerable smarting, while the slower-acting drugs may continue right on to deep inflammation without any great pain. The vaso-dilatation at first affects the more superficial capillaries situated in the papillæ, afterwards also the deeper arteries in the skin and the subcutaneous tissue. This is due to a reflex produced by the sensory nerves, either an axon reflex or one passing through the centre. If the irritant be now removed—drugs that are used only until this stage is reached are called *rubefacients*—the injection soon disappears and the skin

returns to its normal condition, although the pain may still continue for many hours. If the drug be allowed to act further, serum begins to exude, to collect between the papillary layer and the epidermis, and to raise the latter; little vesicles filled with a clear fluid are formed, which gradually run together into a large bulla covering the whole of the area to which the irritant was applied. After the large blister has stood for some time, its contents are no longer quite clear, but slightly yellow because the diapedesis of leucocytes has begun. At this point the action is often interrupted—drugs that are employed until a blister is formed are termed *vesicants*—the blister is snipped to let the serum run out, and the distended epidermis sinks together like a wrinkled membrane. Beneath this protective covering the epithelium is rapidly renewed. The healing is accomplished without leaving any scar, but not without a lasting mark, as numerous new pigment-granules appear in the papillary layer, forming brown areas that many years after indicate the place on which a vesicant has been applied.

If a blister be allowed to lie longer than the time when this effect has been attained, deeper changes take place, of which, however, use is now seldom made. The vesicles acquire a yellower colour, and at last their contents assume the character of pure pus. The purulent infiltration extends downwards into the corium and the subcutaneous fat, and the ultimate result is a suppuration which destroys to a greater or less extent the papillæ and the deeper layer of the skin. This does not heal without leaving a scar.

Irritants that are unable to pass through the stratum corneum, and can only penetrate it by the openings of the glands, or are themselves inert and only converted into active compounds by the secretion of the cutaneous glands, do not elicit the above-described diffuse inflammation, but cause circumscribed infiltrations, small, slowly-forming, deep red papulæ, and later variola-like pustules, which leave white, depressed scars. With prolonged use of the irritant, large abscesses form from the coalescing of many small pustules; and these do not heal without considerable loss of substance.

Remote Effects. All irritation affecting the surface of the skin is transmitted to the central nervous system, and thus produces vaso-motor changes and alteration in the heart-action and the respiration, varying according to the intensity of the irritation.

With regard to the **circulation** Naumann has found that slight irritation of the skin causes extensive vaso-constriction, especially in the skin (this, of course, not applying to the area actually irritated), heightened blood-pressure, and accelerated heart-action,

with rise of temperature within the body. With great irritation, vaso-dilatation soon follows the initial constriction, with reduced blood-pressure, and, as a consequence of the cooling of the blood in the surface vessels, a fall of temperature. It is doubtful, however—according to Jacobson's comprehensive clinical experiments—whether these vaso-motor changes, in man, affect large parts of the vascular system when the irritants are applied to very limited areas. Jacobson found no changes worth mentioning in either temperature or blood-pressure.

Respiration. Sudden, powerful impressions upon large areas of the skin (cold shower) cause, in man, a momentary arrest of respiration followed by deep inspirations. Irritation of medium strength has a stimulating effect upon previously depressed respiration, and elicits inspiratory movements, an action which has long been known and utilised, *e.g.* in the treatment of the apparently drowned and asphyxia in new-born infants. In its employment in conditions of collapse there is also the advantage that great irritation of the skin acts upon the brain and may arouse consciousness.

Irritation of the entire surface of the skin, *e.g.* salt-water baths, increases the **metabolism.** Paalzow has shown that also mustard-plasters (in animals) cause an increased consumption of oxygen and excretion of carbonic acid, and other investigators that the elimination of nitrogen is also increased.

That skin-irritants can *promote the healing of adjacent inflammation* has been experimentally demonstrated by Wechsberg, who produced suppuration in the hind legs of rabbits by the injection of acrid substances, and then treating one leg with a skin-irritant, while leaving the other alone. It appeared that the abscess in the treated leg became smaller sooner and healed more quickly than that in the leg that had not been treated. It has long been thought that analogous clinical results could only be explained by the assumption that the hyperæmia in the treated region of the skin produced anæmia in the adjoining deeper parts ("diverting" treatment). This theory is untenable. The vaso-dilatation not only affects the surface, but extends to a considerable depth. The cause of the cure or improvement is now supposed to lie in the circumstance that the œdema produced and the greater flow of blood dilute the deleterious substance, facilitate absorption, and account for the presence of a greater number of alexins in the diseased tissue. Injected dyes were also more quickly removed by the aid of skin-irritants.

An irritation or inflammation of the skin often appears able to reduce *inflammation in deeper or more remote organs*, and to relieve the pain. An explanation of this remote action is perhaps fur-

nished by recent investigations of reflex phenomena. It is well known that in diseases of internal organs, pain and hyperæsthesia appear in limited, clearly-defined regions of the skin. Head has made investigations in diseases of numerous organs as to which were the hyperæsthetic spots for each organ, and found that there is a certain conformity and that the pain from each organ is, in the majority of cases, reflected to definite zones. It is a very plausible assumption that the effect of an irritation of the skin at one place, in the form of vaso-motor changes, or as an analgesic influence, may be transmitted in the opposite direction. An extended knowledge of the mutual connection between certain organs and certain skin-areas will furnish new guides to the points at which skin-irritants should be applied in various diseases, and perhaps show that it is not always right—as is now generally thought—to apply a poultice or plaster as near as possible to the diseased organ.

The above-mentioned zones have a developmental explanation. In the lower animals the body seems to be a fusion of a number of segments or sections, each of which forms a physiological unit, and possesses a certain independence as regards innervation, as the spinal cord consists of a corresponding series of segments, each supplying its body-section with motor and sensory nerves, which are connected with one another by a cord consisting of nerve-fibres. The same principle may be traced up to the higher vertebrate animals, and it is the remains of an original segmented structure—with the diversities consequent upon nerve-anastomosis and the displacement and unequal development of various organs—that is supposed to be found again in man in the regular projection of reflex pain and reflex hyperæsthesia.

Therapeutic Uses. The diseases most frequently treated with skin-irritants are those connected with *inflammation of serous membranes, e.g. pericarditis, meningitis*, and, above all, *pleurisy*. They are prescribed in dry pleurisy with the object of relieving the pain and counteracting the inflammation, and in serous pleurisy to procure the absorption of exudates of which the spontaneous disappearance is slow. The rule once laid down, and corresponding with that applying to the employment of astringents and all powerful irritants in inflammation of mucous membranes, namely, that vesicants and other similar drugs shall not be employed in the first and most acute stage of the disease, when the inflammation is greatest and the fever is at its height, has lost its validity, since clinical experiments have removed the anxiety lest the general condition and local affection should be influenced unfavourably by immediate counter-irritation (the temperature rises a little, however). Skin-irritants are also employed in *pulmonary diseases, e.g.* in *bronchitis* (turpentine poultice for a cold), particularly when there is dyspnœa, in

chronic infiltration (but not tuberculous) and in *œdema of the lung*. Their former employment in rheumatic fever has now been superseded by the salicyclic treatment.

A further important indication for irritants is *pain*. They seem to be most efficacious in *acute neuritis*, but alleviate pain also in many other cases. Pain often disappears or decreases (perhaps is only noticed less) when a new " vicarious " pain begins, no matter by what means the latter is produced. In pain or inflammation in large nerve-trunks, flying blisters are sometimes used, *i.e.* blisters applied along the path of the nerve, one after another, upon the spots that are tender to the touch. The employment of vesicants for nerve-pain is restricted, however, now that massage and electrical treatment have come to be known. One kind of pain that often disappears with a quickly-acting irritant is *cardialgia*. *Vomiting* can also be stopped with such treatment.

A general rule regarding drugs the use of which may produce a wound is that they shall not be prescribed when the nutrition of the skin is poor, as in enfeebled and aged persons and in diabetic patients. Cantharides especially, in such conditions, produces ulceration that does not easily heal. With infants there is no question of anything but the mildest drugs. A deeply-acting irritant must not be applied where only thin subcutaneous tissue separates the skin from underlying bone-substance, nor in places where scars or other marks would be disfiguring. It should be especially remembered with women that cantharides leaves permanent brown marks.

The selection of the right drug to prescribe in each case depends upon whether the benefit is to be expected from the pain produced by the drug, or from the inflammation of the skin. In cardialgia or vomiting, the instantaneously-acting oil of mustard is chosen, in pleurisy cantharidin, which, though not beginning to act for several hours, is more thorough in its action ; and between these two is oil of turpentine. The various skin-irritants will be mentioned below, grouped under these three types.

Oil of Mustard

Black mustard seeds contain the glucoside *sinigrin* and the ferment *myrosin*, which, on the addition of water, decomposes the glucoside into sugar, potassium hydrogen sulphate, and *volatile oil of mustard*, or allyl-isothiocyanate, C_3H_5NCS, and thus

$$C_{10}H_{18}KNS_2O_{10} = C_6H_{12}O_6 + KHSO_4 + C_3H_5NCS.$$

Before decomposition the glucoside is not irritant. When mustard-seed is chewed, there is at first only the taste of the fixed

oil, of which the seed contains more than 30 per cent. ; and it is only after half to one minute, when the decomposition has begun, that there is a burning sensation in the mouth.

Oil of mustard is the most rapidly-acting of all skin-irritants. It produces almost instantaneously redness and pricking pain, and soon after extreme hyperæmia, and smarting as intense as if molten metal were lying on the skin. A mustard plaster cannot therefore be applied to large regions of the skin at once, as the pain would be intolerable ; nor can it be kept on for a long time. Its action goes deep, for the light, volatile oil speedily penetrates to the deep layers of the skin, where it also sets up inflammation ; and when once vesicles have formed, they very often leave suppurating ulcers that are very slow in healing.

Mustard—that is to say, the powdered mustard-seed with the oil pressed out—is a much used condiment. A large internal dose produces violent irritation of the stomach and intestine, and acts as an emetic, for which purpose it may be used in an emergency.

The formerly popular *employment* of mustard-plasters and similar cruel methods of treatment are now very properly restricted, as the remedy is often worse than the disease. Mustard-leaves are now only rarely prescribed in *headache with congestion*, *obstinate cardialgia*, and *vomiting*. A hot foot-bath containing mustard is a gentler form of treatment.

Ordinary oil of mustard is often called allyl oil of mustard to distinguish it from many nearly-allied, sulphurcous volatile oils with similar action that are found in other garden herbs with a pungent taste, belonging to the *Cruciferæ*, *e.g. Cochlearia Armoracia* (*horse-radish*), *Raphanus sativus* (*radish*), and *Lepidium sativum* (*cress*).

Cochlearis officinalis, which is still official in some places, and has been tried as an anti-scorbutic, contains the isobutyl derivative answering to the oil of mustard and is formed in the same manner by fermentative decomposition of a glucoside. In the sister-plant of common mustard, *Brassica alba*, myrosin also occurs, but with another glucoside, sinalbin, which on decomposition yields a vesicant, non-volatile oil.

Preparations and Doses

Sinapis Nigra (U.S.P.), black mustard, the reddish brown seeds, of about the size of a pin's head, of *Brassica nigra* (*Cruciferæ*), growing in the north temperate zone of the Old World. *Dose*, as an emetic, 10 grms., 2½ grs. of the powdered seeds in tepid water ; external, a mixture of ordinary household mustard with 5—10 parts of flour, made into a thick paste with lukewarm water. Boiling water destroys the enzyme. For a foot-bath, about 100 grms. of mustard.

Emplastrum Sinapis (U.S.P.), mustard-leaf, deolcated, powdered black mustard in a solution of india-rubber, spread on paper, calico, cloth, or other fabric, is the most convenient form for use, dipped in warm water

and applied to the skin, where it remains for 15 minutes. The skin is well dried to remove the oil.

Oleum Sinapis Volatile (U.S.P.), a colourless or pale yellow oil, with a very pungent odour and acrid taste. *Dose*, 0·008 mil, $\frac{1}{8}$ min.

Emulsio Sinapis, contains 3·5 per cent. of the volatile oil.

Sinapis Alba, white mustard, the seeds of *Brassica alba*, a plant growing wild in Europe, Asia and Northern Africa. The seeds are rather larger than those of black mustard, and of a yellow colour. *Dose*, as an emetic, the same as of black mustard.

Armoraciæ Radix (B.P.C.), horse-radish root.

The Turpentine Group

In many species of *Pinus* and *Abies* there is a viscid oleo-resin which exudes from wounds made in the stem, and consists of resinous acids dissolved in terpenes. By distillation of this oleo-resin, *oil of turpentine* is obtained, the residue left being resin. Oil of turpentine contains a mixture of terpenes, $C_{10}H_{16}$, diterpenes, $C_{20}H_{32}$, and other hydrocarbons with the same formula but differing in their boiling-point and optical conditions.

Much that has been said about the **action** of the volatile oils applies to that of **oil of turpentine,** as many of the former consist in a great measure of terpenes.

A brief application ($\frac{1}{2}$—1 hour) to *unbroken skin* produces only redness and great burning; a longer application causes vesication. As a volatile liquid, oil of turpentine has in common with oil of mustard the property of penetrating the skin, and can therefore be employed only as a rubefacient and not as a vesicant, as the deep skin-inflammation and disturbance of nutrition may cause slowness in the healing of the sores left by the blisters.

The irritant effect is still greater on *mucous membrane*, and shows itself after large internal doses by the usual symptoms of acute gastro-enteritis.

The effect on the *mucous membrane of the respiratory tract*, as investigated by Rossbach and Fleischmann, is of special interest on account of its practical application. When air passed through oil of turpentine and thus saturated with its vapour, was blown upon a limited area of the tracheal mucous membrane, the secretion of mucus steadily decreased and at last entirely ceased, so that in that spot the membrane was perfectly dry. When the experiment was discontinued, the secretion soon recommenced. Control-experiments with ordinary air, carried out in the same way, showed that under the slightly irritant influence of the current of air the secretion of mucus increased, thus proving that the dryness observed during the first experiments must be due to the oil of turpentine. Clinical experience also goes to show that,

when given internally, oil of turpentine decreases the bronchial secretion. During excretion its action upon the *renal epithelium* is to somewhat increase the flow of urine.

Small quantities of oil of turpentine have no appreciable *general effect.* After the absorption of large quantities there is irritation of the central nervous system, heightened blood-pressure, rapid respiration, and increased reflex activity. Very large doses, *e.g.* a dessertspoonful, a tablespoonful, or more, produce drowsiness, sleep, unconsciousness, convulsions, and at last coma, although doses of even 120 grammes have been taken without proving fatal to adults. In children a fatal result has been known from 16 grammes (child of 14 months), and after a smaller dose (1 teaspoonful to a child of 18 months) symptoms appeared which resembled those of opium-poisoning, viz. narcosis, rattling respiration, contracted pupil, relaxation of all muscles, now and then interrupted by convulsions ; but the child recovered.

Oil of turpentine *is absorbed* very readily from the skin, the lungs, and the alimentary canal. It seems to remain for some time unchanged in the blood, and *is excreted* partly through the skin, where it may produce exanthemata, and through the lungs. The greater part, however, is excreted through the kidneys, in part unchanged, in part in combination with glycuronic acid. The well-known odour of violets that the urine acquires is probably due not to any newly-formed compound, but to unchanged oil of turpentine, for the same odour is obtained by simply agitating urine with oil of turpentine.

Therapeutic Uses. Oil of turpentine is employed **externally** with all the indications for skin-irritants mentioned in the introduction to this chapter, and they need not be repeated here. By itself (turpentine poultice) it is a very favourite remedy for *bronchitis, neuralgia* and all kinds of *rheumatic pains ;* with the addition of oil it forms a constituent of skin-irritant plasters, ointments and liniments, and some more or less useful industrial products (rheumatism paper, pine-needle wool), which owe their effect to the often trifling amount of turpentine they contain. In rheumatic affections, very diluted oil of turpentine is employed as a mild irritant for the skin of the whole body in the form of the popular pine-needles bath ; the effect of this is mainly due to the hot water. According to Billroth, its local employment on wound-surfaces may stop even profuse *bleeding.*

Internally, or for inhalation, oil of turpentine is prescribed for the purpose of decreasing and disinfecting the secretion in *bronchitis,* especially in catarrh of long standing, with abundant purulent and offensive-smelling secretion, both non-specific and tuberculous. It is also used in *gangrene of the lung. Neuralgia*

can be relieved, it is said, not only by the external use of oil of turpentine, but also by its internal use. In *biliary colic* it is employed in large doses either alone or mixed with ether (Durande's mixture). As a diuretic and anthelmintic it has been superseded by other drugs that are less irritating to the kidneys and the intestinal canal.

Oil of turpentine, like many other volatile oils, has the property, when exposed to the air, of taking up oxygen and forming from it hydrogen peroxide and organic peroxides (not ozone). Old oil of turpentine is therefore a powerful oxidising agent. Phosphorus that is moistened with it is oxidised to phosphorous acid, and loses its power of shining in the dark. Upon this foundation, old oil of turpentine (known by the bleached cork of the bottle) is used in *acute phosphorus poisoning*, with the object of oxidising the phosphorus still unabsorbed in the stomach to the non-poisonous phosphorous acid and other oxygen compounds. (See also "Sanitas"—Preparations and Doses.) Freshly distilled oil of turpentine, on the contrary, will in all probability only do harm, as it dissolves the phosphorus and thus assists in its absorption. Oil of turpentine has no effect upon the phosphorus already absorbed.

After standing for a long time in water, or better still by treatment with alcohol and nitric acid, oil of turpentine takes up 3 molecules of water and is converted into the crystalline **terpine hydrate**, which has the advantage over the volatile oil of having only a faint taste and odour. It is employed in *bronchitis*, and of late also as a diuretic in *dropsy in heart and kidney diseases* with variable results. As its diuretic action is solely due to irritation of the renal epithelium, it is well to exercise caution, *i.e.* by frequent examination of the urine.

From numerous species of *Pinus*, *Abies*, *Larix* and *Juniperus*, volatile oils are obtained which differ from one another in the different terpenes they contain, but have the same pharmacological action as the ordinary oil of turpentine, with the one exception that some are more irritant. The strongest action belongs to the *oil of savine*, which is obtained by distillation from the young branches of *Juniperus Sabina*. In large doses it sets up intense inflammation of the stomach and intestine, irritation of the kidneys (hæmaturia) and great congestion of all the abdominal organs, and causes menorrhagia and abortion. In several countries savine has toxicological interest as a frequently employed abortifacient, its abuse for this purpose having caused a good many fatal cases of poisoning. The symptoms are unconsciousness, convulsions, coma, followed by death after several days have elapsed.

Two gum-resins, **Ammoniacum** and **Galbanum,** contain volatile oils with slight turpentine action, and have been employed internally in catarrh of the respiratory and urinary passages.

Galbanum was further credited with some action on the uterus, and was esteemed as an emmenagogue.

Preparations and Doses

Oleum Terebinthinæ (B.P., U.S.P.), oil of turpentine, distilled from various species of *Pinus*. Employed externally for inunction or poultice (flannel wrung out of hot water and sprinkled with oil of turpentine). In ¾—1 hour vesication has almost begun, and the poultice is removed. If it is to be retained for a longer time, equal parts of a fixed oil are added, which weakens the action.

Oleum Terebinthinæ Rectificatum (B.P., U.S.P.) is employed both externally and internally. *Dose*, 12—60 centimils, 2—10 mins.; as an anthelmintic, 12—15 mils, 3—4 fl. drs. (B.P.); 0·3 mil, 5 mins. (U.S.P.). For inhalation, 1 teaspoonful on the bedclothes, or in a cupful of boiling water. *Emulsum Olei Terebinthinæ* (U.S.P.), contains 15 per cent. of oil of turpentine. *Dose*, 2 mils, ½ fl. dr.

Linimentum Terebinthinæ (B.P., U.S.P.), for inunction.

Linimentum Terebinthinæ Acidum (B.P.) contains about 10 per cent. of glacial acetic acid.

Terebenum (B.P., U.S.P.), terebene, obtained by shaking up oil of turpentine with concentrated sulphuric acid. *Dose*, 3—10 decimils, 5—15 mins. (B.P.); 0·25 mil, 4 mins. (U.S.P.). Has a rather agreeable aromatic odour, and is therefore pleasanter to inhale. The same may be said of the two following oils:—

Oleum Abietis (B.P.), the oil of the Siberian fir, *Abies Sibirica*.

Oleum Pini Pumilionis (U.S.P.), from the dwarf pine, *Pinus pumilio*, growing in the mountain districts of Central Europe.

Terpini Hydras (U.S.P.), terpine hydrate, $C_{10}H_{18}(OH)_2 + H_2O$, colourless crystals with only a slight taste and odour, sparingly soluble in water. *Dose*, 0·25 grm., 4 grs.

Colophonium (B.P.), *Resina* (U.S.P.), resin, colophony, is the residue left after distilling the oil of turpentine from oleo-resin.

Emplastrum Colophonii (B.P.), adhesive plaster, lead-plaster with resin added to make it adhere. *Emplastrum Adhæsivum* (U.S.P.), a mixture of rubber, resins, waxes and absorbent powder.

Ceratum Resinæ (U.S.P.).

Terebinthina Canadensis, Canada balsam, is the oleo-resin obtained from *Abies balsamea*, a native of Canada. Its peculiarity is that the resin does not crystallise, but after the evaporation of the terpenes is left in a transparent, amorphous condition, and is therefore well adapted for the mounting of objects for the microscope.

Sanitas. The potency of this disinfectant depends upon the fact that oil of turpentine can be oxidised in the presence of water to terpene hydrate, hydrogen peroxide and camphoric acid.

Cantharidin

The active constituent of the Spanish fly and of certain other beetles is *cantharidin*, $C_{14}H_{12}O_4$, a white, crystalline substance which is the anhydride of cantharidic acid, an acid not known in a free state.

Action. Cantharidin has a very powerful action. Even $\frac{1}{10}$ milligramme dissolved in oil produces vesicles. The *inflammation of the skin* nevertheless appears slowly, and the pain is moderate. As a solid, non-volatile substance the cantharidin only comes in contact with the superficial cuticle, and therefore the vesicles formed heal quickly and without forming scars. It is this property, energetic and yet superficial action, that makes cantharides so suitable as a vesicant, as opposed to the previously mentioned volatile substances which penetrate too readily into the deeper layers of the skin. On the other hand, if powdered cantharidin comes in contact with skin that has lost its epidermis, very great inflammation is produced, necrosis and prolonged suppuration.

Cantharidin *is absorbed* through the skin and mucous membranes, but from an ordinary cantharides plaster only in very small quantities, and circulates in the blood in such a dilute condition that it produces no general effect. It is only in *the kidneys*, where it is again excreted and is thus concentrated, that an irritation similar to that of the skin may be set up, revealing itself in frequent and somewhat painful micturition. This is often seen in children, and it forbids the use of cantharides in diseases of the kidneys. If the urine contains much cantharidin, acute nephritis comes on with pain in the region of the kidneys, great albuminuria and hæmaturia. Not only the bladder, but also the urethra becomes infected and inflamed, with consequent painful erections and increased sexual desire. An abuse is therefore made of cantharides as an aphrodisiac. In women the analogous condition (nymphomania) is less often seen. Serious cases of poisoning may cause abortion.

If cantharides in solution comes in contact with *mucous membranes*, the inflammation rapidly attains great intensity. Vesicles are formed in the mouth, throat, stomach and intestine ; in spite of great thirst, swallowing is impossible ; intense pain is felt in the abdomen, and vomiting, diarrhœa, dyspnœa, and sometimes delirium and convulsions ensue. Death may result with the usual symptoms of collapse. If there is recovery it is slow, owing to the considerable lesions of the mucous membrane.

The toxic gastro-enteritis is sufficient by itself to explain these general symptoms, but it is probable that cantharidin has also a direct paralysing action upon the *central nervous system*, as it is a benzol derivative, and the fatal poisoning symptoms resemble those of poisoning with carbolic acid and allied substances. From $1\frac{1}{2}$ to 3 grammes of cantharides, answering to about 0·07—0·15 gramme of cantharidin, is considered to be the lethal dose ; but there have been cases in which considerably larger doses have not caused death. The result in this, as in so many other kinds of poisoning, is dependent upon how soon the vomiting begins.

The large mammals that have been examined react like man to cantharidin, while several other animals exhibit the most remarkable immunity. Thus the hedgehog (average weight 600 grammes) can consume daily 30 grammes of living Spanish flies without succumbing, although the cantharidin is absorbed ; intravenous injection of 0·02 gramme has no effect upon either its general health or kidneys, and 0·045 only a slight toxic effect, with nephritis from which it soon recovers. Fatal inflammation of the kidneys only occurs after huge doses (Ellinger). The same is the case with fowls and ducks. Rabbits and white mice possess local immunity, but are killed by a few milligrammes. Among the lower animals the frog is insusceptible, and in pharmacies insect-larvæ feed upon Spanish flies with impunity.

Therapeutic Uses. Cantharidin is now only employed externally in the form of the vesicant preparations given below, for *inflammation of serous membranes*, especially *pleurisy*, and for *neuralgic and other pains*.

In 1891, Liebreich suggested subcutaneous injection of very small doses of potassium or sodium cantharidinate for lupus and tuberculosis, especially tuberculosis of the larynx. The cantharidin was to produce round the tuberculous foci a serous exudation, which in some way or other should either injure the bacilli, or, as Landerer has asserted with regard to cinammic acid (see p. 260), set up an inflammation leading to scar-formation, thus shutting off the disease. The treatment, which at one time attracted much attention, has now been abandoned, but has in any case shown how exceedingly sensitive man is to this poison, for it proved that even 0·1—0·2 milligrm. might cause both local irritation and irritation of the kidneys.

In cantharides-poisoning mucilaginous drinks are given to weaken the local action and retard absorption. If there is not sufficient vomiting, it is produced by injection of apomorphine, or lavage of the stomach may be performed. The pain is relieved by opium, and symptoms of collapse are treated in the usual way.

The crystalline vesicant, *capsaicin*, is obtained from **Capsici Fructus** (African pepper, cayenne pepper, chillies, used as a condiment), and with it a reddish brown oil with a very pungent taste and skin-irritant properties. Preparations of capsicum are employed externally for inunction to relieve pain, and for gargling in angina tonsillaris.

Many other substances resembling the above-mentioned in their action occur in the vegetable kingdom. Numerous species of *Ranunculaceæ* contain the highly irritant anemone camphor. The acid anhydride mezerein, of which even the smallest quantity produces great and persistent tickling in the throat, occurs in several species of *Daphne*, among them *Daphne Mezereum*, a tiny bush growing wild in Europe, with fragrant, bluish pink flowers, which bloom in early spring upon still leafless branches. Children have frequently been poisoned by eating the berries of this plant. Its bark when moistened raises blisters on the skin. To the same group belong the poisonous cardol, a reddish oil obtained from *Anacardium*

occidentale, and the interesting *toxicodendrol*, a glucoside that has not yet been produced in pure form, has only recently been isolated by Pfaff, and is the origin of the formerly mysterious, ulcerative dermatitis that *Rhus toxicodendron* and *venenata*—also *Anacardiaceæ*—frequently cause in North America. This substance is one of the most active of all known bodies; $\frac{1}{10}$ milligrm. applied to the skin of the fore-arm in Pfaff's experiments produced hundreds of vesicles and great œdema, $\frac{1}{200}$ milligrm. high inflammation, swelling of the entire fore-arm and pain, and even $\frac{1}{1000}$ milligrm. dissolved in 2 drops of olive oil occasioned itching, numerous vesicles, and some œdema. Another remarkable thing about it is that after the application of the poison there is an average latent period of 4 or 5 days before the inflammatory symptoms appear. The disease is best treated with a poultice of a saturated solution of lead acetate in 50—75 per cent. of alcohol. Similar malignant cutaneous inflammation is produced in predisposed persons by the favourite pot-plant, *Primula obconica*, also after an incubation-period lasting from a few to 14 days. The unknown poison is found in the secretion of the glandular hairs.

Preparations and Doses

The British pharmacopœial preparations are based upon cantharidin, those of the United States upon the Spanish fly itself.

B.P.

Cantharidinum, $C_{10}H_{12}O_4$, colourless, glistening, inodorous, crystals, soluble in chloroform and in fixed oils.

Emplastrum Cantharidini contains 0·2 per cent. of cantharidin. Its action is slow. During the first 2—4 hours there is only redness, and after 8—10 hours one or two large blisters corresponding to the size of the plaster are formed. The plaster is carefully removed so as not to break the epidermis, the blisters are snipped and emptied, and when all remains of the plaster have been removed with warm water or oil, an indifferent ointment is applied.

Liquor Epispasticus, blistering liquid, 0·04 per cent.

U.S.P.

Cantharis, Spanish fly, Russian fly, a beetle, *Cantharis vesicatoria*, which lives upon the leaves of various *Oleaceæ* and *Caprifoliaceæ* of Central and Southern Europe, and in some years, especially in Russia, appears in great swarms. The beetles are shaken down from the trees in the early morning while they are still torpid after the night's coolness, collected in bottles, and killed with ether, benzine, or oil of turpentine. They are of a beautiful metallic green colour, blue in the heat, and contain no less than 0·6 per cent. of cantharidin.

Ceratum Cantharidis.

Emplastrum Cantharidis is of approximately the same strength as the British preparation, and is employed in the same way (see above).

Tinctura Cantharidis. Dose, 0·1 mil, 1½ mins. Was formerly used as a diuretic, but has now fallen into disuse.

Capsicum (B.P., U.S.P.), cayenne or African pepper, chillies, the dried, elongated conical fruit of *Capsicum minimum* (B.P.) and *C. frutescens* (U.S.P.), *Solanaceæ*, natives of South America. *Dose*, 0·03—0·12 grm., ½—2 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.).

Tinctura Capsici (B.P.), 5 per cent.; (U.S.P.), 10 per cent. *Dose*,

3—10 decimils, 5—15 mins. (B.P.); 0·5 mil, 8 mins. (U.S.P.); for angina tonsillaris, ½ teaspoonful in a tumblerful of water as a gargle.

Unguentum Capsici (B.P.).

Piper, black pepper, the ordinary spice, is the unripe fruit of *P. nigrum* of Eastern Asia. Contains volatile oil, an acrid, amorphous substance, and the alkaloid piperine. Used in domestic medicine as a skin-irritant.

Oleum Chaulmoogræ (U.S.P.), Chaulmoogra oil, gynocardia oil, the fatty oil extracted from the seeds of *Taraktogenos Kurzii* (*Bixaceæ*), a native of South-Eastern Asia. Is a skin-irritant, and has recently been tried for leprosy, the results being reported as favourable but not lasting. *Dose*, 1 mil, 15 mins. Poisoning (gastro-intestinal irritation) has been caused by its employment in the manufacture of margarine.

Æthylis Chaulmoogras (U.S.P.), Ethyl Chaulmoograte. A pale yellow liquid with a characteristic fruity odour, insoluble in water, soluble in alcohol, ether and chloroform. Used as a substitute for chaulmoogra oil as it is less likely to cause gastro-intestinal upset. Value still *sub judice*. *Dose*, 1 mil, 15 mins., orally or intramuscularly.

The British Pharmacopœia contains the following remedies for the treatment of leprosy :—

Oleum Hydnocarpi (B.P.), obtained by expression from the seeds of Hydnocarpus Wightiana; a yellowish oil or fat with an acrid taste, insoluble in water, soluble in ether and chloroform. It contains the glycerides of chaulmoogric and hydnocarpic acids.

Oleum Hydnocarpi Æthylicum (B.P.), the ethyl esters of hydnocarpus oil. A faintly yellow oil with a characteristic odour and an acrid taste. *Dose* of both of the above preparations, 0·3—1 mil, 5—15 mins., gradually increasing to 4 mils, 60 mins.; by subcutaneous injection, 2 mils, 30 mins., gradually increasing to 5 mils, 75 mins.

The value of these preparations seems to be established, but care must be exercised in their administration. When given by mouth small doses should be used at first and gradually increased in order to avoid gastro-intestinal disturbances. They should be emulsified and suitably flavoured, or dispensed in gelatine capsules. For intramuscular injection these drugs may be mixed with olive oil and a small quantity of creosote and camphor added as anodynes. Injections are more effective than oral administration, but they must be continued for several months. As a result of this treatment there is a gradual retrogression of the various cutaneous lesions of leprosy. The mode of action of these drugs is not yet clear; it was formerly believed that their contained hydnocarpic and chaulmoogric acids exerted a specific toxic effect upon the leprosy bacillus, but this view is now disputed.

7. ASTRINGENTS

The Tannic Acid Group

The action of these drugs is built upon a property that is common to all of them, namely, *the superficial hardening of the tissues by the formation of insoluble compounds with albumin*. Chemically, the astringents may be divided into two groups: (1) salts of alumina and of many heavy metals, and (2) tannic acid substances. In all their principal features the action of these groups coincides,

the essential one being that in and around the cells there is formed, so to speak, a close, fine precipitate. For this reason lime-water also acts as an astringent, as from it the alkaline carbonates all over the tissues and free carbonic acid precipitate insoluble calcium carbonate ; and even chemically inert substances, such as talc, act to a certain extent in the same way when they are applied to a mucous membrane or a raw surface as fine powder. Among astringents in a narrower sense, however, are reckoned only substances that precipitate albumin, *i.e.* metallic salts and tannic acid substances.

The general remarks below apply to both these groups. The metallic salts will be discussed more fully elsewhere, and special mention will be made in this chapter only of the substances containing tannic acid. Under this head are included a great many widely-distributed vegetable substances which have the following characteristic properties in common : they behave as acids, precipitate protein from acid and neutral solutions, form fixed, invariable compounds with gelatinous tissue (tanning of hides, leather), and also precipitate most alkaloids and salts of heavy metals. Some tannic acid substances are compounds of gallic acid and sugar (*i.e.* glucosides) or phloroglucin, and many are little known chemically. They seem to occur in an infinity of varieties, and are called after their vegetable source—coffee-tannin, oak-tannin, kino-tannin, rhatany-tannin, etc.

Action. On mucous membrane, where astringents are most frequently applied, the action is as follows : Wherever such a substance comes in contact with the tissues, albumin is precipitated or coagulated. The surface cells lose their normal soft consistency and are transformed into a denser and more compact layer, which occupies less space than before. In the mouth these drugs elicit a feeling of constriction and the well-known astringent taste. The mucous membrane *shrinks* and becomes *pale*, as all small vessels are constricted, and hæmorrhage is arrested by the coagulation of the blood. The dissolved drug makes its way through the excretory ducts down into the glands, works changes in the secreting cells similar to those in the surface cells, and the secretion ceases ; the mucous membrane becomes *dry*. Most astringents also have a *slight local anæsthetic action*, perhaps by precipitating protein in the terminal expansions of the nerves. Finally, an important feature of the action is that the chemical change in the surface makes it an *unfavourable soil for bacteria*. As already mentioned, tanned hides (leather) resist putrefaction, and putrefying blood loses its smell and may be kept for weeks by the addition of a tannin solution ; and the metal albuminates also resist bacteria for a long time. In this way astringents may

often exhibit a more lasting antiseptic action than many of the actual antiseptics which act strongly for the moment, but are not fixed to the spot and are soon washed away again.

The above-described changes are produced only by bodies of which the action is confined to the surface. If the chemical effect goes deeper and leads to the complete destruction of the tissues and to visible loss of substance, the effect is called corrosion. Astringence and corrosion by substances that precipitate protein are thus not sharply-divided processes, but differ only quantitatively, so that the same substance can act as an astringent in a dilute solution and as a caustic in concentrated form.

The **general indications** for use are easily deduced from the above account of the nature of the action. The principal employment of astringents is in *catarrh of mucous membrane*, for the chief symptoms of this disease—swelling, injection and increased secretion—are exactly the reverse of the cardinal effects of the astringents—shrinking, pallor and dryness; and catarrh of mucous membrane is often caused by bacteria, the continued growth of which these drugs impede in the way described.

The entire nature of the action shows that the astringents are indicated, above all, in *chronic catarrh*. If, however, the process is beginning, and there are symptoms of great inflammation, the chemical change on the surface acts as an irritant and is responded to by the sensitive tissues with a strong reaction, expressing itself in increased swelling, injection and, most of all, pain. In acute inflammation, therefore, the employment of astringents is postponed until the symptoms of most violent irritation have subsided. A fresh conjunctivitis, for instance, is not at first treated with Goulard's water or zinc solutions; and in gonorrhœa a few days are generally allowed to pass before injections are prescribed. From the fact that the action rests upon the precipitation of albumin, it follows that astringents can only exert an influence on localities in which they come directly into contact with dissolved albumin; that is to say, only upon easily accessible wound-surfaces, mucous or serous membranes. In the intestine their activity is soon weakened or arrested, as they are fixed by the albumin in the intestinal contents, and thus prevented from reaching the epithelium. *Specific action* cannot, of course, occur, for substances that throw down albumin are either not absorbed, or in any case can only circulate in the blood in the form of compounds that no longer have an affinity for albumin, and therefore no astringent action.

Therapeutic Uses. As the action is associated solely with the behaviour towards albumin and gelatinous substances, and as in

this respect all tannic acid substances behave alike, it would appear to be immaterial which of them should be employed. Practically, however, there are small differences which make it advisable to make separate mention of some of the more important drugs.

Tannin has a bitter-sweet, astringent ("inky") taste, distinctly perceptible even in dilutions of 1 in 10,000. More concentrated solutions make the mucous membrane rough and dry and, as it were, tanned; the tongue feels stiff and not easy to move; taste is blunted, and the sensitiveness of the pharyngeal mucous membrane is diminished. In the stomach tannin combines with the albumin of the contents. If the doses are moderate, this action is not accompanied by unpleasant subjective symptoms. Larger doses produce more important changes (the emptier the stomach, the more easily do these take place) and give the mucous membrane a cracked, leathery appearance; such doses cause great pain, vomiting and diarrhœa, and sometimes prolonged and obstinate constipation due to the formation of hard masses of excrement and to the decrease in the intestinal secretion. With ordinary doses the influence of the tannin does not seem to extend far down into the intestine; its activity soon diminishes, both because alkaline tannates, which do not precipitate albumin, are formed in the intestine, and because tannin is very quickly converted into the non-astringent gallic acid, which is partly absorbed, partly excreted in the fæces. Tannin disappears so completely that, even after doses of 4 to 8 grammes, Mörner and Rost could not detect it in the fæces.

Tannin is absorbed sparingly and slowly as alkaline tannate and as tannin albuminate, which can pass through the intestinal wall, because it is soluble in an excess of albumin. After large doses, small quantities of gallic acid are sometimes, but by no means always, found in the urine. The remainder is converted into unknown products. The urine never contains tannin.

Therapeutic Uses. Tannin is used as an astringent for catarrh and inflammation upon directly accessible mucous membranes, as a mouth-wash and gargle in *stomatitis* and *angina tonsillaris*, for painting and inhalation in *chronic laryngitis* and *bronchitis* with plentiful secretion, for lavage in *inflammation of the urogenital mucous membrane*, and as enemata or for thorough irrigation in *catarrh of the large intestine* with profuse secretion. Washing out the intestine with several quarts of a weak tannin solution has been tried by Cantani for *cholera*. Poultices made with concentrated solutions are said to be useful in chronic *eczema*.

In recent years tannic acid has been used with striking success in the treatment of superficial burns. Its value lies in

the formation of a coagulum by the interaction of the astringent drug with the injured tissues. In this way toxic substances are "fixed" which would otherwise be absorbed. As a result of this action, the state of shock which was so frequently a late and fatal sequel to extensive burns is usually averted. Tannic acid treatment is also of some value in the relief of pain arising from the burns, and in the prevention of loss of excess of fluid and chlorides, but additional treatment of these conditions should not be neglected. The treatment consists in spraying the burned area with a freshly prepared aqueous solution of 2 per cent. tannic acid. Much stronger solutions, *e.g.* up to 20 per cent., have been used of late. The application must be repeated at intervals of about half an hour until a brownish-black pellicle forms. After about ten days the pellicle gradually separates and usually leaves a healthy granulating surface. Occasionally, however, it is necessary to remove the coagulum in order to permit drainage of pus.

Inunctions of tannic-glycerin is a practical hardening remedy for tender skin, and is employed as a prophylactic for *footsoreness* on long marches. As a local *hæmostatic*, tannin is efficient in small hæmorrhages, and is a milder, pleasanter remedy than the caustic ferric chloride. When taken internally, before it reaches the alimentary canal, the action becomes far less certain. Even in the stomach its hæmostatic action is unreliable and still more so in the intestine, where it will generally have disappeared, caught by all manner of irrelevant substances, and changed into inert compounds, before it reaches the bleeding vessel. It is sometimes employed for *dyspepsia combined with hyperacidity*, and not infrequently for *sub-acute and chronic diarrhœa* with or without ulceration; but here the disadvantage is that after a time it may easily produce dyspepsia. Tannin, or in its absence black coffee or strong tea (without cream, as the cream fixes the tannic acid), is a valuable *antidote* in *poisoning with alkaloids* (but not morphine, see p. 88), with *tartar emetic* and other *metallic salts*, which are precipitated by the tannic acid. This treatment can only be regarded, however, as a temporary remedy to be followed by more thorough treatment (washing out the stomach, emetics, aperients), as the precipitated tannates are not entirely insoluble, and will gradually be absorbed if they remain in the intestinal canal.

It will be evident, from what has been said of the nature of the astringent action and the behaviour of tannic acid in the organism, that it is useless to give it internally to decrease secretions such as sweating or bronchial secretion, in nephritis, in hæmorrhage from the kidneys or lungs, or to obtain any action

of the same kind as that which appears at the site of direct application. These uses have now ceased also clinically.

Drugs and Compounds Containing Tannic Acid. For diarrhœa various drugs containing tannic acid are more frequently prescribed than tannin alone, as they give less trouble to the stomach, and are supposed to retain their activity for a longer distance into the intestine ; the reason for this is that tannic acids are accompanied by colloid constituents which prevent absorption and the liberation of the tannin for some time. The pharmacopœias contain a superabundance of such drugs, of which the following may be noted.

Krameriæ Radix, rhatany. The tincture is employed as a mouth-wash and for painting swollen and easily bleeding gums ; the infusion is used for diarrhœa. **Hæmatoxyli Lignum,** logwood —known best from its containing the hæmatoxylin used for staining microscopical specimens—is used for diarrhœa on account of the small quantity of tannic acid it contains. Crude extracts of the leaves or exudations from the stems of several tropical trees (*kino, gambir, catechu*) were formerly often used for the same purpose, but are now seldom prescribed. **Uvæ Ursi Folia,** bear-berry leaves, is a drug remarkable for the large amount of tannic acid it contains, but it probably owes its activity to other bodies, and is mentioned among the bivalent phenols (p. 248).

It is possible to carry tannic acid in an active form to the intestine, without irritation of the stomach, by certain synthetic insoluble tannin compounds which are inert in the stomach, but are gradually decomposed in the intestine and liberate free tannic acid. This principle of forming compounds which are not dissolved until they reach the intestine is also adopted in other fields—*e.g.* salol and creosote carbonate. The first preparation of this kind produced was **Tannigen,** or diacetyltannin (H. Meyer, 1894), which remains unchanged and inactive in the acid-reacting contents of the stomach, but is decomposed in the intestine into acetic acid and free tannin. The fact that the fæces give a tannic acid reaction shows that the decomposition takes place so slowly that the tannigen can act upon the entire length of the intestine. This is also the case with **Tannalbin** (Gottlieb, 1896), an albuminous compound containing 50 per cent. of tannin, almost insoluble in the gastric juice, but giving off its tannin on the alkaline reaction of the intestine with the co-operation of the pancreatic juice. These two preparations have been much employed in sub-acute and chronic catarrh of the large and small intestines, and in diarrhœa of all kinds, including infantile diarrhœa. Preparations chemically identical are now official in the U.S.P. (see Preparations and Doses, p. 323). The gelatinous

compound *tannocol* is of similar composition and action, as are also *tannopin* and *tannoform* (compounds of tannin and hexamethylene tetramine and formaldehyde respectively); all are recommended for diarrhœa, the last also as a dusting-powder on foul sores.

Preparations and Doses

Tannic and Gallic Acids

Acidum Tannicum (B.P., U.S.P.), tannic acid, gallo-tannic acid, a white or pale yellow powder with acid reaction and a strongly astringent taste, readily soluble in water. *Dose*, 3—6 decigrms., 5—10 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). Prescribed for internal use in the form of pills, powders, lozenges (see below), or a mixture with an aromatic or mucilaginous vehicle. As a gargle or for inhalation, 2 per cent. solution; for injection into the urethra, 1—2 per cent., into the vagina, 5 per cent.; as an enema, 1—2 per cent.; for thorough irrigation of the intestine, ¼—½ per cent.; for painting and poulticing, 5—20 per cent.

Trochiscus Acidi Tannici (B.P.), containing, of tannic acid, 3 centigrms.

Glycerinum (*Glyceritum*) *Acidi Tannici* (B.P., U.S.P.), 20 per cent., a good remedy for footsoreness. *Dose*, 0·6—2 mils, 10—30 mins. (B.P.).

Unguentum Acidi Tannici (B.P., U.S.P.), 20 per cent.

Suppositorium Acidi Tannici (B.P.), for piles. Contains 20 centigrms. (3 grs.) of tannic acid in each suppository unless otherwise prescribed.

Tannafax is a tannic acid jelly for the treatment of burns. Its advantage lies in the fact that it can be stored without deterioration and is therefore a suitable preparation for first-aid treatment. The base is a water-soluble one consisting of tragacanth, and there is a small quantity of phenol present to act as a preservative.

Drugs

Gallæ (U.S.P.), galls, nut-galls, hard excrescences formed on the young branches of *Quercus lusitanica*, var. *infectoria* (countries on the eastern shores of the Mediterranean) by the puncture of the gall-fly, *Cynips gallæ tinctoriæ*, which deposits its eggs under the bark. They are of the size of a cherry, olive-green in colour, and generally tuberculated. In section, the pale brown web-like structure is seen to surround a central cavity, which contains the dried-up egg, or a cylindrical passage leading to the surface, through which the larva has worked its way out. Oak-apples contain up to 70 per cent. of tannin.

Krameria (B.P.), krameria root, rhatany root, the reddish brown, woody, branching root of species of *Krameria* (Ord. *Leguminosæ*), Peru and Bolivia. *Dose*, 0·6—2 grms., 10—30 grs.

Extractum Krameriæ Siccum (B.P.). *Dose*, 3—10 decigrms., 5—15 grs. *Trochiscus Krameriæ* (B.P.), containing 6 centigrms. (1 gr.) of the extract.

Tinctura Krameriæ (B.P.), 20 per cent. *Dose*, 2—4 mils, ½—1 fl. dr. For painting tender, easily bleeding gums, or for a mouth-wash, *e.g. Tinct. Krameriæ, Tinct. Myrrhæ*, aa. equal parts, ½—1 teaspoonful to a tumblerful of water.

Trochiscus Krameriæ et Cocainæ (B.P.), contains 6 centigrms. (1 gr.) of dry extract of krameria and about 3 milligrms. (about $\frac{1}{20}$ gr.) of cocaine hydrochloride.

Hæmatoxyli Lignum (B.P.C.), *Lignum Campechianum*, logwood, the heart-wood of *Hæmatoxylon Campechianum* (*Leguminosæ*), Central and South America. The wood is of a dull orange to purplish red colour externally, and internally reddish brown. A tablespoonful of a 10 per cent. decoction is given as a mild astringent in diarrhœa in adults and children.

Kino (B.P.C., U.S.P.), the dried juice of *Pterocarpus Marsupium* (*Leguminosæ*), East India, in small, brittle, angular, reddish black fragments. *Dose*, 0·5 grm., 8 grs. (U.S.P.).

Tinctura Kino (U.S.P.), 10 per cent. *Dose*, 2 mils, 30 mins.

Pulvis Kino Compositus (B.P.C.), see under "Opium," p. 90.

Catechu (B.P.), gambir, a dried extract of the leaves and young shoots of *Uncaria Gambir* (*Rubiaceæ*), East India, in cubical or rectangular pieces of a porous consistency and a reddish brown colour. *Dose*, 3—10 decigrms., 5—15 grs.

Tinctura Catechu (B.P.), 20 per cent. *Dose*, 2—4 mils, ½—1 fl. dr.

Hamamelis (B.P.), Witch Hazel Leaves. The dried leaves of *Hamamelis virginiana*.

Extractum Hamamelidis Liquidum (B.P.). *Dose*, 2—4 mils, ½—1 fl. dr.

Medicinal requirements are abundantly satisfied with the above preparations. The British Pharmacopœia has, in addition, the following: *Acaciæ Cortex*, *Belæ Fructus*, *Buteæ Gummi* (*Bengal Kino*), *Catechu nigrum*, *Hamamelidis Cortex*, *Kino Eucalypti*, *Myrobalanum* and *Sappan*. For properties, preparations and doses, see the B.P.C. or N.F.

Synthetical Preparations

Acidum Acetyltannicum (U.S.P.), a yellowish grey powder, insoluble in water. *Dose*, 6 decigrms., 10 grs.

Albumini Tannas (U.S.P.), a pale grey, insoluble powder. *Dose*, 10 decigrms. *per dosem*, up to 6—8 grms. *per diem*; for infants, 25—50 centigrms., 4—8 grs. Official dose, 2 grms., 30 grs.

Tannocollum, tannin-gelatine, a greyish white powder, almost insoluble in water. *Dose*, 10 decigrms., 15 grs.; for children, 25—50 centigrms., 4—8 grs.

8. VEGETABLE PURGATIVES

General Remarks

Purgatives are drugs or compounds that serve to produce evacuation of the intestine. They are very important drugs ("*qui bene purgat, bene curat*"), and from the early ages, when they were employed to a greater extent than they are now, have had many names which indicate various degrees in their action. The mildest are called aperients (opening), lenitives (softening), laxatives (loosening), eccoprotics (κοπρος = dung), cathartics (καθαιρω = I cleanse) and purgatives (cleansing)—all in contrast to the strongly-acting drugs which are called drastic purgatives. The division is somewhat arbitrary, however, as the effect is in some measure dependent upon the size of the dose, since a drug in small doses may be laxative and in large a drastic purgative.

Action. Purgatives may be divided into two main groups according to their mode of action, namely, the aperient mineral

salts and the vegetable purgatives, with which sulphur is also classed. The activity of the mineral salts is mainly due to their peculiar behaviour towards water, of which special mention will be made later. On the other hand, the vegetable purgatives, which will be discussed in this chapter, empty the intestine by causing *increased peristalsis*. They all contain substances that irritate the epithelium of the intestinal mucous membrane, this irritation causing energetic movements. The action is not peculiar to purgatives, for all intestinal irritation is followed by reflex

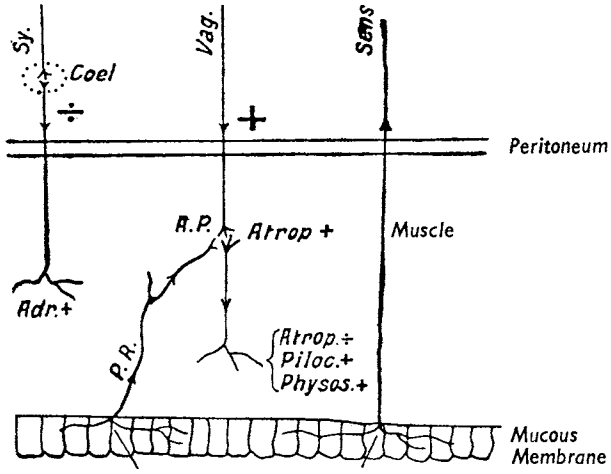


FIG. 27.—Diagrammatic representation of the points of attack of certain drugs acting on the intestine. *Sy.* The sympathetic. *Vag.* The vagus. *Sens.* Sensory nerves. *Coel.* The cœliac plexus. *A.P.* Auerbach's plexus. + means stimulation, ÷ inhibition.

Adrenaline stimulates the ends of the sympathetic (repose of the intestine), pilocarpine and physostigmine stimulate the vagus ends (movement), atropine stimulates Auerbach's plexus, and, on the other hand, paralyses the ends of the vagus, and can consequently produce both movement and rest (*cf.* p. 111). The vegetable purgatives irritate the sensory nerves of the mucous membrane and cause movement, chiefly perhaps through the peripheral (hypothetical) reflex arc, *P.R.*

movements, and diarrhœa is well known to be a regular symptom of poisoning with irritant and caustic substances ; but only those substances the action of which is mild and confined to the surface of the mucous membrane can be employed as purgatives. It is an open question whether the point of attack is always exclusively the intestinal wall, or whether certain substances have not a specific influence on the nervous mechanism that governs the intestinal movements. In support of the latter theory it is stated that several of these purgatives cause evacuation when injected hypodermically, but this may be explained by their excretion into the intestine.

The evacuations produced by a laxative are of a looser consistency than normal, this being a consequence of stronger peristalsis in the large intestine. The contents of the small intestine are always fluid and mobile. In the large intestine progress is slow, water is absorbed and the fluid contents are concentrated into solid excrements, so that it is here that difficulties may arise, as the movement of the solid masses requires powerful contractions of the intestine. The *large intestine* is therefore *the most important site for the action* of purgatives. If the time during which the contents of the intestine remain in this section is shortened, the concentration is prevented, and the evacuations resemble the contents of the small intestine ; they remain semi-solid or quite fluid, contain 80 to 90 per cent. of water instead of the 50 per cent. of normal fæces, and also far greater quantities of sodium chloride originating in the bile, pancreatic and enteric juices.

It is probable that besides the prevention of absorption of water, *increased secretion from the glands of the intestinal mucous membrane* also contributes to make the evacuations of a loose consistency. Nothing definite is known about this, however. Introducing purgatives into isolated loops of intestine has given varying results, often quite negative ; nevertheless it seems probable that the stimulation that elicits peristalsis also increases the activity of the glands. Formerly the thin consistency was interpreted in another manner, the large amount of water being regarded as the consequence of a serous transudation or exudation, a transfer of liquid from the blood to the intestine. It has now been ascertained that in ordinary circumstances nothing of the kind takes place, the irritation of the intestine being too slight for this. The fact that in diarrhœa the blood becomes poorer in fluid proves nothing except that normal absorption from the intestine cannot take place whilst the fluid is so quickly removed by powerful peristalsis. Inflammation like that produced by vesicants on the skin is only seen after drastic purgatives ; in such cases serous exudation may occur and contribute to the fluid of the fæces. If the drug is highly irritant, pus and blood may also be present.

The *pain* that almost always accompanies the action of purgatives must be ascribed partly to the vigorous movements of the intestine, partly to irritation of the mucous membrane. If the irritation after a drastic purgative causes inflammation, the abdomen becomes tender to pressure. The local irritation of laxatives gives rise to *hyperæmia in the intestine*, and congestion of the mesenteric circulation. If the irritation is very great, the vaso-dilatation spreads to the pelvic organs, including the uterus

and appendages, and so increases menstruation, or perhaps, in cases of pregnancy, causes abortion.

Much attention has been paid to the *behaviour* of purgatives *towards bile and the biliary secretion.* The more quickly the contents are conveyed from the upper sections of the intestine to the rectum, the more of the characteristic components of the contents of the small intestine will the evacuations show, one of these being a greater quantity of bile than normally. It was formerly considered that several purgatives, *e.g.* rhubarb, jalap and aloes, also increased the biliary secretion, but according to later investigations this does not appear to be the case. There is, however, a certain connection between the bile and the activity of some of the purgatives, inasmuch as the bile plays a part in their solution or otherwise changes them from inert to active compounds. According to clinical experience, this applies especially to rhubarb, aloes, jalap and colocynth. From observation of men and animals with biliary fistula it appears that there are only very few real *cholagogues* (see under "Salicylic Acid," p. 264).

As the purgatives have to be brought into the most complete contact possible with the intestinal mucous membrane, they must be *slow of absorption.* With regard to these drugs, therefore, unlike most others, it is not justifiable to use their active constituents, for the latter in pure condition are often absorbed so quickly that they have little effect upon the intestine. In leaves, barks and roots or preparations of them they are enclosed in cells or accompanied by mucilage, gum, or other colloid substances, which envelop them and prevent early absorption. Although themselves indifferent, the colloid bodies may in this way be of great significance to the action. Pure cambogic acid, for instance, is less active than the same amount of gamboge, which contains, besides that acid, a large quantity of gum.

Some purgatives set the entire intestine from end to end in motion, while others have the property, that in many cases is more highly esteemed, of acting especially upon the large intestine. The difference may be traced to the fact that some drugs from the very first are local irritants (croton oil), or rapidly become so in the intestine (castor oil), while others have little activity in themselves, and are only slowly converted into active compounds by the aid of bile, ferments, or the alkali of the intestine: these compounds may be assumed to increase in amount as time passes, and will therefore be most plentiful in the lowest section of the intestine. This difference, as will soon be seen, is of great practical importance.

Therapeutic Uses. A detailed treatment of this wide subject

will be found in text-books of medicine. Only the general indications will be given here.

Purgatives are given to produce peristalsis, when for some reason or other it has ceased or is deficient, *i.e.* in *acute and chronic constipation*. It is a good rule, in the latter condition, to look upon laxatives as palliative, for they represent only a symptomatic treatment, which is far inferior in value to the causal. Chronic constipation is most frequently a disease of civilisation, caused by an artificial mode of living. The first aim of the treatment is therefore to correct this as far as possible by muscular work, gymnastics, massage, dietary regulations, etc. These measures alone are often impracticable, however, or are useless, because the disorder is of too long standing, and a regular course of laxatives must then be begun. After some time these become indispensable, as the constipation, especially in elderly inactive women, not infrequently increases until spontaneous defæcation hardly ever takes place. In these circumstances drugs are employed which act upon the large intestine (see below), both because the stagnation takes place there, and because drugs which act with equal strength upon the whole intestine are suitable only for acute constipation; their prolonged use injures nutrition, for the absorption of nutritive substances in the small intestine is imperfect when the contents pass through it too rapidly. In this lies the significance of purgatives in obesity cures. In chronic constipation the smallest possible quantities are always given to begin with, and it will often be seen that doses far smaller than those generally quoted as "aperient doses" may be sufficient to give the necessary assistance to impaired peristalsis. Sometimes one drug—*e.g.* rhubarb—may act satisfactorily for years, but it is more frequently found that the intestinal mucous membrane becomes gradually tolerant to the constant use of the same irritant, while another proves efficacious. Change then becomes necessary, and although it is generally a wise principle that many drugs should not be prescribed together, yet in this instance pills and similar preparations containing small quantities of several laxatives may be prescribed with advantage. The utility of this is shown by the popularity of numerous exceedingly composite remedies. The addition of a little nux vomica or belladonna extract often seems to increase the activity of the aperients.

Another main indication for laxatives is given by conditions in which it is important to remove *deleterious intestinal contents* such as poisons, intestinal worms, old, hard fæcal masses, food that is undergoing abnormal decomposition, or bacteria. The fact that there is diarrhœa—as is often the case—is no contra-indication for purgatives. The treatment of children's and

summer diarrhœa is frequently begun, as we know, with a purgative. In these circumstances the drugs that act upon the whole intestine and thus bring about a thorough cleansing are the right ones. As the intestine is, moreover, often the seat of catarrhal inflammation, the drugs employed ought to be as little irritant as possible. Castor oil and the aperient mineral salts best fulfil these conditions.

Cathartics were formerly largely employed for the purpose of " drying up " and *absorbing* dropsies and exudates, but have now been superseded by diuretics. The purging treatment saps the strength, and the loss of liquid through the intestine (mainly due to deficient absorption of water) is often neutralised by a diminished flow of urine.

In *hyperæmia and inflammation in remote organs, e.g.* in diseases of the eye, meningitis and congestion of the brain, aperients are prescribed to deplete the body-fluids. The treatment of febrile diseases is also often begun by evacuation of the intestine, but this practice is irrational and sometimes harmful.

Drastic purgatives are principally *contra-indicated* by *acute inflammation of the intestine or neighbouring regions* (*peritoneum*), as vigorous peristalsis may make a limited inflammation diffuse. During *menstruation* purgatives preferably should not be given, and in tendency to *uterine hæmorrhage* and during the later months of pregnancy, only the milder drugs should be employed ; those which induce congestion of the pelvic organs and therefore risk of hæmorrhage or abortion (aloes) should be especially avoided. A tendency to diarrhœa, general weakness, anæmia, and advanced age, all give grounds for caution or suggest the use of the mildest remedies, such as castor oil. With piles, mild aperients are employed, but not those like aloes which cause pelvic congestion.

The vegetable purgatives may be divided into three groups. The first of these comprises fixed oils ; the second, drugs containing anthracene derivatives, which are largely inert, but in the intestine yield active compounds ; the third, various vegetable products of which the active constituents are substances (often resinous acids) which not only excite peristalsis, but also, in large doses, produce inflammation of the intestine (drastic purgatives). *The pharmacological action answers in its principal features to this chemical division, the anthracene derivatives being drugs for the large intestine, while the fixed oils and drastic purgatives, even in the small intestine, excite vigorous peristalsis.*

Castor Oil and Croton Oil

Castor oil consists principally of the triglyceride of *ricinoleic acid*, a peculiar, unsaturated fatty acid, which is its active con-

stituent but is not suitable for practical employment, as it has a more disagreeable odour and taste, and produces greater nausea, than castor oil. The oil itself, *i.e.* the undecomposed glyceride, is quite inert and only becomes aperient when it has been to some extent saponified in the intestine by the bile and the fat-decomposing ferment of the pancreatic juice to glycerin and free acid. The remaining unsaponified oil supports the action mechanically by making the intestinal wall and the hard fæcal masses smooth.

Castor oil occupies a prominent position among purgatives, because it combines with certain action the property of being only slightly irritant and causing little hyperæmia. It can therefore be utilised also in inflammation of the intestine, and is the least doubtful drug in conditions in which there may be a difference of opinion as to the expediency or propriety of purgatives. From 1 to 2 tablespoonfuls will produce soft motions without, or almost without, pain in the course of a few hours. As the saponification commences as soon as the oil mixes with the pancreatic juice, the action begins in the duodenum. In barium-fed animals, X-ray photographs show that the contents pass much more rapidly than usual through the jejunum and the ileum. Castor oil is therefore a very suitable remedy for *ordinary acute constipation*, in *poisoning*, gross *errors of diet*, and other similar cases in which thorough evacuation is desirable. For the same reason it is the purgative most frequently employed in *acute diarrhœa* due to food poisoning, and in the *chronic diarrhœa alternating with constipation*, which originates in irritation of the intestine occasioned by old or hard scybala. Administered *per rectum*, castor oil also acts as an aperient, and when added to enemata enhances their effect.

Castor oil is unsuitable for the treatment of *chronic constipation* as continued use produces dyspepsia and impairs the appetite.

Castor oil is a constituent of many " hair oils " ; it gives lustre to the hair and is supposed to promote its growth.

Croton oil consists of glycerides of several fatty acids and a highly irritant resin. For this reason it is extremely irritant even in an unsaponified condition, and when rubbed into the unbroken skin produces injection, œdema, vesicles and finally pustules, and by subcutaneous injection, phlegmonous inflammation with sterile pus (aseptic injection assumed).

Croton oil is the strongest of all purgatives. From $\frac{1}{2}$ to 1 drop produces prolonged burning in the mouth and throat, analogous symptoms from the stomach, often nausea, and after from $\frac{1}{2}$ to 2 or 3 hours, first hard, then several soft motions. The lethal dose (about 20 drops) causes violent intestinal inflammation, choleraic diarrhœa and collapse.

Croton oil is a very rarely employed purgative, being only prescribed for the most *obstinate constipation*, when all other means fail. It has been recommended, *inter alia*, for lead colic. Its external employment as a skin-irritant has been abandoned.

Preparations and Doses

Oleum Ricini (B.P., U.S.P.), castor oil, a colourless or slightly yellow, viscid oil, with a very disagreeable taste, expressed from the seeds of *Ricinus communis* (*Euphorbiaceæ*), growing in the tropical regions of Asia and Africa, and largely cultivated in Southern Europe, especially in Italy. In northern latitudes it is cultivated under the name of "*Palma Christi*," as an ornamental plant. *Dose*, 4—16 mils, 1—4 fl. drs. (B.P.); 15 mils 4 fl. drs. (U.S.P.). It is taken best when slightly warmed, as it then becomes thinner and glides down more easily than when cold. None of the various emulsions that are recommended taste much better than the pure oil, and they seem to be less certain in their action, perhaps because the oil in its finely-divided form is absorbed. For use as a hair-oil, mixed with four parts, or more, of spirit or eau-de-Cologne.

Mistura Olei Ricini (B.P.C.), about 37 per cent. of castor oil. *Dose*, 30—60 mils, 1—2 fl. oz.

Oleum Crotonis (B.P.C.), a brownish yellow oil with an acrid taste, expressed from the seeds of *Croton Tiglium* (*Euphorbiaceæ*), East India. *Dose*, 3—6 centimils, ½—1 min. Should be given in another oil, such as castor oil or olive oil, to minimise gastric irritation.

Addendum

When the fixed oil has been expressed from the castor-oil seeds, a substance with a very peculiar and poisonous action, ricin, is left. After intravenous injection of the minutest quantities (for a rabbit the lethal dose of the purest preparation at present produced is $\frac{1}{10000}$ milligrm. per kilo of body-weight) there is at first a latent period in which there is nothing abnormal to be observed; but, just as after certain bacterial poisons, the animals at once begin to lose weight, although there is no rise in temperature. When one or more days have passed, a rapid paralysis of the vasomotor centre and of the respiration occurs, and after diarrhœa and convulsions with irregular respiration and steadily falling blood-pressure, death takes place. Ricin has hitherto defied all attempts to produce it in pure condition; it does not pass into castor oil, and is of no therapeutic importance; but it is extremely interesting for other reasons, as it evidently belongs to the same class of bodies as those which, in the animal organism, are produced by various pathogenetic bacteria. It was used by Ehrlich in 1891, as an easily obtainable toxin, in investigations that have acquired fundamental importance in the modern doctrine of immunity and in serum therapeutics. The chief result of these important investigations is that animals (white mice and rabbits) when they daily receive small, non-lethal doses, soon become immune to ricin, the immunity appearing in a very characteristic manner. During the first 4 or 5 days there is scarcely any indication of increased tolerance, but about the sixth day it appears with a suddenness that involuntarily invites comparison with the crisis in certain infectious diseases, *e.g.* pneumonia, and suggests that this is due to a similar process. If the injections are continued, with constantly increasing doses of ricin, the animals can be brought up to a very high degree of

immunity. Rabbits, for instance, have attained a degree of immunity of 5,000, that is to say, are not killed by a dose 5,000 times as large as that which would be fatal to an animal that had not been treated with ricin. The immunity lasts a long time, at any rate 6 months if it has been developed far. It may be assumed that it is due to the formation of a large surplus of "antiricin," and can be conveyed from animal to animal by serum injections. The ricin immunity protects only from ricin, not from other similar vegetable poisons, such as abrin. The analogy to the toxins and antitoxins of the infectious diseases is, therefore, complete.

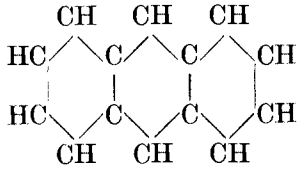
In croton seeds there is a poison, *crotin*, resembling ricin, but weaker. A similar substance, called *abrin*, is obtained from the seeds of *Abrus precatorius* (*Papilionaceæ*). Animals can be immunised with it as with ricin.

The Anthracene Derivatives

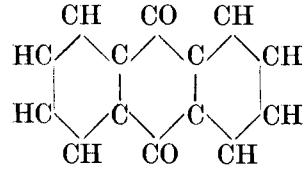
Rhubarb, *Cascara*, *Frangula*, *Senna* and *Aloes* form a special, well-defined group of purgatives, of which the characteristic feature is that their active constituents are derivatives of anthracene, an aromatic hydrocarbon found in large quantities in coal-tar. These anthracene derivatives are oxymethylanthraquinones, which occur partly in a free condition, but principally as glucosides that are not themselves purgative, but are slowly decomposed in the intestine, so that the active compounds are gradually set free. Those most frequently occurring are *emodin* (trioxymethylanthraquinone) and *chrysophanic acid* (dioxymethylanthraquinone).

All that is to be said in general of this group of purgatives is that as regards activity and irritation of the intestinal canal they occupy an intermediate position between castor oil and the cathartics to be mentioned in the next section. As their activity, owing to the gradual freeing of the active principles, is greatest in the lowest section of the intestine, they are especially adapted for the treatment of chronic constipation. Each drug, moreover, has its peculiarities, due to many substances accompanying the active bodies, and to the particular anthracene derivatives it contains. The number of the latter is very great; of trioxymethylanthraquinones, or emodin, alone there are fifteen isomeric forms possible.

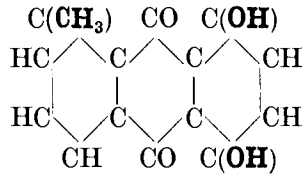
The following formulæ give a general survey of the above-mentioned chemical compounds :—



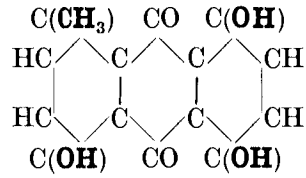
Anthracene, $C_{14}H_{10}$.



Anthraquinone, $C_{14}H_8O_2$.



Dioxymethylanthraquinone, Chrysophanic acid, $C_{15}H_{10}O_4$.



Trioxymethylanthraquinone, Emodin, $C_{15}H_{10}O_5$.

Rhei Rhizoma. Rhubarb contains a tannic acid, free oxymethylanthraquinones (chrysophanic acid, emodin, rhein), glucosides from which these originate, and large quantities of oxalate of lime.

This combination of an astringent with purgatives makes the action vary according to the size of the dose. In small doses, only the tannin asserts itself, and they therefore cause constipation and a decrease in the secretions, and are given for catarrh of the stomach and intestine combined with *diarrhœa, especially in children.* In large doses, on the other hand, rhubarb is a gentle laxative, producing after 6 to 10 hours, with only slight griping, if any, a liquid motion, and thus, on account of its mild action, is suitable for children, weak or anæmic persons and convalescents. In *chronic constipation* rhubarb may act for years, but the action is said to be followed, more frequently than with other purgatives, by constipation, for which the tannic acid is probably to blame.

As the chrysophanic acid is easily absorbed and excreted unchanged through the kidneys, the urine acquires, after the use of rhubarb, a deep yellow or yellowish brown, almost icteric colour, which becomes red on the addition of alkalies. The same colouring matter passes into the milk, and makes it slightly aperient.

Cascara Sagrada and **Frangula.** Both these barks contain anthraquinone derivatives of which little is known. During the drying and storing of the bark, important chemical changes take place in it. The fresh bark is more purgative than the old, and often causes indisposition, nausea and vomiting, secondary effects that must be due to a substance that in time is changed or decomposed. Several pharmacopœias therefore enjoin the keeping of the bark for a year before taking it into use. The substance which produces these unpleasant effects may also be destroyed by heating up to 100° C. for a short time.

In the form of various extracts, cascara sagrada is a practical and popular remedy for *chronic constipation.*

Senna. Senna leaves contain glucosides of a kind similar to those occurring in rhubarb, small quantities of an emodin that is the same as the aloes emodin, and a yellow colouring matter

which passes into the urine, and seems to be identical or isomeric with chrysophanic acid. Senna is a rather more drastic purgative than the preceding drugs. The action takes place after medium doses (1—2 grammes) in about 6 hours, and is more or less mild, though often accompanied by pain. Large doses (*e.g.* 4—5 grammes) cause repeated evacuations, at first semi-solid, later liquid. Investigations carried out in the manner mentioned under " Castor Oil " (barium-meal and radiography) show that senna is especially a drug for the large intestine. Neither in animals nor in man are the movements of the stomach and small intestine greatly altered ; but as soon as the contents have passed the ileo-cæcal valve, the bismuth shadow hastens precipitately through the colon. On account of its powerful action senna is a very popular and safe remedy for *acute constipation*, but less suitable for *chronic constipation ;* and it is contra-indicated where there is great intestinal irritation.

Aloes is a very old and highly esteemed drug, of which the chemistry is an exceedingly wide and much disputed subject. According to the latest investigations of Leger, Tschirch and others, the various kinds of aloes contain crystalline aloins, which by decomposition yield sugar and emodin, and, moreover, an abundance of amorphous glucosides of similar constitution, which have not been isolated in a pure state. Aloin also purges when injected subcutaneously, because it is excreted into the intestine, where it can be demonstrated in man, dogs and cats. In rabbits it is excreted in the urine, and causes a fatal nephritis. Aloes acts more quickly when given with alkalies or iron salts, which promote the decomposition. The presence of bile also appears to be necessary, in any case as far as man is concerned. It is stated that in jaundice very large doses may be given without result as long as the motions are clay-coloured.

Aloes, in doses of 0·20—0·50 gramme, after 8—12 hours, produces soft motions without or almost without griping, and without subsequent liability to constipation. It is a practical remedy for *chronic constipation*, as tolerance does not ensue. Aloes is not suitable for cases of very obstinate acute constipation, as in the large doses necessary for this it is more liable than other purgatives to cause congestion of the intestine and pelvic organs. It can therefore also be employed as an *emmenagogue*, but is contra-indicated in hæmorrhoids, in tendency to genital hæmorrhage, and during menstruation, and must be used with caution during pregnancy.

In small doses aloes acts, in the opinion of many, as a bitter, and is often given *with iron in chlorosis and other forms of anæmia*, and in *dyspepsia* and *chronic gastric catarrh*.

Phenolphthalein may be conveniently considered in this group of purgatives. Though insoluble, its salts which form in the upper intestine dissolve readily and cause mild irritation of the bowel with purgation in about eight hours. Its action is comparatively mild, but as the drug is excreted in the bile there is a tendency for several evacuations to result from a single dose. It is also excreted in the urine, which becomes deep red in colour if the reaction is alkaline. Phenolphthalein is recommended as a laxative for children and for old people ; it is also used in pregnancy and in general when pelvic congestion would aggravate existing symptoms, *e.g.* in hæmorrhoids, during menstruation, etc. Cutaneous eruptions have been described following its use.

Preparations and Doses

Rheum (B.P., U.S.P.), rhubarb, the decorticated rhizome of species of *Rheum* (*Polygonaceæ*), natives of China and Tibet. Yellowish red and white marbled, heavy, irregular, often split pieces, which feel gritty between the teeth when chewed (crystals of oxalate of lime). Doses of 1—5 decigrms. are astringent and constipating, larger doses laxative. For chronic constipation, ½—1 teaspoonful of the grated root is given in the evening. *Dose*, 2—10 decigrms., 3—15 grs. (B.P.) ; 1 grm., 15 grs. (U.S.P.).

Extractum Rhei (U.S.P., B.P.C.), the dried extract. *Dose*, 12—50 centigrms., 2—8 grs. (B.P.C.) ; 0·25 grm., 4 grs. (U.S.P.). Is prescribed as pills.

Pilula Rhei Composita (B.P.), with aloes, myrrh and peppermint. *Dose*, 25—50 centigrms., 4—8 grs. Good remedy for chronic constipation.

Pulvis Rhei Compositus (B.P.), Gregory's powder, an old, well-known remedy, containing rhubarb (25 per cent.), magnesia and ginger. *Dose*, 6—40 decigrms., 10—60 grs.

Syrupus Rhei (B.P.C.). *Dose*, 2—8 mils, ½—2 fl. drs.

Syrupus Rhei Aromaticus (U.S.P.). *Dose*, 10 mils, 2½ fl. drs.

Tinctura Rhei Composita (B.P.), 10 per cent., with cardamom and coriander. *Dose*, 2—4 mils, ½—1 fl. dr. for repeated administration, 8—16 mils, 2—4 fl. drs. for a single administration.

Tinctura Rhei Aromatica (U.S.P.), 20 per cent., with cinnamon, cloves and nutmeg. *Dose*, 4 mils, 60 mins.

Cascara Sagrada (B.P., U.S.P.), the bark of *Rhamnus Purshiana* (*Rhamnaceæ*), a bush growing in North America. *Dose*, 1·2—4 grms., 20—60 grs. (B.P.) ; 1 grm., 15 grs. (U.S.P.).

Extractum Cascaræ Sagradæ Siccum (B.P.), **Extractum Cascaræ Sagradæ** (U.S.P.). Given as pills. *Dose*, 12—50 centigrms., 2—8 grs. (B.P.) ; 0·3 grm., 5 grs. (U.S.P.).

Extractum Cascaræ Sagradæ Liquidum (B.P.), **Fluidextractum Cascaræ Sagradæ** (U.S.P.), a very favourite remedy for chronic constipation. *Dose*, 2—4 mils, ½—1 fl. dr. (B.P.) ; 1 mil, 15 mins. (U.S.P.).

Elixir Cascaræ Sagradæ (B.P.), a palatable preparation containing cascara sagrada, liquorice, soluble saccharin, oil of coriander, oil of anise, alcohol, glycerin, and water. *Dose*, 2—4 mils, 30—60 mins.

Fluidextractum Cascarœ Sagradœ Aromaticum (U.S.P.). *Dose*, 2 mils, 30 mins.

Frangula (not official), buckthorn, the bark of *Rhamnus frangula*, a European plant. *Dose*, 1 grm., 15 grs. *Fluidextractum Frangulœ*. *Dose*, 1 mil, 15 mins.

Sennœ Fructus (B.P.), Senna Pods. The dried fruits of *Cassia acutifolia* and of *Cassia angustifolia*, Upper Nile Territories and Southern India. *Dose*, 0·6—2 grms., 10—30 grs.

Extractum Sennœ Liquidum (B.P.). *Dose*, 0·6—2 mils, 10—30 mins.

Sennæ Folia (B.P.), **Senna** (U.S.P.), the unequally lanceolate, yellowish or greyish green leaflets of *Cassia acutifolia* and *C. angustifolia* (*Leguminosœ*), North Africa and East India. The simplest mode of employment is the home-made infusion, 1 teaspoonful of the leaves to a cupful of hot water. *Dose*, 0·6—2 grms., 10—30 grs. (B.P.); 2 grms., 30 grs. (U.S.P.). Senna leaves are used in the preparation of Confection of Senna and Compound Liquorice Powdor; all other official preparations are made from Senna Pods (see below).

Fluidextractum Sennœ (U.S.P.). *Dose*, 2 mils, 30 mins.

Confectio Sennœ (B.P.), a very composite preparation, containing among other things figs, prunes, tamarinds, cassia-pulp and liquorice, and suitable for children. *Dose*, 4—8 grms., 60—120 grs.

Infusum Sennæ Recens (B.P.), 10 per cent. *Dose*, 15—30 mils, ½—1 fl. oz. for repeated administration, *e.g.* every other hour until an action is obtained; 60 mils, 2 fl. oz. for a single administration. Official dose, ½—2 fl. oz.

Infusum Sennæ Concentratum (B.P.), eight times concentrated, and 8 per cent. of strong tincture of ginger added. *Dose*, 2—8 mils, 30—120 mins.

Mistura Sennæ Composita (B.P.), "black draught," a preparation of which variants are found in many lands. It combines the action of a vegetable purgative with that of a saline aperient, namely, magnesium sulphate (25 per cent.). *Dose*, 30—60 mils, 1—2 fl. oz.

Syrupus Sennæ (B.P., U.S.P.) is suitable for children. *Dose*, 2—8 mils, ½—2 fl. drs. (B.P.); 8 mils, 2 fl. drs. (U.S.P.).

Pulvis Glycyrrhizæ Compositus (B.P.), **Pulvis Sennæ Compositus** (U.S.P.), containing senna and sulphur. An old, tried remedy, used for both acute and chronic constipation. *Dose*, 4—8 grms., 60—100 grs. (B.P.); 4 grms., 1 dr. (U.S.P.).

Aloe (B.P., U.S.P.), the inspissated juice of the leaves of several species of Aloe (*Liliacecæ*), growing principally in South and East Africa. Hard, brown, dull, or glistening masses, with a nauseous, bitter taste. Prescribed as pills. *Dose*, 12—30 centigrms., 2—5 grs. (B.P.); 0·25 grm., 4 grs. (U.S.P.).

Pilula Aloes (B.P.), aloes (58 per cent.), soap, caraway. *Dose*, 25—50 centigrms., 4—8 grs.

Pilulæ Aloes (U.S.P.), each containing 0·13 grm. *Dose*, 2 pills.

Pilula Aloes et Asafetidœ (B.P.), 20 per cent. of each. *Dose*, 25—50 centigrms., 8—15 grs.

Pilula Aloes et Ferri (B.P.), 20 per cent. of aloes, 10 per cent. of ferrous sulphate. *Dose*, like the preceding.

Aloinum (B.P., U.S.P.). *Dose*, 0·015—0·06 grm., ¼—1 gr. (B.P.); 0·015 grm., ¼ gr. (U.S.P.).

Aloes is also contained in Pilula Rhei Composita (p. 334), in several preparations of Colocynth (p. 338), and in Tinctura Benzoini Composita (p. 261).

Phenolphthaleinum (B.P., U.S.P.). Phenolphthalein is dihydroxy-diphenyl-phthalide, $(C_6H_4OH)_2C.C_6H_4.CO.O$. A white, or yellowish-white, amorphous or crystalline, powder. Tasteless and odourless. Almost insoluble in water, soluble 1 in 13 alcohol. *Dose*, 0·06—0·3 grm., 1—5 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.).

Synthetically-produced Purgatives. Since the recognition of oxymethyl-anthraquinones or their glucosides as the active principles of rhubarb, etc., numerous artificial compounds of a similar nature have been tried and found to be purgative. Among them are *Purgatin* (or Purgatol) and *Exodin*, both yellow, insoluble powders, which are given in doses of 0·5 to 2 grms. Another is *Istizin*, an insoluble powder of an orange colour, given in doses of 0·15 to 0·6 grm.

The Jalap and Colocynth Group

Jalap, *Scammony*, *Colocynth* and *Podophyllum* are all powerful purgatives and, in large doses, drastic; with the exception of the last, they act rapidly.

Jalapæ Resina contains the resinous acids *jalapin* and *convolvulin*, which, when treated with mineral acids, yield sugar, and are thus glucosides. Bile appears to be of the utmost importance to the purgative action, for when there is no bile in the intestine, no action takes place. Jalap, therefore, does not act in obstructive jaundice, but is otherwise a reliable purgative, which in very small doses is useful in *habitual constipation*, retains its influence, and may be used for a long time without danger; but in large doses, *e.g.* ½ gramme, it proves to be a powerful cathartic, which even in the course of an hour or two produces a number of watery evacuations accompanied by griping. It cannot, therefore, be used in cases in which the intestine is inflamed.

Several members of the convolvulus family, among them being *C. scammonia*, from which the official **Scammoniæ Resina** is obtained, contain similar constituents, and in their action resemble jalap.

According to Power and Moore the active constituents of **Colocynth** are an exceedingly bitter alkaloid and several resinous substances. Colocynth is a true drastic; it produces a number of watery motions, and is only used for chronic constipation in very small doses combined with other drugs. Its action is associated with considerable griping pain and great irritation and hyperæmia in the intestine. Colocynth is a type of the so-called hydragogue purgatives, which were formerly very frequently prescribed for dropsy and œdema. The active constituents are

excreted in the urine (renal hyperæmia), and in the milk, which thus becomes aperient, so that colocynth must not be given to nursing mothers. Allied substances are also found in other *Cucurbitaceæ*, for instance, in *Ecballium elaterium* the *elaterin*, which acts in doses of a few milligrammes and is still used occasionally in England and America.

Podophyllum resin, a drug that has long been known in America, but only during the last few decades in Europe, differs from the foregoing drugs in the slowness with which its action appears, generally not before 12—24 hours or even longer, while in other respects it has the character of a drastic purgative, and in overdoses causes much griping and such irritation of the intestine as to cause bleeding. Small doses are recommended in *chronic constipation* as of mild and certain action. Like jalap, podophyllum is a drug the action of which is dependent on the presence of bile. Many writers ascribe to podophyllum a cholagogue action which is denied by others. The active constituents are *podophyllotoxin*, $C_{23}H_{24}O_9 + 2H_2O$, and its isomer, *picropodophyllin*, both crystalline bodies and probably anhydrides. The former is the more active, and when injected subcutaneously in animals produces vomiting and copious evacuations of the intestine, which, also with this method of administration, do not commence for several hours.

Gamboge is a gum-resin of which the active constituent, *cambogic acid*, has no irritant action in the mouth and stomach, but acquires such action in the intestine by the aid of the bile. Fat also assists the action, as does also the gum in the gum-resin (see p. 326). As a purgative, gamboge resembles colocynth, and produces, after comparatively small doses, repeated thin evacuations. It is now seldom used, and has been omitted from several pharmacopœias, but is still met with as a constituent of proprietary drugs, the incautious use of which may occasion poisoning.

Preparations and Doses

Jalapa (B.P.), the resinous, dark brown, heavy tuberous root of *Ipomœa purga* (*Convolvulaceæ*), Mexico. *Jalapa Pulverata* (B.P.), jalap reduced to a fine powder and adjusted to contain 10 per cent. of the resin. *Dose*, 3—12 decigrms., 5—20 grs.

Pulvis Jalapæ Compositus (B.P.) contains jalap and potassium bitartrate. *Dose*, 6—40 decigrms., 10—60 grs.

Ipomœa (B.P.), Mexican Scammony Root. The dried root of *Ipomœa orizabensis*. Yields scammony resin. *Dose*, 0·3—1·2 grm., 5—20 grs. Actions and uses are similar to those of jalap.

Scammoniæ Resina (B.P.). *Dose*, 3—20 centigrms., $\frac{1}{2}$—3 grs.

Colocynthis (B.P.), "bitter apple," the peeled, light, globular, white,

spongy, intensely bitter fruit of *Citrullus Colocynthis* (*Cucurbitaceæ*), growing in Africa and Asia. *Dose*, 0·2—0·3 grm., 2—5 grs.

Extractum Colocynthidis Compositum (B.P.) also contains aloes and scammony. *Dose*, 12—50 centigrms., 2—8 grs.

Pilula Colocynthidis Composita (B.P.C.) also contains aloes, scammony and potassium sulphate. *Dose*, 25—50 centigrms., 4—8 grs.

Pilula Colocynthidis et Hyoscyami (B.P.), colocynth and extract of hyoscyamus. *Dose*, like the preceding (see also p. 118).

Pilulæ Catharticæ Compositæ (U.S.P.) also contain jalap, gamboge and calomel. *Dose*, 2 pills.

Podophyllum (B.P., U.S.P.), the rhizome and root of *P. peltatum* (*Berberidaceæ*), North America. *Dose*, 0·12—0·6 grm., 2—10 grs. (B.P.). *Podophyllum Indicum* (B.P.) has the same uses and doses.

Podophylli Resina (B.P.), **Resina Podophylli** (U.S.P.). *Dose*, 16—60 milligrms., ¼—1 gr. (B.P.); 0·01 grm., ⅙ gr. (U.S.P.).

Podophylli Indici Rhizoma (B.P.), the rhizome and root of *P. emodi*. Resembles *P. peltatum*, its preparations having the same strength and being given in similar doses.

Cambogia, gamboge, the dried sap of *Garcinia Hanburii* (*Clusiaceæ*), Further India. Reddish yellow, cylindrical pieces, marked with longitudinal stripes from the bamboo canes in which they are dried. When powdered it forms a yellow emulsion with water, and is used as a pigment in water-colour painting. *Dose*, 0·125 grm., 2 grs.

9. ANTHELMINTICS

The most important animal parasites that, in northern latitudes, inhabit the human intestine are the three tape-worms, *Tænia solium*, *Tænia mediocanellata*, and *Bothriocephalus latus*; the round worm, *Ascaris lumbricoides*, and the tiny *Oxyuris vermicularis*, found in great numbers in the rectum. In several places in Southern and Central Europe and elsewhere yet another parasite is found, which is far more dangerous than the others, namely, *Ankylostomum duodenale*, which, when permitted to live undisturbed, may cause profound anæmia that may even result in death. It was first observed in Egypt (" Egyptian chlorosis ") and during the great tunnellings of the Alps (" St. Gothard Tunnel anæmia ").

The intestinal parasites are expelled by the aid of *anthelmintics*, which act upon them either by killing them or, more generally, by so weakening them that they are expelled without resistance by powerful intestinal movements. Anthelmintics do not, however, possess any strictly specific toxicity for intestinal worms, and, as numerous cases of poisoning show, act quite as much upon their hosts. It is therefore necessary for anthelmintics to be of such slow absorption that toxic amounts cannot be taken up in the course of the hours during which the drug must remain in the intestine. The *Ankylostomum duodenale* is found, as the name indicates, in the duodenum, the other intestinal worms farther

down the intestine—another most important reason for slow absorption that can ensure the arrival of the active substances at the haunt of the parasite.

In addition to the activity of the drug itself, the manner in which the treatment is carried out, especially for tape-worm, is of great importance. As a preparatory proceeding a powerful purgative is given, *e.g.* 2 or 3 tablespoonfuls of castor oil, to reduce the contents of the intestine in order that the subsequently administered anthelmintic shall not be too much diluted. The traditional preparatory dieting with salt herring, onions, spices and similar things supposed to be unpleasant for the parasite is superfluous, and the formerly adopted fasting treatment only does harm, as it weakens the patient and increases the danger of poisoning. The following day the drug is taken on an empty stomach, or, still better, after a light meal ; and the patient then lies down, as this is the best way of preventing the vomiting which otherwise often occurs and spoils the result. An hour or two later another purgative is taken—an important proceeding—with the double purpose of removing the poisonous drug and of expelling the parasite, which is often not killed, but only half dead or weakened ; it may obtain a hold once more if not speedily removed. The purgative chosen is again castor oil (see, however, under " Male Fern "), calomel, or some other drug that produces a semi-liquid motion, which removes the not quite dead parasite better than a watery evacuation.

Bothriocephalus latus is the tape-worm which it is easiest to expel ; *Tænia mediocanellata*, with its powerful sucking-discs, is the most difficult, and therefore the best test of a good remedy.

Male Fern (Filix mas, Aspidium)

Male fern is a very old anthelmintic, and a good one both for the three tape-worms and for *Ankylostomum duodenale*. The active constituents are a number of characteristic non-nitrogenous acids, among them being *filicic acid* (filicin), $C_{35}H_{38}O_{12}$, which occurs in a crystalline, inert form, and an amorphous, active form, and several allied, beautifully crystallising substances isolated by Boehm. There is also an amorphous, active body called *filmaron* (Kraft). All these bodies have a great mutual resemblance, and are all compounds of butyric and isobutyric acids with the trivalent phenol, phloroglucin, and several of its homologues. They are secreted by numerous microscopic stalked glands (glandular hairs), which penetrate freely into the large intercellular space of the spongy rhizome. In addition to these

constituents, male fern contains tannic acid and large quantities of a dark green, viscid fixed oil, which constitutes the greater part of the official extract (or oleo-resin).

Action. All the substances enumerated are poisonous. The best known of them, filicic acid, acts on the intestinal canal and the central nervous system in mammals. It produces an ascending paralysis of the spinal cord and, at the same time, an increase in the reflex irritability, appearing first in the form of slight muscular twitchings, which gradually become more frequent, and finally merge into long, very violent attacks of tetanus. As the poisoning proceeds the motor paralysis becomes more prominent, and lessens the violence of the convulsions. Death occurs either immediately after a bad attack of convulsions or from gradually increasing respiratory paralysis, while the heart-action still continues for a short time. The urine often contains a reducing substance, not infrequently sugar. In the stomach and intestine are found swelling of the mucous membrane, hyperæmia and small extravasations of blood. The other acids act in the same way as filicic acid, with slight modifications dependent on the predominance now of the paralysis, now of the convulsions.

Investigations by Straub of the effect upon various lower animals (worms, echinoderms, molluscs and crustaceans) show that the smooth muscles of invertebrate animals are very sensitive to filicic acid, and that the efficiency of the extract as a remedy for tæniasis is probably due to the fact that the muscle of the worm is paralysed. The effect appears even with very dilute solutions. The small tape-worm of the cat, for instance, loses its power of movement and dies in the course of three or four hours in a slightly alkaline saline solution of body-temperature containing 0·01 per cent. of filicic acid, while control specimens in the same solution without filicic acid live much longer.

Filicic acid was formerly considered to be harmless to man, but since the recent employment of larger doses there have been numerous cases of *poisoning*, several of which have ended fatally. Toxic doses produce, both in man and in other mammals, sometimes symptoms of gastro-intestinal irritation, such as nausea, vomiting, abdominal pain and diarrhœa, sometimes serious symptoms from the central nervous system, *e.g.* fainting, prolonged unconsciousness, convulsions which may attain great violence and acquire the character of tetanus, cardiac weakness and shallow respiration, cyanosis, jaundice, albuminuria and, in some cases, temporary weakness of vision or permanent blindness, with atrophy of the optic nerve. In the great majority of cases, however, even doses of 8—10 grammes taken in the course of a few hours can be tolerated without any ill effects worth mentioning. The reason for the possibility of poisoning must be that the patient is already in a weak condition or that, owing to unknown,

unfortunate circumstances, the active principles have been too largely absorbed.

The best *precautions* consist in avoiding extreme preparatory treatment, and in taking care that after one or two hours the extract is removed by thorough purging. The remarkable frequency of poisoning with simultaneous or subsequent employment of castor oil shows that there is every reason for substituting for that purgative some other, such as calomel, senna, Glauber's salt, or Epsom salts. The fixed oil is probably harmful in that, by not quickly producing evacuation, it is favourable to the absorption of the poisonous acids. *Contra-indications* are great weakness, gastric ulcer (on account of the local action upon the gastric mucous membrane) and pregnancy; and great caution is necessary in liver and heart affections. If the treatment is unsuccessful, it must not be repeated until 2 or 3 weeks have passed.

The treatment of poisoning is evacuation of the stomach and intestine, and for the rest symptomatic, mainly with stimulants, camphor injections being apparently especially useful.

In addition to *Aspidium* (*Dryopteris*) *Filix mas*, from which the official rhizome of all pharmacopœias is obtained, there are several other ferns which have an anthelmintic action, among them being the two common European species, *A. spinulosum* and *A. dilatatum*, both of which contain the same and other similar crystalline acids as *A. Filix mas*, with the exception of filicic acid. In America other species of *Aspidium* are employed, and in South Africa, *A. athamanticum*, which, according to Heffter, contains 3 different bodies resembling filicic acid. The fern family, with their strongly-marked morphological characters, have also acquired special chemical distinction by the abundance of substances of this type which they contain.

Cusso (not official)

As regards stimulating beverages and drugs, one is often struck by the remarkable certainty with which, from the earliest ages, man has discovered and utilised those plants which contain some useful or active substance, long before chemistry had demonstrated the occurrence of the same substance in all these plants. The plants containing caffeine, for instance, were all in use hundreds or thousands of years before caffeine was known (*cf.* p. 175). This is also the case with the ferns. Those which contain large quantities of filicic acid, etc., are the very ones that in the most diverse quarters of the globe have been found and

used as anthelmintics, whereas the knowledge of the existence of these substances is of quite recent date. Great interest attaches, in this connection, to the fact that another old anthelmintic called *Cusso*, coming from quite a different order of plants (*Rosaceæ*), has now proved to resemble entirely, in chemical respects, the anthelmintic ferns. The flowers from which cusso is produced contain several substances (of which the most important is the amorphous *kosotoxin*, $C_{36}H_{34}O_{10}$), which, with a few minor differences, have the same action as filicic acid, and like it are compounds of butyric acid with phenols of the phloroglucin series. Kosotoxin, like filicic acid, is a well-marked muscle poison in lower animals, and thus probably acts as an anthelmintic, but has little effect upon the central nervous system.

The action of cusso is very dependent upon the quality of the drug. The comparatively fresh, red kind is a very efficient anthelmintic. Nausea and vomiting are often seen among its secondary effects, but rarely toxic symptoms of a more serious nature resembling those occurring after filicic acid.

Kamala (not official)

The red glands of the fruit of *Rottlera tinctoria*, an old Indian dye-stuff and anthelmintic, have also been occasionally used in Europe during the last 60 years in cases of tape-worm, but the drug has of late fallen into disrepute owing to its frequent adulteration. Good kamala is said to act with more or less certainty on tape-worm, and, in its quality of a mild drug with no unpleasant odour or taste, should be employed for children and feeble persons, and, in general, where it is desirable to avoid the strongly acting filicic extract. The active constituent *rottlerin*, $C_{33}H_{30}O_9$, a resinous substance which crystallises in reddish yellow laminar crystals, is also a phloroglucin derivative, and resembles filicic acid in its action. As kamala is mildly aperient, it is as a rule unnecessary to conclude the treatment with a purgative.

Granatum and Pelletierine

In the bark of the pomegranate-tree there occur four alkaloids, isolated by Tanret, of which the best known is *pelletierine*, $C_8H_{15}NO$. Both in the frog and in warm-blooded animals it produces increased reflex irritability and convulsions. After large doses curara-action develops, which leads to failure of respiration (Major and Loup).

Pelletierine is a specific poison for tape-worm. *Tænia serrata*, which almost invariably occurs in the cat's intestine, can live for several days in a saline solution (1 per cent. of NaCl + $\frac{1}{10}$ per cent. of Na_2CO_3 at a temperature of 37° C.), but according to von

Schröder's experiments, dies in the course of five to ten minutes when pelletierine is added in the proportion of 1 in 10,000, while far stronger solutions had no effect upon a species of round worm (*Ascaris mystax*).

The bark of the pomegranate-tree is used solely for tape-worm, and is one of the surest remedies when the fresh drug is obtainable. On account of its large percentage of tannic acid (*circ.* 22 per cent.), it often produces nausea and vomiting, which it is endeavoured to prevent by the assumption of a horizontal position and the swallowing of fragments of ice. The drug should be followed after 1 or 2 hours by a purgative. In India, Granati Cortex is much employed for dysentery and chronic diarrhœa. The disadvantages of the crude drug are largely overcome by employing the alkaloid pelletierine which is official in the form of the tannate (B.P., U.S.P.).

Areca Nut (not official)

The seed of the Areca palm—the areca nut or betel nut—is used principally in veterinary medicine for the tape-worm. It contains several alkaloids, of which *arecoline*, $C_8H_{13}NO_2$, is the most important. Its action resembles that of muscarine and pilocarpine, and among other effects causes an abundant secretion of sweat and contraction of the pupil. Among the Malays, betel-chewing, that is to say, the chewing of small pieces of areca nut mixed with betel leaves and a little lime, supersedes to a great extent the use of tobacco.

Santonin

Whereas there are numerous remedies for tape-worm, the only remedy until recently known for round worm was *santonin*, $C_{15}H_{18}O_3$, an acid anhydride occurring in the flowers of *Artemisia pauciflora*, a plant growing on the salt steppes of Turkestan. Originally a white substance, it turns yellow on exposure to light, but without any appreciable loss of efficiency.

Although santonin expels the round worm, it does not appear to be very poisonous to it. According to von Schröder's experiments, these parasites, when placed in an alkaline saline solution of body-temperature containing $\frac{3}{4}$ per cent. of sodium santoninate, continue to live and move for at least 24 hours; nor do they die when placed in olive or castor oil containing so much santonin that they gradually become covered with the crystals deposited. They only appear to be uncomfortable, are restless, and make attempts to escape over the edge of the glass. This exactly corresponds with what is found in treatment with san-

tonica or santonin. The ascarides are expelled alive, apparently in full vigour, and only become motionless after some time from the exposure to cold, to which they are very sensitive. Santonin does not therefore kill round worm, but makes its abode in the small intestine so unpleasant that it escapes from the advancing drug into the large intestine, whence it is easily removed by a purgative. Santonin is also a muscle-poison. Preparations of isolated muscle, without nerve-cells, of earth-worms, leeches and ascarides, which remain motionless for days in a pure Ringer's solution, immediately contract on the addition of a little santonin to the solution (Trendelenburg).

In man, large doses of santonin cause *poisoning*. The slightest symptoms of absorption are manifested by anomalies of colour perception. All objects appear at first to have a bluish or violet tinge, later a bright yellow hue. The first stage is brief, and is often unnoticed by the patient, while the xanthopsia is more lasting. During this stage it is especially clearly-illuminated objects that appear yellow, while dark blue and violet are only slightly perceptible, or appear black. The reason is probably in the first place irritation and then paralysis of the elements of the retina or the optic nerve which appreciate violet, so that the eye becomes violet-blind and the complementary colour yellow appears abnormally vivid. Anomalies of smell and taste may appear simultaneously with aberrations of sight.

The chromatopsia described occurs frequently without other symptoms of poisoning. When large quantities of santonin are absorbed, numerous more important symptoms appear—vomiting, abdominal pains and diarrhœa, strangury, hæmaturia, unconsciousness, and finally convulsions of various kinds, sometimes epileptiform attacks, sometimes tonic spasms, which originate in the brain and spinal cord. The medulla oblongata appears to escape, and only in very advanced poisoning does respiratory paralysis occur. It should be remembered that santonin convulsions—as a case described by Binz shows—may be one-sided, which is a condition of the greatest rarity in poisonings. When, in forensic medicine, the often difficult question of poisoning or disease has to be decided, it is customary to consider unilateral spasm as indicative of the latter state.

The greater part of the santonin taken internally leaves the body unchanged with the fæces. A part, however, is absorbed and oxidised in the organism, and is excreted through the kidneys as compounds which give to the urine a deep yellow or greenish yellow colour, changing to purplish red on the addition of alkalies. As already mentioned, the urine exhibits the same changes of colour after the use of purgatives containing emodin and chryso-

phanic acid, *e.g.* rhubarb. From which of these it here derives its colour may be determined by shaking the urine with ether, which takes up emodin, etc., but not the santonin colouring matter; or, by adding lime-water, which precipitates the former but not the latter.

In cases of poisoning with santonin the stomach should be emptied as quickly as possible by the stomach-tube (if the convulsions permit) or an emetic, *e.g.* an apomorphine injection, and the intestine by a purgative or enema. For the convulsions, if very violent, ether or chloroform inhalations are given, or repeated doses of chloral; and in cases of great collapse the usual stimulants are applied.

In order to avoid the risk of poisoning it is advisable not to give santonin on an empty stomach, as it is soluble in the acid gastric juice, and, as already mentioned, is absorbed in the stomach. If taken fasting, the toxic action will therefore be very liable to dominate the anthelmintic.

Chenopodium

Oleum Chenopodii is a new drug which originated in America, and of late years has also been frequently employed in Europe for tape-worm, round worm and hook-worm. Its chief constituent is the liquid ascaridol, $C_{10}H_{16}O_2$. The anthelmintic action is due to first stimulation and then paralysis of the worm's muscle. Preliminary starvation and purgation are unnecessary, but a brisk saline purge should be administered about 2 hours after the last dose of the drug. In ankylostomiasis three doses of 0·5 mil of the oil may be given at hourly intervals. A single dose of 0·5 mil is sufficient for the removal of round worms. A similar amount is sometimes emulsified and added to an enema of infusion of quassia (10 per cent. Infusum Quassiæ, B.P.) or saline in the treatment of thread-worm infection; in intractable cases, the oil may be given by mouth, but it should be emulsified and flavoured with a suitable preparation of ginger. When rightly employed the oil appears not to be dangerous; but several fatal cases of poisoning have been seen after too large doses, the symptoms being gastro-intestinal irritation, noises in the ears, deafness, coma and convulsions.

Carbon Tetrachloride

This anthelmintic is used exclusively in ankylostomiasis, especially when due to *Necator americanus*. The drug is insoluble

and is therefore administered in capsules. Alternatively, it may be mixed with milk which masks the burning taste of the drug; this, however, is less desirable. A dose of about 3 mils is given early in the morning while the patient is fasting and 2 hours later the bowel is emptied with a saline purgative. As carbon tetrachloride is soluble in oil and alcohol, fatty food and alcoholic beverages must be avoided during the treatment. Its effects *on absorption* recall the actions of the methane series of general anæsthetics which are lipoid-soluble. Thus the drug acts as a narcotic and is particularly liable to cause fatty degeneration of the liver.

Large numbers of cases of hook-worm disease have been treated successfully with a mixture consisting of 60 per cent. of carbon tetrachloride and 40 per cent. of oil of chenopodium.

As in the case of many other volatile substances, carbon tetrachloride may be employed externally as a counter-irritant. If inhaled, however, the vapour may cause serious bronchitis.

Thymol

The value of thymol as an anthelmintic is mentioned on p. 247.

In addition to the above, several other less important anthelmintics are employed, a few of which were formerly official. Two of these are mentioned below.

In several European countries, *Cucurbitæ Semina* is a household remedy for tape-worm, consisting of the seeds of the numerous cultivated varieties of the pumpkins *C. maxima* and *C. Pepo*, deprived of their shells. It is given in doses of 100 grms., the seeds being bruised with a little water and honey to a creamy consistency; or it may be given as a decoction (200 grms. of seed in 1 litre of water reduced to half the amount by boiling); it is said to act well and without inconvenience. Pumpkin-seed contains 40—50 per cent. of a fixed oil with a pleasant, mild flavour; the active constituents are not known. This drug may also be employed with advantage immediately before treatment with filicic extract.

The flesh and milk of the *cocoa-nut*, taken in large quantities, are also said to effect the expulsion of the tape-worm with its head. As a very innocent remedy, it at any rate deserves a trial.

Preparations and Doses

Filix Mas (B.P.), *Aspidium* (U.S.P.), male fern, the large, spongy rhizome of *Dryopteris Filix mas* (and of *D. marginalis*, U.S.P.), covered with the brown scales of the bases of the petioles, and of a pale green colour within. The first of these ferns is distributed over large areas of the northern hemisphere, the second is a native of North America. *Dose*, 4—12 grms., 60—180 grs. (B.P.).

Extractum Filicis (B.P.), **Oleoresina Aspidii** (U.S.P.), a greenish, oily liquid with a disagreeable taste. *Dose*, 3—6 mils, 45—90 mins. (B.P.); 4 grms., 60 grs. for a single dose, once a day (U.S.P.). Larger doses are

often employed, however (some European pharmacopœias give 10 grms. as the maximum dose), *e.g.* 6—8 grms. to be taken in capsules in the course of 3—4 hours. For children the maximum dose may be given as 0·5 grm. for each year of the child's age, up to 4 grms. After 1 hour a purgative, *e.g.* calomel, senna (black draught), or a saline purgative.

Cusso (B.P.C.), kousso, the pistillate flowers of *Brayera anthelmintica* (*Rosaceæ*), Abyssinia. *Dose*, 8—16 grms., 120—140 grs. Taken stirred into peppermint water or as a 10 per cent. decoction in the course of 2 or 3 hours, after which a purgative is given.

Kamala (not official), a red powder, consisting of glands and glandular hairs (see p. 342). *Dose*, 6—12 grms. taken in the course of 1—2 hours; for children under 5, 1—2 grms. in honey.

Granatum (not official), pomegranate bark, the bark of *Punica Granatum* (*Punicaceæ*), a native of Western Asia, cultivated as an ornamental plant in many parts of the world. *Dose*, 2 grms., 30 grs. Much larger doses are generally taken, *e.g.* 20—40 grms. as a 10—20 per cent. decoction, drunk slowly in the course of an hour. Very efficacious if it does not cause vomiting. An hour later 2 tablespoonfuls of castor oil.

Pelletierinæ Tannas (B.P., U.S.P.), a mixture of the tannates of the pomegranate alkaloids. *Dose*, 12—50 centigrms., 2—8 grs. (B.P.); 0·25 grm., 4 grs. (U.S.P.). The effect is uncertain; the alkaloids are probably absorbed too soon.

Santoninum (B.P., U.S.P.), white, flat prisms which become yellow on exposure to light; insoluble in water. *Dose*, 6—20 centigrms., 1—3 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.); for adults up to 30 centigrms. a day; for children of 2—8 years, 6—12 centigrms., 1—2 grs. a day. Castor oil or calomel is given as a purgative.

Trochiscus Santonini (B.P.C.), containing 6 centigrms., 1 gr.

Oleum Chenopodii (B.P., U.S.P.), American worm-seed oil, a volatile oil of camphoraceous odour and bitter taste distilled from the seeds of *Chenopodium anthelminticum* (*Chenopodiaceæ*), North America. *Dose*, 0·2 mil, 3 mins. Taken in capsules or on a piece of sugar. Many writers recommend larger doses—especially against hook-worm, *e.g.* 15 drops two or three times at intervals of an hour, and 2 hours after the last dose 2 tablespoonfuls of castor oil. For tape-worm and round worm smaller doses are said to be sufficient. For children, as many drops as the years of the child's age, up to 8 drops, but only once, and then castor oil. If 3 hours have passed without an evacuation, another purgative is given. Official *dose*, 0·2—1 mil, 3—15 mins. (B.P.); 1 mil, 15 mins. (U.S.P.).

Carbonei Tetrachloridum (B.P., U.S.P.), a clear, colourless, volatile liquid. Not inflammable; insoluble in water. *Dose*, 2—4 mils, 30—60 mins. (B.P.); 2·5 mils, 40 mins. (U.S.P.).

Butolan, a proprietary remedy administered by mouth in the treatment of thread-worm infection; a convenient and effective drug. It lacks the unpleasant taste of oil of chenopodium.

III.—SALTS OF LIGHT METALS, ALKALIES, ACIDS, HALOGENS, OXIDISERS, ETC.

1. ION-ACTION AND SALT-ACTION

SOLUBLE inorganic salts exert their own specific chemical action, *ion-action*, and also a common action due to physical changes, the so-called *salt-action*. To explain this, a few preliminary remarks on solutions must be made.

When common salt or sugar is placed in water, the solid matter gradually disappears and a clean solution is formed. Until recently it was taken for granted that these two liquids were of the same constitution and contained respectively salt and sugar molecules evenly diffused through the water. A comparison of the physical conditions of the solutions, however, reveals several differences. If the two solutions are equi-molecular—*i.e.* if they are so prepared that they contain, in equal volume, the same number of molecules—they would both, if the old theory were correct, exert the same osmotic pressure, and both show the same differences from pure water with regard to boiling and freezing points. This, however, is not the case. The salt solution has a far higher osmotic pressure, a lower freezing point, and a higher boiling point than the sugar solution. The salt solution thus behaves as though it contained a greater number of molecules than the sugar solution, and, moreover, it is a conductor of electricity, whereas the sugar solution is non-conducting. Upon these differences is based the theory that the salt solution not only contains sodium chloride as molecules, NaCl, but that all or some of them are split up into electrically-charged parts or *ions* (from ἰων = going, because they go to their respective poles), namely, positive sodium ions (Na^+) and negative chlorine ions (Cl^-). Each of these ions has the same influence upon the osmotic pressure as an entire molecule, and they therefore give to the salt solution a higher tension than that of the sugar, the molecules of which are not dissociated into ions. Many circumstances that formerly appeared to be inexplicable deviations from the laws of osmosis and diffusion have thus been made clear; and the apparent irregularities with regard to freezing and boiling points are satisfactorily explained by the fact that each ion has the effect of an entire molecule. The division of molecules into ions

is called *electrolytic dissociation*, and the substances undergoing dissociation are electrolytes. Ions alone can convey electricity, therefore only electrolytes are conductors. Dissociation takes place by solution, for dry salt is not a conductor of electricity, nor yet is pure water.

A salt solution thus contains, according to the theory of electrolytic dissociation, both non-dissociated NaCl molecules and Na and Cl ions. The dissociation increases with the dilution of the solution, and in very dilute solutions is complete, so that the salt in them is only in the form of Na and Cl ions. Even in a 1 per cent. solution, 86 per cent. of the salt is dissociated.

As with common salt, so is it with all salts, acids and bases that are electrolytes, *i.e.* conductors of electricity. The salts are split up into positive metal ions and negative acid ions, the bases into negative OH ions and positive metal ions, the acids into positive H ions and different negative ions for each acid. *In most*, if not all, *chemical reactions in solutions, it is not molecules, but ions, that take part in the reaction*. The whole of analytical chemistry rests upon ion-reaction. An example will make this clear. It is well known that the presence of chlorine is demonstrated by the aid of a nitrate of silver solution, which gives with chlorine insoluble silver chloride, but the reaction takes place only when Cl ions are present; potassium chloride gives the well-known white deposit of AgCl, because the salts are dissociated according to the formula $\overset{+}{K} + \overset{-}{Cl} + \overset{+}{Ag} + \overset{-}{NO_3} = AgCl + \overset{+}{K} + \overset{-}{NO_3}$, and thus both silver and chlorine are present as ions. Potassium chlorate, on the contrary, gives no reaction, because it is dissociated as follows: $KClO_3 = \overset{+}{K} + \overset{-}{ClO_3}$. Chloroform, although it contains about 90 per cent. of Cl, is unaffected by nitrate of silver because the chlorine does not occur as ions.

The specific actions which dissociable compounds exert upon the body are also due to ion-reaction, and are absent when the element or group in question does not occur in the form of ions. Ferrocyanide of potassium is quite devoid of the cyanide action, because it is dissociated in the following manner: $K_4Fe(CN)_6 = \overset{+}{K} + \overset{+}{K} + \overset{+}{K} + \overset{+}{K} + \left\{\overset{-}{Fe}\ \ \overset{-}{(CN)_6}\right\}$. Similarly those organic compounds which contain the metals firmly fixed are deficient in the characteristic metal reactions and actions. Ferrocyanide of potassium, for instance, does not possess the physiological iron actions; the solid organic arsenical compounds are not poisonous in the same way as arsenic; and such mercurial compounds as are not dissociated into the Hg ions so poisonous to bacteria are

scarcely antiseptic at all. The intensity of the action rises and falls with the number or concentration of the ions. If the dissociation of a salt of mercury is repressed by the aid of a compound that has an ion in common with the salt, its activity is weakened. Corrosive sublimate, which is dissociated to $Hg^{++} + Cl^{-} + Cl^{-}$, is highly antiseptic ; but on the addition of common salt, which also yields Cl^{-}, the dissociation becomes less complete, the number of Hg ions decreases, and with it the antiseptic action. This is illustrated in the clearest possible manner by the following experiment by Paul and Krönig, which shows the effect of an aqueous corrosive sublimate solution with increasing additions of sodium chloride upon anthrax spores.

Molecular strength of solution.	Percentage of solution.	Number of spores capable of germinating after 6 minutes.
1 $HgCl_2$	1·69 $HgCl_2$	8
1 ,, + 1 NaCl	1·69 ,, + 0·365 NaCl	32
1 ,, + 2 ,,	1·69 ,, + 0·73 ,,	124
1 ,, + 3 ,,	1·69 ,, + 1·095 ,,	282
1 ,, + 4 ,,	1·69 ,, + 1·46 ,,	382
1 ,, + 6 ,,	1·69 ,, + 2·19 ,,	803
1 ,, + 10 ,,	1·69 ,, + 3·65 ,,	1,087

The action of the dissociated inorganic salts is dependent now upon the metal ion, now upon the acid ion ; and which of these is to determine the issue is mainly a question of which ion is the greater poison to the organism. In potassium chloride the potassium ion is the determining one, because every cell is already saturated with Cl ions, while in potassium bromide the action of the bromine ion is so conspicuous that the potassium ion has no significance. Sodium ions are present everywhere in the body, and the specific action of the sodium salts is therefore only dependent upon the negative ions. It will be seen from these examples that it is a mistake, in speaking of the action of the salts, to place all the potassium salts in one group, all the sodium salts in another, and so on. They must be classed in another manner, namely, according to the ions that determine the action.

The so-called **salt-action** is quite different from the specific, chemical action. The salt-action depends upon the osmotic conditions of the solution, and consequently upon the *number* or the *concentration* of molecules and ions, without regard to their chemical nature.

If distilled water and a salt solution are poured carefully—so as not to mix the liquids—into the respective arms of a U tube,

an interchange of constituents, or diffusion, immediately begins at their surface of contact. Water passes over into the salt solution, and salt from the solution into the water, until the liquid contains the same number of molecules or ions throughout its volume-unit. When this point is reached the liquid has everywhere the same pressure or tension, and the solutions in the two arms of the tube are said to be *isotonic*.

If the water and the salt solution are separated by a membrane which permits equally of the passage of water and of salt, the interchange takes place in the same way, and the level in the arms of the tube remains unaltered ; if, however, the arms of the tube are divided off by a semi-permeable membrane through which water can permeate but not salt, only the water is diffused over to the salt, and not the salt to the water. The level therefore rises in the arm containing the salt solution, until a pressure results, the *osmotic pressure*, determined by the concentration, *i.e.* by the number of molecules and ions, and prevents the continued entrance of water, and also prevents the water taken up from returning. The osmotic pressure may thus also be defined as the force with which the salt holds the water. If there are solutions of different osmotic pressures, one on each side of the membrane, the water finds its way from that with the lower pressure, the *hypotonic* solution, to the more concentrated or *hypertonic* solution, until *isotony* is established. Thus hypertonic solutions attract water from hypotonic. All animal membranes are permeable by water, whereas the behaviour of the salts varies, some passing almost as freely as water, most of them less easily, and others only with great difficulty or, practically speaking, not at all. With regard to these last, therefore, the cells are like semi-permeable membranes.

The contents of most animal and vegetable cells consist of inorganic and organic, more or less easily diffused salts (crystalloids) and organic compounds, *e.g.* albumins (colloids), which do not diffuse. The maintenance of the special proportion of these constituents for each cell is a condition for the normal working of the cell. Even very small changes may have far-reaching consequences for the activity of the cells, and greater changes may cause their death. More or less vital changes in composition and osmotic tension—*salt-action*—occur when salt solutions which are hypertonic or hypotonic in relation to the cells and the fluids of the body are introduced into the organism. Osmotic currents are produced which endeavour to bring about isotony. If the new solution is hypertonic, it deprives the tissue of its water (and gives up some of its salt, if the latter is diffusible in relation to the cells) ; if it is hypotonic, the cells take up water and increase in volume.

This may be demonstrated on a large scale by letting the yolk of an egg represent the cell. If the yolk of an egg be placed in a concentrated solution of common salt, it shrinks up, and its contents assume a brighter yellow colour. If placed in distilled water it swells up and becomes pale in colour and translucent, and some of its salts are diffused into the water ; but as the water makes its way much more quickly into the yolk than the salts make their way out, the yolk at lasts bursts like a closed receptacle the contents of which exert too great a pressure upon its walls. A similar sudden end probably comes to specially exposed cells, *e.g.* those of the gastric mucous membrane, by the prolonged influence of very hypotonic solutions (drinking cures).

This experiment, however, like the comparatively simple experiments with various membranes outside the body, gives only a very rough idea of the salt-action. In the living organism, with its very composite solutions containing both colloid substances and salts, some of which make their way into the cells while others fail to do so, and each of which acts with its own partial pressure, the conditions are infinitely more complicated. The behaviour of the various cells to the salts differs very widely, and often shows a special affinity for certain substances. The salts of several of the solid alkalies, and several kinds of sugar, which are very easily taken up by the intestinal epithelium, hardly make their way at all into the red blood-corpuscles ; again, sodium sulphate passes quickly through the vascular walls, but is very slowly taken up through the intestine. This elective power of the cells, which plays so great a part in absorption in the intestine, cannot at present be satisfactorily explained.

2. SALT-ACTION (*continued*)

WATER AND COMMON SALT

Water is dissociated according to the formula $H_2O = H + OH$, but the dissociation is so trifling (in $12\frac{1}{2}$ million litres, 1 gramme-molecule, 18 grammes water dissociated into ions), that it has no physiological influence. Pure water, therefore, produces only osmotic changes without complicated ion-action. The behaviour of the salts differs according to their chemical nature. The indifferent, readily soluble and easily absorbed sodium chloride, which forms a normal constituent of the cells of the body, has practically only osmotic action within the organism, while other readily soluble and absorbable salts, *e.g.* alkaline carbonates, iodide and bromide of potassium, etc., exert both salt-action and specific ion-action.

As has been explained in the foregoing pages, the nature of

the osmotic change is determined by the difference in concentration between the salt solution employed and the contents of the cell. Whether a solution is isotonic with certain cells can be ascertained by observing whether it alters their volume. Constant volume is a product of equal external and internal pressure, and, therefore, a solution that has the same osmotic pressure as the cells leaves their volume unchanged. It does not follow from this that it is inert, for if the solution contains salts that are diffusible in relation to the cell, and if the cell and the solution have not exactly the same constitution, a mutual diffusion or exchange of constituents takes place without any change in volume, but with a change in the chemical nature of the cell. Physical isotony is not, therefore, identical with *physiological isotony*. Strictly speaking, even the so-called physiological saline solution is not physiological, for besides sodium, each cell contains other metals, potassium, magnesium, calcium and iron, whose ions are to some extent displaced by sodium ions (Loeb). In the animal organism, however, common salt is so much in excess of the other salts that its action may be regarded as representing *the true salt-action* which is to be considered in this chapter. Water will also be mentioned here, as its action answers to that of very dilute salt solutions.

Special Salt-Actions. Water and hypotonic salt solutions, wherever they are in contact with the tissue for a sufficient length of time, cause the cells to swell up by making them more watery and depriving them of some of their diffusible salts. In this way water may be injurious. Many salt-water fish, for instance, may die in ordinary water, and fresh-water fish in distilled water, even if a constant supply of air is provided. On the other hand, hypertonic solutions cause the tissues to shrink by withdrawing water.

All tissue is not affected equally, however. Water has no great influence on the human **skin**, as it is saturated with the secretion of the sebaceous glands, which, like the oiled feather-covering of swimming birds, prevents the entrance of water. A superficial softening takes place only with prolonged bathing, principally on the palms of the hands, the soles of the feet, and the finger-tips, where there are no sebaceous glands: there is no absorption. Riess found that in diseases of the heart and kidneys, or emphysema, obstinate œdema might disappear during a bath lasting for 24 hours or more, notwithstanding that the flow of urine was constant, or decreased, so that the loss of water was through the skin. Bathing in strong salt solutions irritates the skin. At first it becomes pale and anæmic, but the vaso-constriction is soon followed by hyperæmia and redness, while the heart-beat, which was at first accelerated, becomes slow. It has

been found that the excretion of urea, and the absorption of oxygen and elimination of carbonic acid are increased. These effects, however, also depend very much upon the temperature of the bath. There is no absorption of salt through the skin.

On **wound-surfaces** both hypotonic and hypertonic solutions have an irritant action and cause smarting, whereas isotonic solutions of neutrally reacting salts give no pain. In surgery, salt solutions which are approximately isotonic with the blood are employed for washing out the peritoneal cavity, and not pure water, which would injure the epithelium of the serous membrane. Highly concentrated solutions dry up the tissues, whether living or dead, so much that the growth of micro-organisms is prevented; hence the preservation of food by salting, and the fact that wound-surfaces are kept clean when strewn with sugar, an old remedy employed before antiseptics were known.

The healthy **gastric mucous membrane** is impermeable by water, which, as is well known, is not absorbed in the stomach. Weak salt solutions probably cause, more especially when the resistance of the mucous membrane is lowered by disease, a swelling which leads to the shedding of the old epithelium and formation of new. This explains the beneficial effect of many mineral waters containing little salt on chronic catarrh. Solutions that are considerably more concentrated than the blood cause irritation, hyperæmia, pain, nausea and vomiting. Large quantities of water-absorbing salts in solid form produce acute gastro-enteritis (suicide in China with dry salt). The dietetic employment of common salt is based, not only upon its importance as an indispensable inorganic salt, but also upon its palatableness as a condiment. In the **intestine,** concentrated solutions produce irritation and peristalsis, and act as aperients if the salt is not soon absorbed. Slowly-absorbed neutral salts are aperient, whether given in dilute or concentrated solution, and will be mentioned in a separate chapter.

Muscle and **nerves** soon die both in hypotonic and hypertonic solutions. The powers of contraction and conduction are preserved better in isotonic salt solutions, but cease comparatively quickly, probably because the sodium ions, as already mentioned, take the place of other ions, especially calcium and potassium. If the solution also contains these metal ions, the activity of the cell continues. The extirpated heart of a frog, perfused with an isotonic salt solution, soon dies in diastole, but death is postponed for some time by the aid of Ringer's solution, which contains also sodium carbonate and chlorides of calcium and potassium.

The **red blood-corpuscles** shrink up in hypertonic, and swell in hypotonic solutions of salts, which penetrate them with difficulty;

but they retain their size unchanged in solutions that are isotonic with the serum. In the case of mammals this is a 0·9 per cent., and of frogs a 0·6 per cent., solution.

The osmotic pressure of the **blood**, which is principally due to the inorganic salts of the serum and the blood-corpuscles, remains steadily constant. Eating, drinking, thirst, sweating, diuresis, and retention of urine in cardiac or renal diseases only very slightly alter the pressure. Even when hypotonic or hypertonic solutions are injected in large quantities directly into a vein, the surplus of water or of salts very quickly disappears from the blood.

This perfect regulation is probably brought about through the medium of capillary walls and kidneys somewhat in the following manner :—

When *water* and *hypotonic salt solutions* are taken up by the blood, the kidneys are supplied with a diluted blood, and excrete an increased amount of urine. Even before the diuresis has begun, the equalising of the osmotic pressure is provided for in another way, namely, by the passing of the fluid from the blood-vessels to the tissues, whence, as soon as the diuresis has begun, it returns to the blood. The injection of large quantities of *isotonic solutions* into the blood does not change the osmotic pressure, but the blood becomes diluted and the relations between blood-cells and plasma are disturbed. Sollmann's experiments show that in this respect also there is a marked tendency to preserve the normal proportions. The injected solution disappears from the circulation even before any diuresis has begun ; both the water and the salts have left the blood-vessels after the lapse of a few minutes, and after ½ hour the composition of the blood is in every respect as before. Subsequently they return slowly and are excreted through the kidneys. If a *hypertonic salt solution* is introduced into the blood, a flow of water passes with great rapidity from the tissues into the blood-vessels, so that the tissues dry up, producing thirst, and the superfluous salt solution in the blood is excreted by a rapid diuresis. On the other hand, some of the injected salt diffuses first into the tissues, and subsequently returns as dilute solution, which is also excreted in the urine. Thus, if the thirst is not quenched, the ultimate result of the salt-diuresis is that the organism loses fluid. Pure salt-diuresis is assisted, in the case of several salts, by the stimulating action of these salts on the renal epithelium.

When *great quantities* of concentrated salt solution are injected subcutaneously or intravenously, the most extreme osmotic effects are obtained. The red blood-corpuscles shrink, and clump together in thrombi in the smaller vessels. In mammals there is increased reflex irritation, tremor and motor weakness, later, unconsciousness and coma, accompanied by convulsions that become more and more frequent and end in tetanus. The blood-pressure remains more or less unchanged until a short time before death, which often takes place after violent convulsions. The symptoms are much the same with all indifferent salts and other substances, like sugar, that absorb water, and are probably due to the fact that the central nervous system is deprived of water (*cf.* the occurrence of convulsions with violent diarrhœa or in cholera).

The Urine. Both water and solutions of indifferent and easily absorbed salts, whether dilute or concentrated, increase the

amount of urine. The composition of the urine is also changed. Large quantities of salt, which cause great diuresis, spare and reduce the elimination of nitrogen, provided that the dehydration of the tissues is prevented by an abundant supply of water. If, on the contrary, the water given is insufficient for the excretion of the salts, so that fluid must be taken from the tissues, there is increased protein breakdown and excretion of urea. It is thus not a direct salt-action, but a symptom of a change in nutrition caused by the loss to the tissue of a part of its normal fluid. After drinking of abundance of water, the urine has a low specific gravity and a pale colour, and is comparatively poor in solids. Nevertheless, the absolute or daily excretion of salts is increased, for the fluid which at first passes from the blood to the tissues returns to the blood-vessels as dilute salt solutions, *i.e.* the tissues have been washed out. The absolute amount of nitrogenous constituents, especially of urea, is also increased ; this is explained by the fact that water increases the protein metabolism. It is doubtful, however, whether the influence is as great as is often supposed, for, as a rule, the amount of urea diminishes again in spite of continued diuresis ; this shows that the first increased excretion is partly, at any rate, due to the circumstance that the urea and similar products of metabolism, like the salts, are only washed out more completely. Chemical exchanges between the normal tissue salts and those introduced into the body will alter the proportion between the inorganic constituents of the urine. The relation of potassium salts to the normal salt of the blood is of special importance. An exchange takes place on the following plan : $K_2CO_3 + 2NaCl = 2KCl + Na_2CO_3$. Thus from the one salt originate two, both of which are to be excreted as superfluous, and both causing diuresis ; *the potassium salts*, therefore, *have a stronger diuretic action than the sodium salts*. By a continued supply of potassium salts, the body is at last impoverished as regards sodium chloride, and there is a strong desire for salt and very salt food.

Bunge shows, in a number of interesting examples, that there is a great need of salt in men and animals that live principally or entirely on vegetable food containing an abundance of potash, while the need of salt is very slight with those taking a meat diet, which contains relatively far more sodium salts. Herbivorous domestic animals, such as the cow and the horse, eat salt with avidity, whereas a dog or a cat shows a dislike for salt meat. Many travellers relate how highly salt is prized by native tribes that live on a vegetarian diet, while by the flesh-eating tribes, which neither sow nor reap, but live on the flesh and milk of their herds, it is not missed, or is even so little of a necessity to them that there is no word for salt in their vocabulary. The same thing in a minor degree appears among civilised nations in the form of a considerable difference in the consumption

of salt between the agricultural, vegetarian population of the country, and the meat-eating dwellers in towns. Statistics show, for instance, that in France the consumption of salt per head in the country is three times that in the towns.

Therapeutic Uses. Salt is widely employed as an *emetic* by the lay public. A tablespoonful of salt is dissolved in a tumberful of warm water and the solution is sipped until vomiting occurs. Alternatively, a teaspoonful of dry salt may be taken and washed down with a small quantity of water. Large quantities of dry salt, however, *e.g.* $\frac{1}{4}$—$\frac{1}{2}$ kilogramme, will cause, like any other water-absorbing substance, violent gastro-enteritis, which may result in death. The addition of salt to an enema increases its aperient action, and saline enemata (an ounce to the pint) are frequently used in thread-worm infection. When saline is given rectally, the continuous drip method is preferable to occasional injections. Patients who are able to take fluids by the mouth should be encouraged to drink isotonic saline, as this is retained much longer in the tissues.

In **collapse** and **great loss of fluid,** *e.g.* in hæmorrhage, prolonged diarrhœa, diabetic coma, etc., isotonic saline solutions are injected subcutaneously or intravenously to raise the blood-pressure. The addition of 6 per cent. of gum acacia to isotonic saline gives the preparation an osmotic pressure equal to that of the blood-proteins, and filtration of this colloidal solution by the kidney is retarded. For intravenous injection gum-saline is therefore preferable to normal saline, but it is not, of course, so satisfactory as blood-transfusion. Formerly it was customary, when large quantities were to be injected, to use Ringer's solution, which, in addition to sodium chloride, contains sodium carbonate and the chlorides of potassium and calcium (see Preparations below). When a hypertonic solution of salt is injected intravenously, water is attracted from the tissue-spaces and cerebro-spinal fluid into the blood-stream, and thus the effects of increased intra-cranial pressure may be relieved temporarily. For this purpose 10—20 mils of 30 per cent. saline are injected *very slowly.* Superfluous sodium chloride ingested by the food or otherwise is rapidly excreted by the kidney, and salt is therefore to be regarded as a *diuretic.* An adequate supply of sodium is essential to life and is ensured by the maintenance of a definite proportion between the salt and water content of the tissues. To promote this, there exists a complex mechanism partly controlled by the hypothalamus and subject to the hormonal influence of the posterior pituitary and possibly the adrenal cortex. Experiments on man and animals prove that to deprive the body of sodium results in grave constitutional disturbances resembling the manifestations

of Addison's disease. In recent years, therefore, common salt has been used with good results in the treatment of this disease, suggesting that the mode of action of the cortical hormone is in some way related to the sodium metabolism.

Sodium chloride is a constituent of many *natural* **mineral waters** ; these are solutions formed by the absorption by water, in its passage through various strata of the earth, of salts, and often considerable quantities of carbonic acid. They are sometimes employed externally in the form of baths, sometimes for methodical drinking cures. Whether each of the various salts exerts its own special irritation of the skin is not known ; this is probably determined principally by its relation to water, and thus the salts with the greatest attraction for water, *e.g.* calcium chloride, are the most active.

Those constituents of which there is only very little in a mineral water play no part in a hydropathic cure. This still seems to be little understood in many places, for one often sees in the prospectuses of bathing-places milligrammes of iodine and bromine compounds carefully emphasised, or a small proportion of iron utilised for the mention of " chalybeate baths." As the salts are not absorbed, and do not either, in very weak solution, act upon the skin, baths in water containing but little salt and carbonic acid are very much like baths in ordinary water ; that is to say, they act only by their temperature, not by their chemical constitution. It is, moreover, obvious that it is immaterial whether the mineral waters come hot out of the earth or are heated by coal ; and it is mere superstition to ascribe any importance to the " natural heat," or even warming by the sun.

With internal employment both the osmotic pressure, or concentration, of the water and the specific action of the several salts have to be considered. Here, too, of course, the constituents occurring in minute quantities are of no importance, and the designations " iodine water " and " bromine water " are generally incorrect, because the amounts of iodine and bromine are, as a rule, only such as homœopaths would ascribe any action to. To mention an instance, one of the best known " iodine waters " contains in 1 litre about 9·5 grammes of sodium chloride, but only 4 milligrammes of salts of iodine ; and it would be necessary to drink about 60 litres of this water to get as much iodine as is contained in one tablespoonful of a 1 in 50 potassium iodide solution, and about 174 litres would have to be consumed daily by the patient to make up the usual 3 tablespoonfuls a day. The fact that the hydropathic establishments, in spite of the minimal amounts of salts, in many diseases attain results that cannot be shown by other treatment is explained by their employ-

ment, in addition to the waters, of other means, which cannot be arranged in the patient's home. Different climatic conditions, a regular life, exercise and being much in the open air, suitable diet, freedom from daily cares, in nervous affections the suggestion which belief in the healing power of the waters carries, and, not least, the hydropathic physicians' experience, acquired in the wholesale treatment of a few classes of disease—all these are factors that are more than sufficient to explain the advantage of resorting to baths.

The following are the most important indications for **saline waters** :—

Chronic gastric and *intestinal catarrh.* In such cases the weak saline waters are employed for drinking cures, which may be considered as a bathing of the mucous membranes. In accordance with what has been said of the local action of salt solutions on mucous membranes, the water, whether more or less highly concentrated than the blood, promotes the shedding of the epithelium. According to recent experiments, the digestion in the stomach is hindered a little by sodium chloride, and the acidity of the contents of the stomach is decreased, as there is excretion of fluids with alkaline reaction, especially if the salt solution is not very weak. Sodium chloride is excreted from all mucous membranes, and is supposed to make their secretion thinner and a better solvent of mucus, and it is on this property that its employment is based in *chronic dry catarrh* of the *organs of respiration,* and *catarrh of the female genital mucous membranes. Diseases of the metabolism* contribute a large number of patients to salt springs, especially those with the *uric acid diathesis* and chronic *rheumatism.* For the latter class of patients the stronger skin-irritant waters are employed ; and here the temperature of the baths plays an important part. In gout the first effect of the baths is often an acute attack ; during the bath treatment, as in ordinary attacks of gout, the excretion of urates is increased, but the ultimate result of a course of treatment is often a long period of freedom from attacks. For *obesity* weak saline waters are often recommended in combination with wise dieting. What *rôle* the actual drinking cure plays at these places as regards the reduction of weight is doubtful.

Many tuberculous conditions, especially lymphadenitis, are treated with the stronger saline waters. Patients are now often sent to special establishments by the sea, coast sanatoria, where sea-bathing, together with the pure sea-air, an out-of-door life and surgical treatment, frequently produces very good results. Among *skin-diseases,* those that are of tuberculous origin are the most favourably influenced. In other cutaneous diseases, *e.g.*

chronic eczema, irritation of the skin may be useful in improving its nutrition and circulation, but may also increase the severity of the symptoms.

Preparations and Doses

Aqua Destillata (B.P., U.S.P.), prepared by the distillation of potable water.

Aqua Sterilisata (B.P.), *Aqua Destillata Sterilisata* (U.S.P.), potable water sterilised by heat. For the technique of sterilisation the Pharmacopœias should be consulted.

Sodii Chloridum (B.P., U.S.P.), sodium chloride, transparent, cubic crystals, or a white crystalline powder, soluble in 2·8 parts of water. *Dose*, internally, as an emetic, 1—2 teaspoonfuls of dry salt; externally, as an enema, 1—2 tablespoonfuls of salt to ½—¾ litre of water; for inhalation, a 1—2 per cent. solution. For a bath for an adult (about 55—70 gallons of water), add 5—10 kilos of the impure, brown, "Spanish salt," or rock salt, where the latter is cheaper.

Liquor Sodii Chloridi Physiologicus (B.P., U.S.P.), 0·85 per cent. Must be sterilised before use.

Injectio Sodii Chloridi et Acaciæ (B.P.), "gum-saline." Physiological saline solution with the addition of 6 per cent. w/v. of gum acacia. It is not excreted so rapidly as ordinary saline.

Ringer's Solution, for which there are several formulæ, *e.g.* 8·5 grms. NaCl, 0·3 grm. KCl, 0·2 grm. $NaHCO_3$, and 0·2 grm. $CaCl_2$ in 1 litre of distilled water. The $CaCl_2$ is dissolved separately in 50 mils of water, and is added last after the other salts are dissolved, as otherwise calcium carbonate is precipitated.

3. SALTS WITH TARDY ABSORPTION

SALINE PURGATIVES

The alkaline salts behave in different ways as regards their absorption in the intestine. Whereas chlorides, bromides, iodides, nitrates, and the salts of monobasic acids as a whole are very easily absorbed, pass into the blood, and, as shown in the preceding chapter, act as diuretics, the alkali salts of a number of the dibasic and tribasic acids are absorbed very slowly. They not only remain in the intestine, but they also prevent the fluid there from being absorbed. The contents of the intestine remain fluid, are not concentrated in the large intestine by absorption of water, and are evacuated without the necessity of any strong peristalsis. The easily dissolved, but slowly absorbed alkali salts therefore act as aperients, and are called *saline purgatives* or, after their best-known representative, the Glauber's salt group. The most important substances belonging to this group are the *sulphates, phosphates and tartrates of the alkaline metals*, and *sulphate of magnesium*.

Action. The characteristic feature of these salts as compared with the vegetable purgatives is that they produce evacuation of the intestine mainly by *restricting the absorption of the fluid*. That they have this action has been proved by experiment. If equal quantities of isotonic solutions of common salt and Glauber's salt be given to a dog with a cæcal fistula, none of the common salt solution reaches the fistula, as it is absorbed on the way, while 75—90 per cent. of the Glauber's salt solution flows out through the opening within an hour. Water is necessary to the action; the salts when given dry also cause evacuation, because there is usually sufficient water in the intestinal canal; but if the animal is allowed to thirst until the water is exhausted, Glauber's salt is without effect. Probably a slight irritation of the mucous membrane is also occasioned, inducing peristalsis and increased secretion, which is instrumental in augmenting the fluid contents of the intestine. Small quantities of hydrogen sulphide, moreover, are formed by the partial reduction of the sulphates in the intestine; but salts as a whole are less irritant, occasion less hyperæmia and act with less pain than the vegetable purgatives.

The reason why the purgative salts *keep back the fluid in the intestinal canal* is simply that they attract water more powerfully than the cells. Their behaviour in the intestine in this respect shows a complete analogy with their behaviour towards dead colloid substances. When thin, homogeneous sheets of glue or gelatine, or pieces of an animal membrane (pig's bladder) are placed in various salt solutions, they take up very varied amounts of water, according to which the salts may be arranged in a series, the last member on the one side being formed by sulphates, phosphates, etc., and on the other side by chlorides and other salts of monobasic acids. In solutions of the latter salts the glue and pieces of membrane take up much water (swell greatly), in solutions of the former far less, for the greater the demand the salts make upon the water, the less is there left for the colloid substances.

Whether Glauber's salt, etc., only keep back the fluid or also cause an *excretion of fluid from the blood to the intestine*, is a frequently discussed question. Experiments with isolated loops of intestine have yielded diverse results. It is probable that the amount of fluid in the alimentary canal simultaneously with the salts is of some significance. If the salts are in weak, hypotonic solutions, water is first absorbed until the solution has become isotonic with the blood, after which what is left of the water remains in the intestine. If, on the contrary, they are in concentrated hypertonic solutions, they presumably succeed in drawing water from the blood, especially if the latter can easily make

good its loss from extra-ordinary sources, such as pathological accumulations of fluid. The fact that œdema disappears during the employment of purgative salts does not, however, necessarily indicate absorption of water from the blood, for the reason may be that the normal loss of fluid through the skin, lungs and kidneys has a desiccant influence when the supply from the intestine has stopped.

Attempts have been made in various ways to find out *why the sulphates and allied salts are so tardily absorbed.* Hofmeister, by very comprehensive investigations, has obtained results which indicate a constant relation between the absorption of the salts and their action upon dissolved albumin (globulins), as he has found that the slowly-absorbed salts act more strongly in precipitating albumin than those which are readily absorbed, probably because the former are stronger attractors of water than the latter, and thus deprive the albumin of the water in which it is dissolved. A precipitation of albumin in the living mucous membrane will cause it to shrink up, and make it less easily permeable ; and thus, according to this view, it is after all the affinity of the salts for water that is the reason of their slow absorption. Wallace and Cushny point out that the slowly absorbed alkali salts all contain acid ions which form insoluble, or almost insoluble, calcium salts ; and it might be imagined that the cause of the slow absorption would be that they produce in the mucous membrane a precipitation, or a fine covering, of an insoluble compound that obstructs their path. These hypotheses are not quite satisfactory, however, for as albumin and calcium are present everywhere, it might be expected that all cells would behave in the same way, which is not the case. The pleura absorbs magnesium and sodium sulphates quite as quickly as sodium chloride, and several of the purgative salts easily penetrate the red blood-corpuscles. The unreceptive behaviour of the intestinal mucous membrane is therefore still unexplained.

If Glauber's salt, or magnesium sulphate, be given in such large doses that the purgative action begins quickly, almost the whole amount of salt is found in the thin evacuations, and the flow of urine diminishes ; if given in too dilute a solution, in such small doses that they have no aperient action, or if their stay in the intestine is prolonged by opium, they are gradually absorbed, taken up into the blood, excreted through the kidneys, and like the easily-absorbed salts, increase the flow of urine.

As the salts in dilute solution are partly split up into ions, the absorption not only of the entire molecule, but also of the ions has to be considered. Among the positive ions, potassium and sodium are absorbed very rapidly, and magnesium very slowly ; among the negative, chlorine most quickly,

followed, with decreasing rapidity, by bromine and iodine, but sulphate very slowly. Thus the basic part of Glauber's salt is absorbed most quickly, so that the urine may acquire an alkaline reaction, but the acid ion of magnesium sulphate more quickly, for which reason there is comparatively more Mg than SO_4 found in the fæces, and comparatively less in the urine. A compound has the strongest aperient action when both the positive and the negative ions are slow in being absorbed (magnesium sulphate).

Therapeutic Uses. The **sulphates of sodium and magnesium** in medium doses produce, generally without much pain, one or two thin motions, which have a stronger odour of hydrogen sulphide than usual. They are employed for *constipation* in general, with the same indications as given in the chapter on vegetable purgatives; but if the constipation is very obstinate or caused by mechanical obstruction (hard fæces), they are less efficacious than the vegetable purgatives. When the object is merely to empty the intestine, Glauber's salt, etc., are given in aqueous solutions, as in this way the effect is produced most quickly, on an average in from 1 to 4 hours. If the object is to *deprive the body of fluid*, for instance, in dropsy, they are given in solid form or in concentrated solution, and in large doses that can keep back all the fluid of the intestinal canal. In nursing women the amount of milk greatly decreases after a couple of large doses of Glauber's salt, and the painful tension of the mammæ connected with the sudden cessation of suckling disappears. As *antidotes to lead-poisoning*, the sulphates serve to evacuate the poisonous metal, and to make it harmless by forming insoluble $PbSO_4$. The old theory that the saline purgatives increased the secretion of bile is not confirmed by more recent experiment.

Of the **phosphates,** *sodium phosphate* is sometimes prescribed as an aperient for children on account of its mild action. It has also been recommended for neurasthenia, where it is of very doubtful virtue, and in Basedow's disease. Potassium phosphate is one of the most important "nutritive salts," but is not employed medicinally. The acid potassium phosphate forms, with potassic chloride, the greater proportion of the inorganic constituents of meat soups and of Liebig's extract of meat.

Of the **potassium salts of tartaric acid,** the normal salt, *Potassii Tartras*, is very soluble, while the bitartrate of potash, *Potassii Bitartras*, is feebly soluble in water, but is converted by the alkaline carbonate of the intestine into the normal salt. In solution it combines the action of a slowly-absorbed alkali salt with the effect of a refreshing and thirst-quenching drink; but as regards the mucous membrane, it resembles tartaric acid, and in large doses is poisonous (4—5 tablespoonfuls have been known to cause death).

Magnesium oxide (magnesia) and **magnesium carbonate,** although insoluble, both have a purgative action, as they are partially converted in the stomach into the chloride, and in the intestine, by exchange with carbonates, into the soluble, not easily absorbed, bicarbonate. As the amount of alkali in the intestine is limited, only a very small quantity of this compound is formed, however, and its effect is far weaker than that of the sulphate. Prolonged use of the carbonate may produce hard concretions consisting of ammonium magnesium phosphate, which are evacuated with great pain. Magnesia is employed for *acid eructations* and *hyperacidity*, to neutralise ferment-acids and hydrochloric acid, and to relieve meteorism (1 gramme of magnesia fixes 1,090 c.c. of carbonic acid). In cases of *acid-poisoning*, magnesia is a far more practical remedy than the oft-recommended chalk, for the latter forms large quantities of carbonic acid, which distend the stomach and, in cases of deep corrosion, may cause it to rupture. When left standing in water, magnesia forms a gelatinous hydroxide, $Mg(OH)_2$, which serves as an antidote in *arsenic-poisoning*, as it forms an almost insoluble compound with arsenious anhydride. It is also employed in cases of poisoning with salts of the heavy metals, when a precipitate of almost insoluble oxides is formed.

Subcutaneous, intravenous or intrathecal injections of magnesium salts produce paralysis of the motor nerve-ends in the voluntary muscles and of the central nervous system. When the doses are not too large, this paralysis appears, according to Meltzer's investigations, in the form of an anæsthesia, during which operations may be performed painlessly. In man, injections of magnesium sulphate have recently been tried for spinal anæsthesia. A deep narcosis is obtained, but the action is of too long duration, and is so often followed by unpleasant consequences (paralysis of the lower extremities, retention of urine), that as yet, in any case, the method cannot be employed. On the other hand, very encouraging results have been obtained in tetanus (24—36 hours cessation of convulsions, recovery after a fresh injection), and in eclampsia, where the secondary effects are of minor consequence as compared with the dangerous nature of the disease.

There are one or two vegetable drugs that belong to the saline purgatives, namely, *tamarinds* and *cassia pulp*, which contain various salts, and *manna*, of which the principal constituent, the sweet alcohol mannite, is more laxative, on account of its low diffusion power and slow absorption, than the ordinary kinds of sugar. In *fresh-fruit* cures (*grape-cure*), it is the organic alkaline salts that, together with the free acids, have a laxative action. The action is supported by the colloid substances in the fruit (see

chapter on Mucilages). *Agar*, or *agar-agar*, a substance well known in bacteriology, also retains fluid in the intestine by inbibition, thus making the fæces larger and softer and more easy of expulsion. The action is feeble, however, so that it has to be supported, as a rule, by some other drug, *e.g.* cascara.

Aperient Mineral Waters. The occasional employment of Glauber's salt or Epsom salts does not injure the digestion (though the former is said to retard it), but their constant use through a long period elicits dyspeptic symptoms, greatly reduces the appetite, and sometimes leaves obstinate constipation. Several of the natural mineral waters, such as Carlsbad and Marienbad, contain sodium chloride and alkaline carbonates besides sulphate. In these cases these deleterious consequences do not occur, but their action, on the contrary, in various digestive disorders is of the greatest benefit. There is no doubt that the healing of *gastric ulcer* is assisted by the methodical use of Carlsbad water and Carlsbad salts, just as *chronic gastric and intestinal catarrh* and several digestive disturbances without ostensible anatomic foundation, *cardialgia*, *hypochlorhydria*, *chronic constipation*, *chronic diarrhœa*, are often very favourably influenced by sodium sulphate waters or the corresponding natural and artificial mineral waters. They act partly by promoting desquamation and regeneration of the epithelium, partly by dissolving mucus and keeping the intestinal canal clean.

The good effect of a Carlsbad cure upon *diseases of the liver* (hyperæmia, jaundice, cholelithiasis) is due to the disburdening of the portal system and, by the excretion of the absorbable salts in the biliary ducts, to the curing of the catarrh of the mucous membrane of those ducts. The favourable influence that Carlsbad has upon slighter forms of *diabetes* is due mainly to the diet. Sodium sulphate and magnesium sulphate springs, especially the latter, are also resorted to by very *stout persons*, their weight being reduced thereby. The salts have no particular influence upon the metabolism. Those with an alkaline reaction may perhaps promote the oxidation of the fat, and those that are laxative restrict to some extent the utilisation of the food by passing it quickly through the intestine ; but, at the baths, diet and exercise are the principal factors in the reduction of weight, the waters only an adjuvant.

Preparations and Doses

Sodii Sulphas (B.P., U.S.P.), sodium sulphate, Glauber's salt, $Na_2SO_4 + 10H_2O$, colourless, efflorescent crystals, soluble in 3 parts of water. The disagreeable, bitter taste is corrected best by a little acid, such as citric

acid or lemon-juice. *Dose*, 2—8 grms., 30—120 grs. for repeated administration, 10—16 grms., 150—240 grs. for a single administration (B.P.), 15 grms., 4 drs. (U.S.P.).

Sodii Sulphas Effervescens (B.P.) also contains sodium bicarbonate and tartaric and citric acids. *Dose*, like the preceding.

Potassii Sulphas (B.P.C.), potassium sulphate, K_2SO_4, white, hard crystals, soluble in 10 parts of water. Rarely used. *Dose*, 1—3 grms., 15—45 grs. The pharmacopœias of several countries include *Sal Carlsbadense Artificiale*, a mixture of 42 parts Na_2SO_4, 36 parts $NaHCO_3$, 10 parts NaCl, and 2 parts K_2SO_4. *Dose*, 1 teaspoonful to 1 dessertspoonful. For curative use, the above quantities, or as much as is required to produce one or two rather loose evacuations, is dissolved in a large tumbler of hot water, and drunk in portions in the morning before breaking fast, a walk being taken between the drinking of the last portion and partaking of the first meal. The purpose of this regulation, which is always given at baths, is to assist the transfer of the mineral water to the intestine.

Sodii Phosphas (B.P., U.S.P.), sodium phosphate, $Na_2HPO_4 + 12H_2O$, colourless crystals with a weak alkaline reaction, soluble in 7 parts of water. *Dose*, as of the sulphate (B.P.); 4 grms., 1 dr. (U.S.P.).

Sodii Phosphas Acidus (B.P.), *Sodii Biphosphas* (U.S.P.), acid sodium phosphate, NaH_2PO_4, colourless crystals with acid reaction, readily soluble in water. *Dose*, 2—4 grms., 30—60 grs. More irritant than the ordinary phosphate. Recommended for making the urine acid, but it is not very effective.

Ammonii Phosphas Acidus (not official), in doses of about 1 grm. three or four times daily, is a better urinary acidifier than the corresponding sodium salt. Doses larger than these do not render the urine any more acid but may cause watery diarrhœa.

Sodii Phosphas Effervescens (B.P., U.S.P.). Composition and doses similar to those of the corresponding preparation of the sulphate.

Potassii Tartras (B.P.C.), potassium tartrate $(K_2C_4H_4O_6)_2 + H_2O$, colourless crystals with a cool, saline taste, readily soluble in water. *Dose*, 2—16 grms., 30—240 grs.

Potassii Tartras Acidus (B.P.), **Potassii Bitartras** (U.S.P.), $KHC_4H_4O_6$, cream of tartar, a white crystalline powder with a pleasant, acidulous taste; insoluble in alcohol, sparingly soluble in water. It is obtained from grape-juice, being deposited with the formation of alcohol, during the process of fermentation. *Dose*, 1—4 grms., 15—60 grs. (B.P.); 2 grms., 30 grs. (U.S.P.). Small doses, *e.g.* 1 grm., a few times daily, have a diuretic action.

Sodii et Potassii Tartras (B.P.), **Potassii et Sodii Tartras** (U.S.P.), sodium potassium tartrate, Rochelle salt, $NaKC_4H_4O_6 + 4H_2O$, colourless crystals or a white crystalline powder with a cool, saline taste, very soluble in water. *Dose*, 8—16 grms., 120—240 grs. (B.P.); 10 grms., $2\frac{1}{2}$ drs. (U.S.P.). In these doses aperient, in repeated small doses (1 grm.) diuretic.

Pulvis Effervescens Compositus (B.P.), *Pulvis Effervescentes Compositi* (U.S.P.), Seidlitz powder, is made up in 2 powders, Rochelle salt and sodium bicarbonate wrapped in blue paper, tartaric acid wrapped in white paper. The powder in the blue paper is dissolved in water, and that in the white paper is then added, either dry or dissolved. Has a refreshing taste of CO_2, and an aperient action. *Dose*, 1 set of powders.

Magnesii Sulphas (B.P., U.S.P.), magnesium sulphate, Epsom salts, $MgSO_4 + 7H_2O$, colourless prisms with a disagreeable, bitter taste, very

soluble in water. *Dose*, 2—6 grms., 30—60 grs. for repeated administration, 8—16 grms., 120—240 grs. for a single administration (B.P.); 15 grms. 4 drs. (U.S.P.); for intravenous injection, 50—150 mils of a 2½—3 per cent. solution, injected in the course of 2 minutes; may, if necessary, be repeated several times a day; for lumbar injection, 5—8 mils of a 25 per cent. solution (or 1 mil per 10 kilos of body-weight).

Magnesii Sulphas Effervescens (B.P.C.). *Dose*, twice as large as the preceding.

Magnesii Oxidum Leve (B.P.), **Magnesii Oxidum** (U.S.P.), light magnesia, MgO, a white, very light, tasteless powder (1 teaspoonful weighs ½ grm.). *Dose*, for hyperacidity, by the teaspoonful, in larger doses (2—4 grms.) as a mild aperient; official *doses*, 0·6—4 grm., 10—60 grs. (B.P.); 0·25 grm., 4 grs. as an antacid, 3 grms., 45 grs. as a laxative (U.S.P.). In arsenic poisoning, 1 tablespoonful stirred into hot water until the gelatinous hydroxide has formed, when a dessertspoonful is taken, or *Magma Magnesiæ* (U.S.P.), a creamy suspension of the hydroxide. *Dose*, as an antacid, 4 mils, 1 fl. dr.; as a laxative, 15 mils, 4 fl. drs.

Mistura Magnesii Hydroxidi (B.P.), Cream of Magnesia. An aqueous suspension of hydrated magnesium oxide; contains the equivalent of 8·25 per cent. w/v. of $Mg(OH)_2$. Half an ounce contains about 13 grs. of magnesium oxide. *Dose*, 4—16 mils, 60—240 mins.

Magnesii Oxidum Ponderosum (B.P., U.S.P.), heavy magnesia, MgO. *Dose*, the same as that of light magnesia.

Magnesii Carbonas Levis (B.P.), *Magnesii Carbonas* (U.S.P.), and *Magnesii Carbonas Ponderosus* (B.P.). Uses similar to those of magnesia. *Doses*, the same as those of magnesia (B.P.); antacid, 0·6 grm., 10 grs., laxative, 8 grms., 120 grs. (U.S.P.).

Liquor Magnesii Bicarbonatis (B.P.), contains 2 grms. in 100 mils of the carbonate, and free CO_2. *Dose*, 30—60 mils, 1—2 fl. oz.

Liquor Magnesii Citratis (U.S.P.), an effervescent solution, containing in 100 mils as much citrate as corresponds to 1·5 grm. of MgO. Made up in bottles containing 350 mils, which may be taken in one dose or divided. The official average dose is 7 fl. oz.

Tamarindus (B.P.), tamarinds, the reddish brown, moist, sugary pulp of the fruit of *T. Indica* (*Leguminosæ*), East India, with an agreeable, subacid taste. *Dose*, from a teaspoonful to a tablespoonful. Seldom used; especially for children.

Cassia (B.P.), cassia pulp, an evaporated watery extract of cassia pods. *Dose*, 4—8 grms., 60—120 grs. Tamarinds and cassia are ingredients of Confection of Senna.

Manna, the dried, saccharine exudation from *Fraxinus Ornus* (*Oleaceæ*), Southern Europe. In yellowish white, often flat pieces with a sweet taste, containing about 80 per cent. of mannite. *Dose*, 15 grms., 4 drs. A constituent of Black Draught (N.F.).

Agar (B.P., U.S.P.), agar-agar, a dried, mucilaginous substance, extracted from various algæ growing along the eastern shores of Asia. *Dose*, 4—16 grms., 1—4 dr. (B.P.); 10 grms., 2½ drs. (U.S.P.).

4. POTASSIUM

Although many of the potassium salts, *e.g.* the chlorate, iodide, bromide and others, are important drugs, the **action of the**

potassium ion is of little therapeutic interest, for in all the compounds used in medicine, the importance attaches to the other ions and not to that of potassium.

The simple potassium action is only found in salts that have a neutral reaction, and where potassium is combined with ions that in themselves have no marked action, *e.g.* chlorine. If potassium chloride solutions are injected directly into the blood, the potassium ion, unlike the sodium ion, proves to be poisonous. Dogs, cats and rabbits die after doses of 0·1—0·2 grm., while many times that amount of sodium chloride is required for a lethal dose, and even then death is not due to any specific toxic action, but to a general salt-action. With intravenous injection potassium chloride acts upon the central nervous system and muscle tissue, and, therefore, especially upon the heart; reflex irritation is reduced, the spontaneous movements become weak and the pulse slow, and the blood-pressure falls considerably. Large doses cause, almost instantaneously, cardiac paralysis. By experiments with excised hearts of rabbits in Bock's laboratory, Hald found that the deleterious concentration begins at 0·08 per cent. of KCl.

It was expected that part, at any rate, of this action would be found to take place in man with the internal employment of the potassium salts, and the question has been discussed as to whether the potassium component has any share in the action of potassium bromide on reflexes. It has also been feared that long-continued use of potassium salts might have a weakening effect on the heart. There can scarcely be any reason for this, however, for no deleterious accumulation takes place, partly because the elimination through the kidneys is effected rapidly, and partly because, according to Bock's experiments, the potassium salts leave the blood so quickly (taken up by the surrounding tissues) that their percentage in the serum hardly increases, even with continued intravenous injection of potassium chloride. The great power of the blood to protect its normal constitution, to which we have already referred, is seen here. It is only when enormous quantities of an easily-absorbed salt are introduced at one time (saltpetre poisoning), that a serious weakening of the heart appears, which, together with the toxic gastro-enteritis, may result in death. On the other hand, the successive administration of considerable quantities apparently does no harm, as is proved by the fact that no heart-weakening is observed in Irish labourers, who are said to consume daily in their ration of potatoes at least 40 grammes of potassium salts. Still less can any perceptible potassium action be expected from the small doses given medicinally. The potassium salts will not, therefore, receive separate mention

here, but will be found dispersed among the various chapters and classified according to their negative ions.

5. HYDRATES AND CARBONATES OF THE ALKALIES (ALKALIES)

The alkaline reaction and the pharmacological *action* of the hydrates of the alkalies, are *dependent upon the hydroxyl ions which arise on solution and dissociation*, thus : $KOH = K + OH$, $NaOH = Na + OH$. That the potassium and sodium ions take no part in the action is easily realised from the fact that they are also present in potassium and sodium chlorides, which have neither alkaline reaction nor corrosive action. The carbonates also yield hydroxyl ions, being dissociated into bicarbonate and hydroxide, but the action is not so strong, as the dissociation takes place more slowly. The bicarbonates are similarly dissociated to hydroxide, but only to a very small extent, and their action is therefore weak.

Action. The local action of the alkalies is of a very complicated character. The solid caustic alkalies neutralise all acids, form with albumin soluble, gelatinous albuminates, and saponify fat. All this, in addition to a strong affinity for water, makes potassium and sodium hydrates powerful corrosives, which rapidly transform the tissues into a grey or brown soft pulp, the action being accompanied by intense pain. Even the **skin** offers only a brief resistance to the caustic alkalies when employed in solid form or in concentrated solution. As no dry, firm crust is formed, which can limit the action, the destruction spreads peripherally, and in the course of two or three days the area first affected is 2—3 times as great as it was originally. With the admission of air, the semi-fluid tissues dry up after a few days into a necrotic crust, which falls off after 2—3 weeks. The cicatrix left after healing is considerable.

The alkaline carbonates have no caustic action on the skin, but with long application they have a somewhat irritant and thoroughly cleansing effect, dissolving the fat of the skin and softening the superficial layer of the epidermis, which falls off, together with all dust and dirt adhering to it.

The **mucous membrane of the alimentary canal** is quickly corroded by caustic alkalies. The first symptoms are burning pains in the mouth, œsophagus and epigastrium, and severe vomiting, the vomited material consisting first of the highly alkaline contents of the stomach, which is later mixed with mucus and blood. The mucous membrane becomes tumid and translucent and soapy to the touch, the epithelium is shed, and in a short time the coat

turns dark brown from extravasated blood. In a minority of cases death takes place very shortly with symptoms of acute gastritis or perforation.

As a rule, little of the ill-smelling caustic liquid is swallowed, and after a few days' illness improvement or recovery takes place. This is only apparent, however, as the deeper ulceration of the mucous membrane often does not heal without leaving a scar, the fibrous tissue of which is very liable to contract ; so that in the course of weeks or months strictures may form in the œsophagus at its juncture with the stomach, or behind the cricoid cartilage, causing difficulty in swallowing and requiring long treatment.

In the **stomach** the carbonates evolve carbonic acid (eructations), neutralise hydrochloric acid and other acids, and dissolve mucus. Large doses render the contents of the stomach alkaline, and consequently prevent the action of the pepsin, while, at the same time, the secretion of gastric juice is reduced. Very large quantities of bicarbonate of soda can be taken for a short time, however, without ill effects, as the modern treatment of diabetic acidosis has shown. It is not known whether the alkalies have any effect upon the movements of the stomach. The normal carbonates are far more alkaline and irritating than the bicarbonates, and the potassium salts more harmful than the sodium salts. The hygroscopic potassium carbonate, whether in solid form or in concentrated solution, produces corrosion. In the intestine, as in the stomach, the alkalies are antacid and solvents of mucus, and in large doses are slightly aperient.

The alkaline carbonates are *very readily absorbed from the intestinal canal* and pass into the blood, where it is difficult to trace their action with precision. Oxidation in the test-tube, as we know, takes place more readily in alkaline than in neutral solutions, and for this reason they have been credited with an action on the **metabolism.** The increase of alkalinity in the blood during the internal administration of alkalies is very slight and soon ceases by their excretion in the urine. Experimental investigations, however, have not yielded any definite results, as the absorption of oxygen and the excretion of carbonic acid during the employment of alkalies were found to be sometimes increased, sometimes unchanged.

A standard for the oxidation has been sought in the relation between the oxidised sulphur of the urine (sulphate) and unoxidised sulphur, but no definite knowledge of the influence of the alkalies has been obtained ; some investigators have found the amount of neutral or unoxidised sulphur to be increased—*i.e.* diminished oxidation—while others have found an increase in the sulphate sulphur—*i.e.* increased oxidation. The *excretion*

of nitrogen in the urine may either remain unchanged, decrease or increase, in the last case, however, not more than can be explained by the diuresis. The amount of urea is often augmented at the expense of the ammonia. Special attention and much research have been devoted to the behaviour of the *uric acid*, but on this point also no decided effect has been found.

The **excretion** of the alkalies takes place in the urine, the acid reaction of which is weakened in proportion to the amount of the alkali given, and becomes alkaline when the daily dose reaches 10—15 grammes of bicarbonate of soda. As the excretion takes place very rapidly, the acid reaction soon returns. Even after 2—3 grammes the urine may show, for a short time, an alkaline reaction. Clinical experience has led to the view that the alkalies are also excreted from the bronchial mucous membrane and the biliary ducts, but nothing definite is known as regards man. In dogs, bicarbonate of soda given internally does not increase either the alkalinity or the amount of the bile.

The alkalies, like other non-poisonous, readily soluble and quickly absorbed salts, are **diuretic.** As already mentioned (p. 356), the potassium salts induce greater diuresis than the sodium salts, because, by their interchange with the salt of the blood, two salts are formed, both of which have to be excreted, thus doubling, so to speak, the action. The acetates and other alkali salts, which are oxidised in the body to carbonates, act in the blood in the same manner as the carbonates.

Therapeutic Uses. External. Caustic potash, which is more hygroscopic and acts more strongly than the corresponding sodium compound, is sometimes employed as an *escharotic* for *septic sores* (anthrax, hydrophobia), large *patches of lupus, pigment deposits in the skin, cavernous skin tumours*, etc. The loss of substance spreads considerably in extent in the course of two or three days, and thus forbids the employment of the drug on the face or in the neighbourhood of joints, large vessels and nerve trunks. A more limited action is obtained by the addition of unslaked lime (Vienna paste), which forms a somewhat firm, dry crust. In more or less concentrated solutions, caustic potash is employed for painting lupus and obstinate *eczema*, and for the removal of *epidermal growths* (corns). The pain of *burns* is best relieved by covering with cotton wool that has been strewn thickly with sodium bicarbonate.

Internally, alkalies are given for the purpose of acting (1) locally upon the alimentary mucous membrane (gastric and intestinal diseases); (2) while they remain in the blood (diseases of metabolism); and (3) during their excretion, especially in the urine. The numerous indications, most of which have been only empirically found and are still not satisfactorily explained, will

be mentioned here in the above order. Neither sodium nor the irritating potassium carbonates are prescribed for internal use, but either bicarbonate of soda or alkaline mineral waters.

Gastric Diseases. Bicarbonate of soda has been found by experience to act with benefit, and to cause immediate relief, in *gastric ulcer, acute* and *chronic dyspepsia* associated with symptoms of hyperacidity, nausea and loss of appetite, and in *cardialgia.* It removes the deleterious acidity by neutralising acids, and the carbonic acid evolved acts like a slight local anæsthetic, allaying nausea and pain. *Chronic gastric* and *intestinal catarrh* are often treated with natural or artificial mineral waters, which also contain neutral alkali salts such as sodium chloride and Glauber's salt. The beneficial action of the carbonates which results from taking these salt-mixtures is probably due to the solution of the viscid mucus which covers the inflamed mucous membrane and permeates the contents of the intestine like a mucilage, hindering both digestion and absorption. It is therefore beneficial to use alkaline water also for *washing out the stomach* when there is a great quantity of mucus, *e.g.* in ordinary alcoholic gastritis.

The *diseases of metabolism* most frequently treated with alkalies are diabetes and uric acid diathesis.

The alkalies were originally recommended for *diabetes* upon the erroneous assumption that the combustion of the sugar was prevented by a decrease in the amount of alkali in the blood, and that it would be promoted by an increase of alkalinity. Careful experiments have since shown that alkaline carbonates have no influence upon the amount of sugar. The fact of the improvement in the condition of many sufferers from the light form of diabetes mellitus, and the diminution in the excretion of sugar during a stay at Carlsbad, Vichy, etc., is probably due, not to the salts of the mineral waters, but to the stricter diet, muscular exercise and a more rational mode of life. In *diabetic acidosis*, an energetic alkaline treatment is rational and necessary. When an abundant excretion of acetone bodies in the urine indicates threatened coma, bicarbonate of soda is given until the urine becomes neutral or only slightly acid. For this, 30—60 grammes, or more, may be required daily. If coma has already set in, the internal treatment is continued, or the same doses, *e.g.* 50 grammes of bicarbonate of soda to 1 litre of water, are injected intravenously until the urine becomes alkaline. This treatment is, of course, only symptomatic, but the intense alkaline treatment is justifiable in that it sometimes prolongs the life of the patient for weeks or possibly months.

Alkaline carbonates, in the form of mineral waters, are highly esteemed for *gout.* At first the treatment often seems to bring

on an acute attack, but the ultimate result of persistent employment is, as a rule, that the attacks become less frequent and milder, and the urate deposits decrease in size. The reason of this favourable action is not at present known, nor yet the form in which the dissolved uric acid occurs in the body and the conditions under which it is deposited as the salts—principally sodium bi-urate—which form the gouty deposits. When once deposited, the bi-urate in the tissues cannot be dissolved by alkaline carbonates, for the solution and excretion of a salt depend not only upon the proportion of the salt to the solvent, in this case the tissue-fluid, but also upon the possible presence of substances that have an ion in common with the salt, as these diminish the solubility. Sodium bi-urate, for instance, according to determinations by Paul and His, dissolves in 1,130 parts of water, but only in 11,000 parts of physiological saline solution, because the dissociation of the sodium urate is kept back by the sodium ions of the common salt. Similarly, other sodium salts, *e.g.* the carbonates, diminish the solubility, and thus another explanation must be sought for the beneficial action in gout than the one hitherto assumed, namely, that they actually have a solvent action upon precipitated urates.

A good indication for the use of the alkalies is given by *uric acid concretions in the urinary passages*. In the experience of hydropathic physicians, the treatment with the alkaline waters here, too, often leads first to an attack of renal colic or excretion of gravel. The reason may be that calculi are carried away by the increased flow of urine, or that large concretions consisting of small particles held together by mucus, fall to pieces when the urine becomes alkaline. No solution of calculi already formed can be procured either by the ordinary alkali salts or by lithium salts, which are recommended because the lithium urate dissolves with comparative ease in water ; but probably a new formation of uric acid calculi may be hindered when the urine is kept more alkaline. If the calculus consists of oxalate of lime, the alkalies are inert ; if it is formed of phosphates, the alkalies promote continued deposit, and are, consequently, injurious. They are employed in *cystitis* and other *inflammatory conditions of the urinary passages*, when the urine is very acid and, in consequence, irritates the mucous membrane, but are not suitable in cystitis with alkaline urine.

Cholelithiasis is also a disease in which alkaline treatment is indicated. A course of Carlsbad or Vichy often lessens the frequency and violence of the attacks (the first result is sometimes an acute attack), and may bring complete recovery. Various theories have been advanced as to the nature of the action. It

has been supposed that the akalinity of the bile is increased, and that thus the formation of fresh calculi is prevented, or that the catarrh which gives the impetus to the formation of concretions is cured.

In *chronic catarrh of the respiratory passages* the alkalies are often employed in combination with common salt. They act best in *dry catarrh* (dry laryngitis, " clergyman's sore throat "), and it is supposed, though nothing definite is known about it, that they are excreted by the respiratory mucous membranes. If the secretion is already abundant, or if there is tuberculosis of the lungs, the warm alkaline waters are considered to be contra-indicated. *Catarrh and exudation in the female genital organs* (endometritis, metritis, parametritic deposits) are also treated at the saline alkaline springs, some of which enjoy a great reputation for the cure of these diseases.

In *dropsy accompanying cardiac and renal diseases* the potassic salts, as already mentioned, have a stronger diuretic action than the sodium salts, but with the disadvantage that they are greater local irritants, and in large doses soon produce dyspepsia. This difficulty is overcome in practice by employing the acetate of potassium instead of the carbonates, as it has a much weaker alkaline reaction, does not injure the stomach, and is oxidised in the blood to carbonate.

In cases of *poisoning* with caustic alkalies dilute acids are given, *e.g.* ordinary vinegar, citric or tartaric acid, and then demulcents, such as white of egg or milk. Washing out of the stomach must not be performed on account of the danger of perforation. After about 3 weeks, even if there are no subjective symptoms of œsophageal stricture, a bougie is introduced. Already-formed strictures are treated by dilatation, the patient sometimes taking thiosinamine to aid in softening the cicatrix.

Preparations and Doses

Potassii Hydroxidum (B.P., U.S.P.), potassium hydroxide, caustic potash, KOH, white pieces or pencils, which very quickly take up carbonic acid and water from the air and liquefy. Used externally as a corrosive in solid form or concentrated solution with equal parts, or twice or thrice the amount, of water ; in a 10—20 per cent. solution for inunction of the skin for lupus, obstinate eczema, and thickening of the epidermis, the surrounding skin being protected by a fenestral plaster. *Pasta Caustica Vienensis*, Vienna paste, consisting of equal parts of lime and caustic potash. Is made into a thick paste with a few drops of spirit, spread upon a piece of linen, and left upon the place to be cauterised for 10—30 minutes.

Liquor Potassii Hydroxidi (B.P., U.S.P.), 5 per cent. For pharmaceutical purposes. Seldom used internally as an alkali.

Sodii Hydroxidum (B.P., U.S.P.), caustic soda, NaOH, in appearance, etc., resembling caustic potash, but of weaker action.

Potassii Carbonas (B.P., U.S.P.), potassium carbonate, K_2CO_3, a white, granular, hygroscopic powder with a strongly alkaline reaction, soluble in 1 part of water. *Dose*, 0·12—0·6 grm., 2—5 grs. (B.P.); 1 grm., 15 grs. (U.S.P.).

Potassii Bicarbonas (B.P., U.S.P.), potassium bicarbonate, $KHCO_3$, dry, colourless crystals, soluble in 4 parts of water. *Dose*, 1—4 grms., 15—60 grs. (B.P.); 1 grm., 15 grs. (U.S.P.).

Sodii Carbonas (B.P.), sodium carbonate, washing soda, $Na_2CO_3 + 10H_2O$. Large, colourless, efflorescent crystals with a strongly alkaline reaction, soluble in 2 parts of water. *Dose*, 3—10 decigrms., 5—15 grs.

Sodii Carbonas Exsiccatus (B.P.), almost devoid of water. *Dose*, 12—30 centigrms., 2—5 grs.

Sodii Carbonas Monohydrosus (U.S.P.), contains 1 molecule of water of crystallisation. *Doses*, about half those of the ordinary carbonate.

Sodii Bicarbonas (B.P., U.S.P.), sodium bicarbonate, $NaHCO_3$, a white powder with a cool, mildly alkaline taste, soluble in 11 parts of water. *Dose*, 1—4 grms., 15—60 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). For hyperacidity, etc., 1 or several grms., 3 times a day as a powder, lozenges, or a solution with *Aqua Laurocerasi* (B.P.C.) as flavouring agent. For washing out the stomach, ½—2 per cent. solution. For diabetic coma, 30—100 grms. daily, or sufficient to make the urine alkaline or only slightly acid.

Trochiscus Sodii Bicarbonatis (U.S.P.), containing 0·18 grm., 3 grs.

Potassii Acetas (B.P., U.S.P.), potassium acetate, $K_2C_2H_3O_2$, a very deliquescent white powder or crystalline masses, with a sharp, saline taste, soluble in 0·5 part of water. *Dose*, 1—4 grms., 15—60 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). Often used, especially formerly, as a diuretic in doses of 1 grm. every other hour.

Sodii Acetas (U.S.P.), sodium acetate, $Na_2C_2H_3O_2 + 3H_2O$, colourless crystals, efflorescent in warm, dry air, and soluble in 0·8 part of water. *Dose*, 1·5 grm., 25 grs.

6. SOAP

Soap is an exceedingly important product, the consumption of which gives some indication of the cultural standard of a people. It consists of salts of the alkaline metals with higher fatty acids, and is produced by the boiling of animal or vegetable fats with caustic potash or soda, by which the fat is "saponified," the alkalies combining with the fatty acids and expelling the glycerin, which is a valuable by-product. The soda soaps are hard, the potash soaps soft.

The common soda soaps are obtained from the liquid mixture arising from the action of the caustic soda on the fat by the addition of common salt ("salting out"), which takes up the water and causes the firm soap to separate from the mother-liquor, which contains glycerin, free alkali, inorganic salts and other soluble impurities. The soap deposited contains, however, a certain amount of lye, and is, therefore, highly *alkaline*. The lye is more effectually removed by the centrifugal machine, and the less efficacious *neutral soaps*, which are also less irritating to the skin, are obtained. A further addition of fat produces the bland *superfatted soaps*

so much employed in the present day, which combine the effects of the soap with that of an indifferent emollient ointment.

The potash soaps cannot be salted out, as they are converted by common salt into soda soap and potassium chloride.

Action and Uses. Soap is an unstable compound, its cleansing action being due to its partial hydrolysis, with formation of free alkali, when it comes into contact with large quantities of water. The alkali saponifies and dissolves the fat of the skin, clears the openings of the follicles, which are filled with the secretion from the cutaneous glands, softens the epidermis, and loosens the connection between the epidermal cells so that the outermost layer of skin can be rubbed off, enveloped in the lather produced by the friction, and removed together with all dirt, dust and vegetable and animal parasites adhering to it. Careful washing with soap, especially when combined with brushing, which is a mechanical aid to the chemical action of the soap, is, therefore, a very thorough cleansing of the skin, and forms a necessary and very important part of all *disinfection of the skin*. The mechanical cleansing effect can be augmented by adding mineral powders to the soap, such as fine sand, powdered marble and pumice-stone. In various *skin-diseases* soap is employed where it is desired to remove the epidermis and make the deeper layers accessible to antiparasitic or other drugs. In former times scrofulous patients were treated with inunction of soft soap; and the methodical inunction of soap has more than once been recommended for *tuberculosis of glands, skin and bone*. The treatment is said to contribute to an improved general condition, the reduction of swollen glands, and the closing of fistulas. As the remedy is not applied at the site of the disease, but wherever the skin can best bear the rubbing, *e.g.* on the back, the results, if confirmed, are due to some general action. On account of its ability to penetrate the skin, soap has further found very extensive employment of late as a *vehicle for drugs* that are intended to be absorbed (mercury), or to act through the entire depth of the skin (sulphur, tar, naphthol, salol, salicylic acid, etc.). After long application the alkaline soaps produce irritation and inflammation of the skin, and are employed for this reason as *counter-irritants* and *absorbents* (soft soap poultice, soap plaster).

The choice of a soap is made according to the purpose it is to serve. The most cleansing and the best for the softening and disinfecting of the skin are the soft potash soaps and other strongly alkaline washing-soaps. With constant use, however, they deprive the skin of too much fat, and make it brittle and liable to desquamation, and should then be replaced by neutral or superfatted soaps. The latter are the only kind suitable as a basis for

drugs that are to remain for a long time in contact with the skin. For ordinary cosmetic purposes they are indicated for skins that are deficient in fat.

Internally there is little employment for soap. A solution of common hard soap is the most quickly-procured alkaline antidote in cases of *acid-poisoning*. In *other kinds of poisoning*, lukewarm soap and water is a more or less certain emetic. In the intestine soap causes increased peristalsis, and, as a practical constituent of *aperient pills*, supports their action. It is in part absorbed, and is oxidised in the blood to alkaline carbonate. Introduced into the rectum in the form of a *suppository* or an *enema*, soap has a prompt aperient action by irritating the mucous membrane and making the intestinal walls and the fæces smooth.

Preparations

Sapo Durus (B.P., U.S.P.), hard soap, white Castile soap, made from olive oil and sodium hydroxide, a hard, white, solid soap.

Sapo Animalis (B.P.), curd soap, made from animal fat.

Sodii Stearas (U.S.P.), a mixture of sodium stearate and sodium palmitate. A white powder, soapy touch and characteristic odour. A basis for suppositories.

Sapo Mollis (B.P., U.S.P.), sapo kalinus, soft soap, made with potassium hydroxide and vegetable oils, a transparent, unctuous soap, which contains, besides the potassic salts of the fatty acids, free alkali, glycerin and carbonate of potash. Is employed externally whenever a strong soap-action is required, *e.g.* for disinfection, for macerating the skin in parasitic diseases and as a skin-irritant poultice.

Linimentum Saponis (B.P.), *Linimentum Camphoræ et Saponis* (U.S.P.), soap liniment, opodeldoc, also contains camphor. *Linimentum Saponis Mollis* (U.S.P.), for inunction for rheumatic pains, etc.

7. SULPHUR, HYDROGEN SULPHIDE AND ALKALINE SULPHIDES

Pure **sulphur** appears to be pharmacologically inert, but becomes active by conversion into sulphuretted hydrogen, sulphides, or oxygen compounds. Sulphur has at first no effect upon *the skin*, but when this has been covered for some time with powdered sulphur, the action is slightly irritant, locally diaphoretic, and, it is said, analgesic. Sulphur is also inert in the lower animals and plants, but becomes poisonous when partially oxidised to sulphurous acid, when sulphuretted hydrogen is evolved, as it is by contact with many organic substances at the temperature of the body, and especially when alkaline sulphides are formed.

Sulphur is not changed in the *stomach*, and has no effect. In

the *intestine* it is converted into sulphuretted hydrogen, which irritates the intestinal wall and causes increased peristalsis. The formation of irritant alkaline sulphides also contributes to the laxative action. Conversion to hydrogen sulphide is brought about by an albuminous body that is found in the intestinal mucous membrane and which loses its efficacy with pepsin digestion but not with boiling; it is therefore not a ferment. The same transformation may also be brought about by white of egg and albuminous substances that are found in the blood and in many organs, but not in the gastric mucous membrane (Heffter). As the sulphuretted hydrogen in the intestine is evolved gradually, the laxative effect is not great, and is to a certain extent independent of the size of the dose. The stools are of a soft consistency, and have a strong smell of sulphuretted hydrogen; increased peristalsis and diarrhœa occur if the sulphur is given in an exceedingly fine form (milk of sulphur).

Most of the sulphur introduced into the body passes out with the fæces unchanged. The hydrogen sulphide formed in the intestine is absorbed, oxidised in part in the blood, and excreted in the urine as sulphates and organic compounds of unknown nature. A small portion leaves the body through the skin and the lungs, and gives an unpleasant smell to the sweat and the breath. The cases of "sulphur poisoning" that have been described appear to have been caused by adulteration with arsenic and selenium.

Sulphuretted hydrogen is a very poisonous gas which can kill almost as quickly as prussic acid, and has practical interest through its occurrence in sewer-gas, which consists mainly of ammonia, carbonic acid, marsh-gas and from 2 to 8 per cent. of sulphuretted hydrogen. There are two distinct forms of acute, fatal poisoning. In one, air containing a large percentage of sulphuretted hydrogen is inspired, and the individual instantly falls to the ground and dies in a few seconds without convulsions. This form, which has been observed in chemical laboratories and sewage work, is called the apoplectic form. The other form is more protracted, the patient lying for several hours unconscious and without spontaneous movement, until he dies in deep coma, in many cases associated with clonic and tonic convulsions—the tetanic form. A percentage of even 0·7—0·8 per cent. H_2S in the air may be fatal to any one remaining in such an atmosphere for several hours.

The inhalation of very small quantities of sulphuretted hydrogen produces faintness, an unsteady gait, breathlessness, and later narcosis, preceded by cerebral excitation. The active agent at several of the old oracles, *e.g.* the famous Delphi, was sulphuretted

hydrogen, which streamed out through cracks in the ground, and threw the prophetess, Pythia, into a state of delirium. Chemists who are constantly working with H_2S suffer, after a few years, from frequent headache and constipation, and are sometimes liable to syncope. The prophetesses of olden days, too, in time became the victims of a chronic intoxication which made them incapable of continuing their oracular duties (L. Lewin).

Sulphuretted hydrogen is as poisonous to animals as to man, only rats and mice possessing a certain immunity, possibly acquired by their life for many generations in localities where this kind of gas abounds. A very peculiar type of poisoning has been observed by Harnack in frogs. After a single inhalation of sulphuretted hydrogen, these animals may fall into an uninterrupted maximal tetanus of a fortnight's duration, or a poisoning lasting for a month, in which convulsions and paralysis alternate.

Sulphuretted hydrogen, when sufficiently concentrated, is also injurious to micro-organisms, and in sufficient strength arrests putrefaction by killing the bacteria which are the cause of it, in the same way that sugar fermentation ceases when a certain amount of alcohol is formed.

Alkaline sulphides have a corrosive action upon the skin like that of the caustic alkalies, and, in particular, are good solvents for horny structures such as hair and epidermal formations. They are very destructive to animal parasites on the skin by disintegrating the skin of the animals and destroying the eggs. The specific action corresponds with that of sulphuretted hydrogen, but is longer in beginning, as the absorption is slow ; and it is accompanied by the usual symptoms of corrosion of the stomach and intestine. Doses of a few grammes may prove fatal. Small quantities are rendered innocuous in the blood by oxidation to sulphates.

Therapeutic Uses. As sulphur is only mildly laxative it is used as an *aperient* principally in cases in which it is only necessary to give a soft consistency to the fæces, and thus save the rectum from the pain of passing hard fæcal masses, as in hæmorrhoids. It is seldom used, however, as it has the disadvantage of imparting the odour of sulphuretted hydrogen to the excrements, flatus, breath and sweat. Sulphur cannot, as has been suggested, be replaced by alkaline sulphides, as the latter are absorbed too quickly in small doses, and in large quantities are poisonous. Externally, sulphur is employed, generally in combination with alkalies, as an anti-parasitic in *scabies*, and for disintegration of the epidermis in *eczema*, *psoriasis* and *acne*, where it acts in analogy with incision by opening the follicles and letting out the accumulated secretion. As a cosmetic the alkaline sulphides serve to

remove disfiguring growths of hair. Powdering with a thick layer of sulphur is a household remedy for neuralgia, and is said to allay pain.

Intramuscular injections of sulphur dissolved in olive oil are recommended by French physicians for *arthritis deformans* and the ordinary *chronic rheumatic polyarthritis*. According to the accounts given, indisposition and a rise in temperature occur about 12 hours after the injection, and in most cases the pain is allayed and there is increased mobility in the diseased joints. It is said that lasting benefit may be obtained.

Sulphur waters (sulphuretted hydrogen waters) were among the first mineral waters used in medicine, being employed in the form of baths for sufferers from *chronic articular and muscular rheumatism*, *neuralgia* and *gout*. Experience has proved in the most undoubted manner that, for rheumatism in particular, sulphur baths are of great benefit ; but it is not easy to determine how much of the result is due to the sulphur compounds, and how much to the temperature of the baths and the often highly-developed bathing technics. A few baths, and especially Aix-la-Chapelle, have long enjoyed a great reputation for their cure of *constitutional syphilis*. Sulphur baths are employed for chronic mercurial poisoning, and *chronic metallic poisoning* generally, for the purpose of promoting the excretion of the metals. The same *skin-diseases* for which a sulphur treatment is employed, especially psoriasis, chronic eczema and acne, are also treated with sulphur baths.

No specific action on syphilis by sulphur has been demonstrated. The importance of the baths is to be found in their influence on the metabolism. The excretions through the skin and kidneys are accelerated. In mercurial treatment the metal is excreted far more quickly when baths are taken at the same time, so that the usual doses can be far exceeded without the appearance of any symptoms of intoxication. Thus a considerable amount of mercury can be kept circulating in the body, and its effect on the disease is all the more intense. It is thus as adjuvants of the specific treatment that sulphur baths possess most importance, and this is also the case with other baths, such as the much used salt waters for syphilis. These also set stored-up poison in movement. In patients who have previously been treated with intramuscular injections of insoluble mercurial compounds which have become encapsuled by inflammatory reaction, the baths may bring the metal into circulation and produce symptoms of acute poisoning. In old afebrile cases of malaria, baths may elicit rigors, which can only be interpreted as the setting in motion of the latent poison. Similar conditions are probably the reason for the not infrequent outbreaks of syphilis during hydropathic cures, and explain the old belief in baths as reagents upon the latent disease.

Treatment of Hydrogen Sulphide Poisoning. The patient is taken into the open air, and artificial respiration is begun. Blood-

letting and saline infusion are recommended. In serious cases all treatment is useless.

Preparations and Doses

Sulphur Sublimatum (B.P., U.S.P.), Flores Sulphuris, flowers of sulphur, sublimed sulphur ; **Sulphur Lotum** (U.S.P.), sulphur washed with ammonia in order to remove the acids, a yellow, micro-crystalline powder, insoluble in water. *Dose*, 12—40 decigrms., 20—60 grs. (B.P.) ; 4 grms., 1 dr. (U.S.P.) ; for intramuscular injections for chronic rheumatism, a 1 per cent. solution in olive oil, beginning with 2 c.c., and increasing to from 5 to 10 c.c., once a week. If the reaction is very strong, only the smaller doses are given.

Pulvis Glycyrrhizæ Compositus (B.P.), and *Pulvis Sennæ Compositus* (U.S.P.) contain 8 per cent. of sublimed sulphur.

Unguentum Sulphuris (B.P.), 10 per cent. ; (U.S.P.), 15 per cent.

Sulphur Præcipitatum (B.P., U.S.P.), Lac Sulphuris, milk of sulphur, precipitated sulphur, a yellowish white, amorphous powder, much finer than the sublimed sulphur, and therefore acting in doses of about half the size. *Dose*, 12—40 decigrms., 20—60 grs. (B.P.) ; 4 grms., 1 dr. (U.S.P.).

Confectio Sulphuris (B.P.), an aperient, also containing acid potassium tartrate. *Dose*, 4—8 grms., 60—120 grs.

Potassa Sulphurata (B.P., U.S.P.), Hepar Sulphuris, liver of sulphur, sulphurated potash, liver-coloured to yellowish green pieces, obtained by the melting of sulphur with potash, thus forming various potassium sulphides. Even the carbonic acid of the air liberates hydrogen sulphide. For artificial sulphur baths, 100—200 grms. of liver of sulphur ; to promote a lively evolution of sulphuretted hydrogen, 1 or 2 tablespoonfuls of concentrated sulphuric acid may be added to the bath-water.

Calx Sulphurata (B.P.C.), sulphurated lime, is a mixture consisting chiefly of CaS and $CaSO_4$. A pale grey or yellowish powder with an odour of hydrogen sulphide. *Dose*, 16—60 milligrms., $\frac{1}{4}$—1 gr. *Vlemingkx's Solution*, an old, famed remedy for scabies, is a solution of 1 in 1 of calcium polysulphides.

Calcium Sulphuratum Hydratum, $Ca(SH)_2$, a soft, brownish grey mass. For a depilatory, may be stirred into a paste with equal parts of glycerine, and allowed to lie on the skin for 10 minutes, after which it is washed off and a bland ointment applied. The corresponding compounds of barium and strontium are employed in the same way.

8. AMMONIA AND AMMONIUM

Ammonia forms salts with acids, these salts being supposed to contain a group not known in the free state, NH_4, or ammonium, which behaves as a monatomic metal, whose compounds greatly resemble the potassium salts. In water, ammonia is dissolved to a liquid with alkaline reaction. Such a solution of ammonia contains some unchanged NH_3, and ammonium hydroxide, NH_4OH, which is dissociated into NH_4 and OH ions.

Action. A strong solution of ammonia acts upon the **skin** and **mucous membranes** through its OH ions, as a corrosive like

caustic potash and soda, but less powerfully, because the concentration of the hydroxyl ions in the ammonia solution is lower. The ammonia gas, which quickly penetrates into the tissues, produces at first no actual corrosion, but burning pain, hyperæmia and erysipelatous erythema, and, finally, vesication, with subsequent desquamation. If evaporation be prevented by covering the skin with a watch-glass, vesicles are raised in the course of 10—20 minutes; and after prolonged action deep corrosion takes place, accompanied by great pain, and the tissues assume the same appearance as when treated with caustic potash. Concentrated solutions of ammonia taken internally produce very severe gastritis, with intense pain, vomiting—the vomited matter containing blood—and collapse. Such poisoning is almost invariably complicated by inhalation of the volatile gas, which causes œdema of the glottis, capillary bronchitis and pneumonia. The mortality from poisoning of this kind is very great, and even in cases of recovery hoarseness or aphonia may last for several months. Inhalation of dilute ammonia produces, by reflex from the nasal mucous membrane to the medulla, vaso-contraction and heightened blood-pressure, cessation of respiratory movements for a moment, and then deeper respiration.

The official ammonium carbonate gives off ammonia in the air, and acts like that gas diluted. It is converted in time, with continued loss of ammonia, into the acid salt, which is less irritant, but in large doses may still produce vomiting.

The **general action** of the ammonium salts varies greatly according to the mode of employment. Injected into the blood they produce as marked symptoms of irritation of the spinal cord and medulla oblongata as those produced by strychnine. There is an instantaneous outbreak of violent tetanus; *respiration* ceases for a moment, immediately after the injection, in convulsive inspiration, and then for some time is very frequent. The *blood-pressure* changes with the respiration—first a fall, which after a few seconds is succeeded by a rapid rise, accompanied by increased rate of the pulse. The action is only transitory, however, for within a few minutes the curve has sunk to the normal, or a little lower. If very large doses are injected, the convulsions may pass, and a paralytic state ensue, when the animal succumbs from asphyxia; but, as we shall see, the ammonium salts soon become harmless in the organism, and life can therefore, as a rule, be preserved by artificial respiration.

All these effects on the central nervous system are absent, or, at any rate, far less marked when the ammonium salts are introduced through the intestinal canal. In chance cases of poisoning in man, there are no convulsions even after very large doses; and

the symptoms arise only from the gastritis induced. The reason of this striking difference between the action of ammonium salts when injected into the blood and when taken in the ordinary way is that, taken by the mouth, they are so quickly converted into urea, and so rapidly excreted, that no effective quantities can concentrate in the body. The synthesis to urea is not, however, carried out with the same ease by all animals. It is only in herbivorous animals that all ammonium salts are converted into urea. In the carnivora and man, the carbonates and other salts which by combustion give off carbonic acid, which itself takes part in the synthesis, are entirely converted into urea; but the salts of the strong mineral acids, *e.g.* ammonium chloride, are not completely transformed, and are excreted, to some extent at any rate, in unchanged form.

Ammonium salts have a slightly *diaphoretic* action, increase the *bronchial secretion*, and make the mucus thin. Excretion in the bronchial secretion is assumed, but has not been directly proved. There is also *diuresis*, but the urine cannot of course be rendered alkaline by the ammonium compounds as it is by the fixed alkalies, the former being excreted either as urea or as neutral salts of mineral acids.

Therapeutic Uses. **Ammonia** is rarely employed as an escharotic, but is frequently used—as a rule in combination with camphor, oil of turpentine, and other skin-irritants—as an ingredient in liniments for *rheumatic and neuralgic pains*, *sprains*, *bruises*, and similar bloodless injuries. A dilute solution of ammonia is used as a wash for *itching skin affections* and *insect bites*. Ammonia is employed as a restorative in cases of *acute collapse* (fainting), its irritation of the nasal mucous membrane causing a reflex stimulation of the respiratory centre and augmented blood-pressure, hence the practice of painting the inside of the nose with solution of ammonia in cases of collapse during chloroform anæsthesia. Ammonia is also given internally in small doses as a stimulant; and for some unknown reason preparations of ammonia have been recommended for snake-bites. In *poisoning by inhalation of corrosive acid vapours*, inhalation of ammonia is the natural treatment.

The treatment of *poisoning with solution of ammonia* is to wash out the stomach when practicable, and to give as an antidote vinegar or lemon juice. Œdema of the glottis may necessitate tracheotomy, and strictures of the œsophagus the employment of bougies or operative measures, *e.g.* gastrostomy.

Ammonium chloride is much employed as a reflex expectorant in the early stages of ordinary *acute bronchitis*, when the secretion is sparing; and it is credited by most writers with an undoubted

power of making the catarrhal process pass more quickly into its second stage. On absorption the ammonium ions are converted into urea which is excreted in the urine. The fixation of the remaining chlorine as chlorides tends to deplete the alkali reserve, and in order to maintain the normal acid/alkali balance of the tissues a larger quantity of sodium acid phosphate is excreted in the urine. Thus ammonium chloride is a potent acidifier of the urine. The increased output of urea and acid phosphate accounts for the diuretic action of this salt. In large doses it produces gastric irritation.

Ammonium carbonate, which was formerly produced by the dry distillation of horn and other similar substances (spirit of hartshorn), and, in consequence, contained pyridine bases and other empyreumatic products, at one time enjoyed a reputation as a remedy for convulsions and " nervous attacks." Taken by mouth in doses of 0·3 gramme, ammonium carbonate is a useful reflex expectorant, as sufficient gastric irritation is set up by the liberation of ammonia and the formation of ammonium chloride to promote a flow of bronchial secretion. Large doses, *e.g.* 1—2 grammes, cause vomiting. In the air ammonium carbonate gives off ammonia, and is used as a *restorative in cases of fainting.* It is a household article employed, as *baking-powder*, in the making of light, porous cakes, pastry, etc. By the heat of the baker's oven it is volatilised, forming innumerable fine channels in the dough.

Urea is also diuretic. It is a low threshold substance and when the concentration in the tissues rises above a certain level the excess is excreted in the urine. The presence of urea in solution in the renal tubules raises the osmotic pressure of the urine and hinders the re-absorption of water which normally occurs. In consequence the output of urine is considerably increased. Hexamethylene-tetramine (urotropine), which is also an ammonia derivative, is mentioned under formaldehyde.

According to manufacturers' statements, *allylthiocarbamide* or *thiosinamine*, when injected hypodermically, possesses the remarkable power of removing, or causing the absorption of, cicatrices, no matter what their position may be. The action appears to be due to the œdema produced, and the migration of the leucocytes into the cicatricial tissue, which becomes soft and yields more easily to mechanical treatment; such mechanical treatment should be carried out simultaneously with the injections. Thiosinamine was first used for external scars, *e.g.* after *lupus* and *burns*, but is now also often employed for internal cicatrices such as *ankylosis, œsophageal and urethral strictures* (combined with dilatation), *syphilitic contractures of the larynx, adhesions after*

otitis, pleuritic adhesions, etc. In *tabes* thiosinamine may relieve the shooting pains, but may also have the opposite effect. In carcinomatous strictures the treatment has had no effect. The injections cause burning pain, but only for a short time; rarely they have other unpleasant effects, such as an urticarial rash, indisposition, headache or polyuria. Sometimes fever lasting several days has been observed, especially in tuberculous cases. It has been supposed that a reaction takes place similar to that which occurs after tuberculin injections, and tuberculosis has therefore been laid down as a contra-indication, for fear of the spread of the bacilli.

Preparations and Doses

Liquor Ammoniæ Dilutus (B.P.), **Aqua Ammoniæ** (U.S.P.), solution of ammonia, a colourless liquid with a strongly alkaline reaction, containing about 10 per cent. of ammonia by weight. *Dose,* 0·6—1·2 mils, 10—20 mins. (B.P.); 1 mil, 15 mins. (U.S.P.), well diluted.

Liquor Ammoniæ Fortis (B.P.), *Aqua Ammoniæ Fortior* (U.S.P.), about 30 per cent. of ammonia.

Linimentum Camphoræ Ammoniatum (B.P.) (see under "Camphor," p. 152).

Ammonii Chloridum (B.P., U.S.P.), ammonium chloride, NH_4Cl, colourless crystals with a cool, saline taste, readily soluble in water. *Dose,* 0·3—0·6 grm., 5—10 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). The administration of ammonium chloride for two or three days prior to injecting Mersalyl in cases of cardiac dropsy enhances the diuretic value of this organic mercurial. Often used together with liquorice in solution or as *Trochisci Ammonii Chloridi* (U.S.P.) (see p. 281).

Ammonii Carbonas (B.P., U.S.P.), the so-called ammonium carbonate, is a variable mixture of acid ammonium carbonate, NH_4HCO_3, and ammonium carbamate, $NH_4.NH_2CO$, and forms translucent, crystalline masses, which are freely soluble in water. It releases ammonia in the air, and is therefore continually changing its composition. *Dose,* 3—6 decigrms., 5—10 grs. (B.P.); 0·3 grm., 5 grs. (U.S.P.).

Ammonii Bicarbonas (B.P.), white crystals or a fine crystalline powder, pungent taste, ammoniacal odour, hygroscopic. Soluble in 6 parts of water. *Dose,* 0·3—0·6 grm., 5—10 grs.

Liquor Ammonii Acetatis Fortis (B.P.), a thin syrupy liquid with an odour of ammonia and of acetic acid. *Dose,* 1—4 mils, 15—60 mins. Used in preparing the dilute solution.

Liquor Ammonii Acetatis Dilutus (B.P.), Mindererus' Spirit. Colourless; smell acetous, characteristic taste. Principally used in saline, diaphoretic mixtures, but its value is almost negligible. *Dose,* 8—30 mils, ½—1 oz.

Spiritus Ammoniæ Aromaticus (B.P., U.S.P.), aromatic spirit of hartshorn, spirit of sal volatile, contains ammonia and ammonium carbonate, together with volatile oils. *Dose,* 10—40 decimils, 15—60 mins. (B.P.); 2 mils, 30 mins. (U.S.P.). Specific action doubtful (see p. 384).

Urea (B.P.), colourless crystals, cool saline taste. Soluble in one part of water. *Dose,* 1—16 grms., 15—240 grs. Used as a diuretic. It is also

given in the Urea Concentration Test and in Fowweather's modification of the Urea Clearance Test.

Thiosinaminum, thiosinamine, allyl sulphocarbamide, allylthio-urea, $CS<\begin{matrix}NH(C_3H_5)\\NH_2\end{matrix}$, colourless or reddish crystals, with an odour of garlic and a bitter taste, soluble in alcohol and in glycerine, and decomposed by pure water. *Dose*, 5—20 centigrms. in a 15 per cent. alcoholic solution, or 10 per cent. glycerinated water, injected subcutaneously, beginning with the smallest dose, twice a week for several weeks or months. The injections are made either in the vicinity of the cicatrix or elsewhere. They have a somewhat irritant local action. *Fibrolysine*, a compound of thiosinamine and sodium salicylate, forming a white powder, readily soluble in water. Injected subcutaneously in doses twice as large as those of thiosinamine. Irritation slight.

9. METALS OF THE ALKALINE EARTHS

Calcium is found not only in the bones of the human frame and the teeth, but also in all the soft tissues of the body, and is probably a necessary constituent of all the cells and fluids. It is continually being excreted, and must continually be replaced, and is thus one of the most indispensable constituents of food. Its importance to the organism is fairly evident from the morbid symptoms that make their appearance in lime-starvation, and have often been investigated in connection with the much discussed question of the ætiology of rickets. When mammals receive food that is sufficient in quantity but lacking in lime, they fall into a state of malnutrition which expresses itself in want of appetite, diarrhœa, loss of weight, atrophy of the skeleton, the bones decreasing both in thickness and weight, and general weakness ; and finally death ensues.

Calcium also shows itself to be essential to the life of isolated organs. A frog's heart soon comes to a standstill in diastole when perfused with a physiological saline solution deficient in calcium, even when the solution has been made slightly alkaline with carbonate of soda ; but the heart, if already arrested, may again begin to beat when a calcium salt is added to the solution. Even the minimal amount of calcium obtained by preparing the saline solution with ordinary instead of distilled water shows a distinct influence. As long as only Ca and Na ions are present, however, the systole of the heart is somewhat prolonged and the dilatation follows slowly ; but as soon as a trace of a potassium salt is added, the movements assume a normal character. All these salts are therefore to be found in Ringer's and Locke's solutions so much employed in physiological experiments. Similarly other striated muscles preserve their contractility, nerves their reaction to an electric current, and the cilia of the ciliary epithelium their move-

ments, for a longer time in a saline solution containing lime than in a pure physiological saline solution. The ova of various animals do not develop, or develop abnormally, in water that is entirely without calcium.

This element is also essential to several processes that take place without the co-operation of living cells. Milk, for instance, is not coagulated by rennet unless a lime salt is present ; and the coagulation of the blood is prevented when its calcium salts are precipitated by oxalic acid. Other calcium-precipitating acids, such as citric acid, have the same effect. It has also been found that in man the blood coagulates more rapidly after the internal employment of calcium salts. This effect, however, according to recent investigations by van den Velden, is very transient. As it commences after two or three minutes and lasts only 20—30 minutes, it cannot be of a specific nature, but must be due to irritation of the gastric mucous membrane, for other irritants and astringents have the same effect.

Although absorption of calcium salts is facilitated by the presence of free hydrochloric acid in the gastric juice, they are taken up very slowly from the intestine. It is established that a considerable excess of calcium over actual requirements must be present in the diet to ensure adequate assimilation.

About half a gramme of calcium is needed daily by the normal adult. In the absence of a sufficient supply of calcium in the diet the deficiency is made good at the expense of the muscles and bones which are the main calcium depots of the body. During pregnancy and lactation the demand for calcium is greater, as it is also in young people who are growing rapidly. The amount actually absorbed is determined to some extent by the needs of the body at any particular time. Nearly all of the unused calcium appears in the fæces in the form of salts and soaps. A small proportion is excreted in the urine as phosphates of calcium.

The effects of lime-starvation have already been mentioned. It must be added, however, that apart from a few sparsely populated regions of the globe, serious deficiency of calcium in the diet is comparatively rare. On the other hand, one of the most important factors in promoting the absorption and proper utilisation of calcium and phosphorus is vitamin D (calciferol). This is discussed in more detail later (p. 523), but it may be mentioned here that lack of calciferol may result in the onset of *rickets* characterised by bony changes, poorly formed teeth, catarrh of mucous membranes, etc. As a rule, signs of abnormal calcium metabolism are associated with insufficiency of vitamin D during the period of growth, rather than an absolute deficiency in the quantity of calcium ingested.

It was shown by Wright, several years ago, that urticaria or local œdema after the injection of antidiphtherial serum is prevented by calcium chloride, but some doubt has been thrown upon this by more recent workers. Chiari and Januschke even claim that this is also the case with the serous pleuritic effusions that may be produced in animals by various poisons, *e.g.* thiosinamine (mentioned in the preceding chapter). The local inflammation of the conjunctiva, produced by irritants, was absent or slighter in experiment-animals that were previously treated with subcutaneous injections of calcium chloride. This inhibitory action on inflammation was independent of the coagulation of the blood, for it also appeared during the simultaneous employment of hirudin. H. Meyer has therefore suggested that calcium chloride changes the vascular walls by making them denser and less permeable, *i.e.* has a *remote astringent action.* Calcium lactate, either alone or with parathyroid hormone, is frequently used with good results in the treatment of chilblains.

The concentration of calcium in the blood is about 10 milligrammes per cent. Despite daily fluctuations in the intake of calcium, this figure remains remarkably constant in health. Normally about two-thirds of the calcium in the blood is in the ionised state and the remainder is combined with protein. An important function of the parathyroid glands is the maintenance of an adequate concentration of calcium in the blood. Deficiency of the parathyroid hormone results in hypocalcæmia, *e.g.* 5 milligrammes per cent., which is accompanied by excessive excitability of skeletal muscle and a tendency to tetanic spasm. The same effects may be produced by severe alkalosis owing to interference with the formation of ionic (diffusible) calcium. Tetany is rapidly abolished by the intravenous injection of calcium gluconate, and a similar but slower response is obtained when the parathyroid hormone is given alone. On the other hand, excess of this hormone increases the total quantity of calcium in the blood and also the proportion of ionised calcium. It might be thought that the administration of calcium salts and parathyroid hormone would be valuable in other convulsive states by producing a sedative effect upon the neuro-muscular mechanism ; in practice, however, this has not found any useful application. By repeated injection of the hormone and also in certain pathological conditions of the parathyroid glands, hypercalcæmia and increased excretion of calcium may deplete the reserves in the bones to such an extent that they undergo softening. This process of emptying the bones of their calcium finds an application in the treatment of chronic lead-poisoning. Considerable quantities of this metal are stored in the bones and as these become rarified

under the influence of parathyroid therapy the lead is liberated into the blood-stream and excreted. The treatment is still more effective when an acid-forming salt such as ammonium chloride is given at the same time. Overdosage may easily precipitate the symptoms and signs of acute plumbism owing to the increased quantity of lead in circulation. This complication is brought rapidly under control by giving large doses of alkali; acidæmia is thus corrected, and as a tendency to alkalosis develops, the abnormal output of calcium from the bones ceases and in consequence the lead is again fixed in the bony tissue.

Introduced directly into the blood, soluble calcium salts increase the force of ventricular systole, an action also found, but in a stronger degree, in the nearly-allied barium (see below). After very large doses, a kind of narcotic condition supervenes, and cardiac irregularities occur which end in diastolic standstill.

Calcium salts *are absorbed* slowly from the alimentary canal. Only a small proportion of the amount absorbed *is excreted* through the kidneys, the greater part being returned to the intestine, by which it leaves the body together with the unabsorbed portion. After small doses of calcium salts the excretion in the urine is scarcely increased at all, while after very large doses, *e.g.* 8—10 grammes of chalk, the amount has been found to be trebled, but to have fallen by the following day to the normal.

Owing to their small capability of diffusion and very slow absorption, the calcium salts cannot, like the alkali salts, elicit those changes in the body that have been previously described under the name of salt-action, for salt-action is only seen with salts that are readily soluble and easily absorbed. The small quantities that are taken up are employed as nutritive and building material, and beyond this there is no specific action to be traced except that after large doses the urine becomes alkaline and turbid with excreted phosphates. Feeding animals with large quantities of phosphate of lime has proved to have no effect upon the amount of ash from the bones.

The local action of *calcium oxide* (quicklime) is *caustic* on moist tissues, as it very readily combines with water, with considerable evolution of heat. Unlike that of the caustic alkalies, the action is superficial, as lime, when dissolved, cannot spread into the tissues, but is held everywhere as hydrate or other sparingly soluble compounds that are formed with the acids and fat of the tissues.

Barium, notwithstanding its chemical relationship to calcium, is a very poisonous metal, its soluble salts acting fatally upon man even in doses of a few grammes. The most important symptoms are burning in the mouth and epigastrium, vomiting, and soon after, diarrhœa coupled

with violent pain and great exhaustion, irregular slow pulse, shallow respiration, and at last death from asphyxia. Consciousness is almost always clear; convulsions very seldom occur. Experimental analysis shows that barium is a specific muscle poison which produces tonic contractions of all muscles, both striated and smooth. The action on the heart is of special interest. The systole of the excised heart of a frog becomes more complete, but the diastole diminishes (Fig. 28), and finally the ventricle

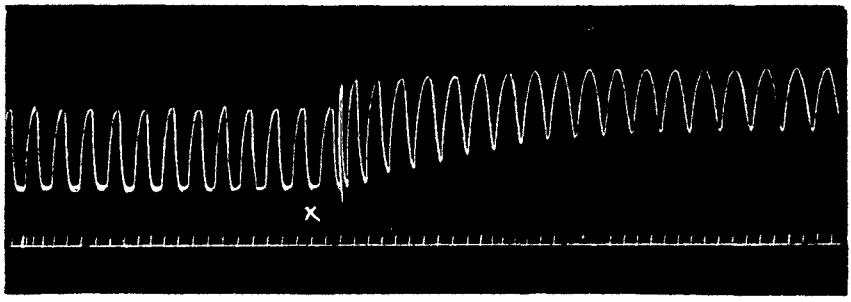


FIG. 28.—On the left, normal action; at ×, that produced by $BaCl_2$, 1 in 2,000. The time is marked in seconds.

remains in tonic contraction (Fig. 29), while the auricles continue to beat for some time longer. In mammals barium causes a slow pulse and raised blood-pressure, to which the stronger cardiac action and still more the constriction of the arteries contribute. The action has thus an outward resemblance to that of digitalis.

Strontium, too, has the digitalis action, although weak; but unlike barium it is not poisonous. Twenty grammes of strontium lactate or nitrate taken internally have proved harmless to man; and even after intra-

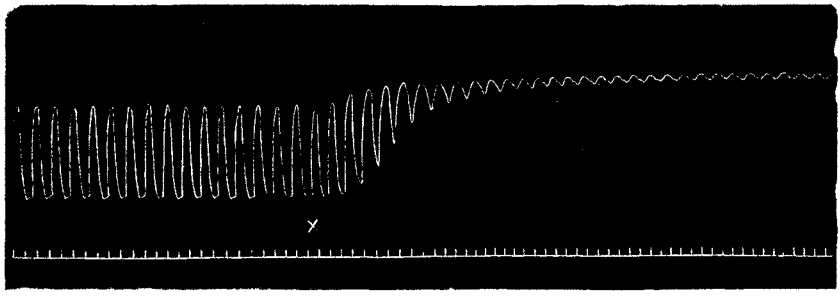


FIG. 29.—On the left, normal action; at ×, that produced by BaCl, 1 in 1,000.

venous injection of 3 grammes of strontium chloride in dogs, Laborde saw no signs of poisoning. By feeding with food lacking in lime, but to which strontium is added, a considerable amount (about 5 per cent.) may be deposited in the bone-tissue instead of lime.

Therapeutic Uses. Recent investigations of the great physiological importance of calcium have also led to the bestowal of much attention therapeutically upon the hitherto little heeded **soluble calcium salts,** calcium chloride and lactate. Endeavours have especially been made to utilise the above-mentioned remote

astringent action found by animal experiments. It appears that not only the *anaphylactic skin-symptoms* occurring after serum-injections, or from idiosyncrasy towards certain articles of food (crab, lobster, strawberries), but also ordinary *nettle-rash*, can be very favourably influenced, and the profuse bronchial secretion attending *iodism* may be diminished. Their most valuable action has been found in *hay-fever*. Even very obstinate forms of this troublesome complaint may often be prevented when the prophylactic daily use of 3 grammes of calcium chloride is begun a few weeks before the advent of the hay-fever season. It may also prove efficacious even when taken only on the outbreak of the complaint. Its employment in *pleurisy* and in *bronchitis* with profuse secretion has yielded negative results.

Another group of more recent indications is determined by the effect that lime insufficiency seems to have upon the nervous system. MacCallum and Voegtlin have found that the amount of lime in the blood diminishes after excision of the parathyroid glands, and that the tetany occurring after the operation may be combated by treatment with lime. Investigations by H. Meyer and his pupils have further shown that in cases of poisoning with lime-precipitating substances, *e.g.* oxalic acid, symptoms of increased nerve-irritability appear. The treatment of *spasmophilia* and *tetany* in children with calcium chloride has given good results clinically. In tetany in adults, such as the *tetany of pregnancy*, the painful tonic contractions may be relieved after a few days' employment of calcium chloride. In *bronchial asthma*, too, the effect may be very satisfactory.

Calcium chloride has also often been tried for *hæmorrhage*, but its very transient effect upon the coagulability of the blood is of scarcely any practical importance. Lauder Brunton recommends calcium chloride as a *heart-tonic*, especially in *pneumonia*. In order to raise the calcium content of the tissues as rapidly as possible, hydrated calcium chloride or calcium gluconate should be injected intravenously.

As calcium chloride has a tendency to cause acidæmia it is a powerful acidifier of the urine and is much more effective than sodium acid phosphate for this purpose.

Lime is employed as a cheap and efficient means of *disinfecting on a large scale*, *e.g.* excretions during cholera-epidemics, common burial in war-time, and so forth. It possesses considerable antiseptic action, a solution of 1 in 4,000 proving fatal to cholera bacilli, and a still more dilute solution to typhoid bacilli, in the course of a few hours. As a caustic, unslaked lime is occasionally employed with caustic potash to prevent the latter from spreading too much (see p. 371).

On raw surfaces finely-divided calcium carbonate is precipitated from **lime-water** by the carbonic acid of the secretions, and all little drops of fat are transformed into insoluble soap ; the fine sediment thus formed acts as a protective covering and has an *astringent* effect, thus making lime-water a practical remedy for the poulticing of *wounds* and running skin-affections. Instead of letting the saponification take place on the wound, it can be produced by shaking lime-water with olive or linseed oil. The product, lime liniment, which is an emulsion consisting of soap particles suspended in the oil, was a popular remedy for *burns*, much used before the introduction of antiseptics. In the stomach, lime-water neutralises acids, and causes milk to coagulate in exceedingly fine particles instead of in thick curds, and is finally deposited upon the epithelium of the intestine as carbonate and phosphate, and as soap. These chemical reactions explain how lime-water reduces the intestinal secretion and may stop *diarrhœa*, for which purpose it is sometimes given to children.

Calcium carbonate has almost the same action on stomach and intestine, and is also prescribed for *diarrhœa* (chalk mixture). In the form of chalk it is used in cases of acid poisoning, but magnesia is to be preferred (see Chapter 10, p. 401). On the skin finely divided calcium carbonate is protective and neutralises acid secretion, hence it is included in many dusting-powders.

As the bone-tissue in rickets contains too little lime, and as rachitic changes in the bone have been found together with lime starvation, various preparations of lime, **calcium phosphate** among others, have been given a thorough trial for *rickets*, but without apparent benefit. This negative clinical result indicates that the cause of the disease is not an insufficiency of lime, and confirms the constantly-recurring experience that rickets often occurs in children that have never lacked food containing lime, and, indeed, is most frequent in bottle-fed children who have been reared on cows' milk, which contains more lime than human milk (see Calciferol, p. 523).

Calcium sulphate occurs in nature in crystalline form as the mineral **gypsum,** of which the constitution is $CaSO_4 + 2H_2O$. When the crystalline gypsum is heated to about 150° C., the water of crystallisation is expelled, and the product remaining, which is called calcined gypsum, has the remarkable property, when brought into contact with water, of once more taking up its two molecules of water of crystallisation, and setting firm in doing so. To this is due its employment for *immovable bandages*.

Barium chloride has repeatedly been recommended for cardiac diseases, and is said to be efficient, but, as mentioned on p. 390, it is not of the same nature as digitalis. The insoluble *barium*

sulphate is now much used in X-ray photography of the stomach and intestine ; it is of great importance that it should be free from soluble barium salts. *Strontium lactate* has been found by Laborde to diminish the amount of albumin in *nephritis*, and is sometimes employed for that purpose. It is also said to be efficient against tape-worm.

A new element belonging to the metals of the alkaline earths is **radium** (Curie and Bemont, 1898), the best-known of the more recently discovered radio-active elements. Its remarkable properties have compelled us to give up our deeply-rooted belief in the atom as the smallest and ultimate division of matter, and have in general induced radical changes in our views on the nature of all matter. The radium atom undergoes an incessant, spontaneous process of disintegration, during which it emits (1) the so-called α-particles, which are material particles charged with positive electricity, now recognised as electrically-charged helium atoms ; they are emitted with a velocity of up to 28,000 kilometres per second ; (2) β-particles, or negative electrons (analogous to cathode rays), of which the velocity is still greater, approximating that of light, and (3) γ-rays, which are regarded as æther-waves produced by the rapid movement of the particles, and are of a nature similar to X-rays. Radium itself thereby becomes *radium emanation*, a gas which is also an unstable body that is rapidly further decomposed, yielding, among other things, the element helium. It is hereby proved for the first time that one element can change into another, thus subverting the old dogma of the immutability of elements. When radium is placed upon the skin, the skin is subjected to an incessant bombardment of the above-mentioned particles and rays, the result being obstinate ulcerations that have the appearance of burns. At the same time the harder or more penetrating rays go deeper, but do not act with equal power on all cells and tissues. The leucocytes, and the so-called lymphatic tissue generally, suffer most, and in the male and female sexual cells sterility can be produced (X-rays have the same effect). Young, growing cells are remarkable for their peculiar susceptibility, especially when the growth takes place in an irregular, atypical manner, as in the case of malignant tumours. Upon the experience thus acquired is based the modern radium treatment of *cancer* that cannot be operated on, in which, by suitable filtration (metal capsules), the superficially-acting "soft" rays which cause inflammation and necrosis of the skin are excluded, and only the above-mentioned more penetrating rays employed. The treatment must be undergone in hospitals that have comparatively large quantities of radium at their disposal, as irradiation that is too weak acts only as a harmful irritant, promoting the growth of the tumour. (Weak irradiation also encourages the germination of plant-seeds, while strong irradiation destroys the germinating power.) A suitable irradiation at the climacteric age can cause the cessation of *menstruation*, and with it of the troubles that are liable to occur at this period. Since the discovery that many of the most noted mineral springs contain radium emanation, the question as to whether this is of medicinal importance has acquired greater interest. From the experiments made with large amounts of emanation it appears that *gout, articular and muscular rheumatism*, and *neuralgia* are often benefited. Artificial radium water (very dilute solutions of radium salts), or inhalation of the emanation is now employed therapeutically. In both cases far larger doses are taken than those

found in the natural springs. Radium emanation is taken up very easily through the lungs and from the alimentary canal, and is rapidly excreted in the air expired.

PARATHYROID GLANDS

It has been pointed out (p. 202) that the physiological importance of the parathyroid glands was first appreciated as a result of observations of the effects of extirpation of the thyroid, the two being closely related anatomically although entirely different in regard to function. The part played by the parathyroid hormone in calcium metabolism is discussed on p. 388. Therapeutically, this hormone has a limited value. It is used rationally in cachexia parathyreopriva. In tetany associated with a low concentration of ionised calcium in the blood, parathyroid hormone may be injected subcutaneously or the desiccated gland may be given by mouth. The action depends upon restoring the normal concentration of calcium in the blood, and this can be accomplished more rapidly by injecting suitable calcium salts intravenously. Although these methods of treatment give immediate relief, they are of subsidiary importance to correcting the cause of the tetanic state, *e.g.* rickets, alkalosis, etc. The use of parathyroid hormone in lead-poisoning has already been mentioned.

Preparations and Doses

Calx (not official), calcium oxide, lime, quicklime, unslaked lime, CaO, greyish white irregular pieces, which, with great evolution of heat, combine with water to form the white, powdery hydrate, $Ca(OH)_2$. One part of lime to 4 parts of water makes a thick mixture called milk of lime.

Calcii Hydroxidum (B.P., U.S.P.), slaked lime, $Ca(OH)_2$. A soft white powder, alkaline slightly bitter taste, slightly soluble in water. *Dose*, 0·3—1 grm., 5—15 grs. (B.P.).

Liquor Calcii Hydroxidi (B.P., U.S.P.), a saturated solution of calcium hydrate, containing only about 1·3 grms. of CaO per litre, as the calcium hydrate is sparingly soluble. This is less than in cows' milk, 1 litre of which contains 1·7 grms. *Dose*, a dessertspoonful alone or in milk, for digestive disorders or diarrhœa in children. Official *dose*, 30—120 mils, 1—4 fl. oz. (B.P.); 15 mils, 4 fl. drs. (U.S.P.).

Linimentum Calcis (not official), lime liniment, Carron oil, composed of equal parts of lime-water and olive or linseed oil.

Calcii Gluconas (B.P., U.S.P.), calcium gluconate. A white, crystalline powder, odourless and tasteless. Soluble in 30 parts of cold water. Administered orally or parenterally; for intramuscular or intravenous injection a 10 per cent. aqueous solution should be freshly prepared. *Dose*, 2—4 grms., 30—60 grs. (B.P.); oral, 5 grms., 75 grs., intravenous, 1 grm., 15 grs. (U.S.P.).

Calcii Chloridum (B.P., U.S.P.), $CaCl_2$, white masses with a disagreeably saline, bitter taste, very deliquescent, and readily soluble in water. *Dose*, 0·6—2 grms., 10—30 grs.; intramuscular injection, 0·03—0·1 grm., ½—1½ grs.; by intravenous injection, 0·3—1 grm., 5—15 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). Given in solution with saccharine as a flavouring agent. For hay-fever, 1 grm. 3 or 4 times a day; for asthma, beginning with 1 grm. every 2 hours. Must not be injected hypodermically (necrosis, abscesses).

Calcii Chloridum Hydratum (B.P.), hydrated calcium chloride. Colourless crystals, odourless; bitter taste, very soluble in water and alcohol.

Doses, 0·06—0·2 grm., 1—3 grs. by intramuscular injection ; 0·6—2 grms., 10—30 grs. by intravenous injection.

Calcii Lactas (B.P., U.S.P.), calcium lactate, $Ca(C_3H_5O_3)_2 + 5H_2O$, a white, almost tasteless powder, soluble in about 18 parts of water. Given as a powder or in solution. *Dose*, 1—4 grms., 15—60 grs. (B.P.) ; 1 grm., 15 grs. (U.S.P.).

Calcii Carbonas (B.P.), *Calcii Carbonas Præcipitatus* (U.S.P.), calcium carbonate, $CaCO_3$, a white powder, insoluble in water. *Dose*, 1—4 grms., 15—60 grs. (B.P.) ; 1 grm., 15 grs. (U.S.P.).

Creta (B.P.), *Creta Præparata* (U.S.P.), prepared chalk, a native form of calcium carbonate, freed from most of its impurities by elutriation. *Doses*, as of the preceding preparation. The chief constituent of many tooth-powders.

Calcii Phosphas (B.P.), a variable mixture of normal basic and acid phosphates of calcium. A white amorphous powder, almost insoluble in water. *Dose*, 0·6—2 grms., 10—30 grs.

Mistura Cretæ (B.P.C., U.S.P.), chalk mixture ; for diarrhœa in children. *Dose*, 15—30 mils, ½—1 fl. oz. (B.P.C.) ; 15 mils, 4 fl. drs. (U.S.P.).

Pulvis Cretæ Aromaticus (B.P.), contains chalk, sugar and carminatives ; for acidity and diarrhœa. *Dose*, 6—40 decigrms., 10—60 grs.

Pulvis Cretæ Compositus (U.S.P.), a mixture of chalk, sugar and acacia. *Dose*, 2 grms., 30 grs. Employed with the same indications as the aromatic chalk powder.

Pulvis Cretæ Aromaticus cum Opio (B.P.) (see p. 90).

Calcii Sulphas Exsiccatus (not official), calcined gypsum, plaster of Paris, $CaSO_4$, a white powder, which, when mixed with half its weight of water, stiffens into a solid mass in the course of a few minutes, or less the warmer the water used. Plaster of Paris bandages that are liable to become damp (on children) are varnished with *water-glass*, a gelatinous solution of sodium silicate in water. Water-glass alone is not so suitable for immovable bandages, as it takes too long to set.

Barii Chloridum (not official), barium chloride, $BaCl_2 + 2H_2O$, colourless crystals with a bitter, nauseous taste, easily soluble in water. *Dose*, 2—3 centigrms., ⅓—½ gr. twice a day in dilute solution.

Barii Sulphas (B.P., U.S.P.), barium sulphate. A fine white powder, odourless and tasteless. Opaque to X-rays and therefore used as a diagnostic agent.

Liquor Parathyroidei (U.S.P.), parathyroid extract. An aqueous solution of the active principle of the parathyroid glands. Used for the relief of the manifestations of hypocalcæmia. *Dose*, by hypodermic injection, 25 units.

10. ACIDS

In aqueous solutions the acids are dissociated into positive hydrogen ions and each its own particular negative ion, *e.g.* $HCl = H + Cl$, $HNO_3 = H + NO_3$, $H_2SO_4 = H + H + SO_4$, etc. Both the acid reaction and the *characteristic acid properties are dependent on the hydrogen ions*. For the animal body, however, there are also other important circumstances to consider, such as a strong affinity for water ; and when the negative ion is very

poisonous, the real acid action is of little significance (prussic acid).

Those acids the action of which is entirely or mainly due to their acidity, *i.e.* the H ions, are, in the first place, the strong mineral acids—sulphuric, nitric, hydrochloric and phosphoric—and among organic compounds the lower fatty acids, especially formic, acetic and lactic acids. The higher fatty acids, which are insoluble in water, do not act like acids in the body, but are valuable food-stuffs, and no more belong to the pharmacological group of the acids than do the aromatic acids or others whose most important action is dependent on their negative ions.

General Action of the Acids. The living protoplasm is alkaline in reaction and cannot continue to exist when the alkalinity is reduced below a certain limit or the reaction becomes acid. The acids are therefore **protoplasm poisons,** and, as such, are *antiseptic.* Acetic acid and most of the strong mineral acids arrest the growth of micro-organisms and prevent putrefaction even in a concentration of 0·2—0·5 per cent., or about the same dilution as carbolic acid. Mould, and several lower animals such as the vinegar-eel (*Anguillula aceti*), which makes its appearance during the manufacture of acetic acid, are all resistant to the influence of dilute acids. In general the antiseptic power of an acid is proportional to the extent of its dissociation or the number of its H ions. The mineral acids, which in aqueous solutions are largely dissociated, are, therefore, better antiseptics than the much more poisonous prussic acid, which is only slightly dissociated.

The concentrated acids have a great affinity for water, expel weaker acids, neutralise all alkalies, and precipitate albumin. These properties make them powerful caustics, which destroy living tissue, causing at the time great pain. The affinity for water makes the effect on moist mucous membranes especially marked. With alkaline corrosion the mucous membranes become swollen, smooth to the touch, and dark-coloured ; with acid corrosion the membranes become at first white, with a dry, tanned appearance, and later brown or black, from extravasation of blood.

The various sections of the **alimentary canal** are affected by acids differently. When diluted, the acids have a slightly astringent, refreshing taste, and give a feeling of roughness and bluntness to the teeth. The stomach, which produces hydrochloric acid, is fairly tolerant of most dilute acids. Pepsin digestion, as we know, is carried out with the aid of acid, and in the test-tube the normal hydrochloric acid may be replaced by almost any of the other acids. In the duodenum, under the influence of acids or the acid contents of the stomach, secretin is produced (Bayliss, Starling), and, passing into the blood, increases

the secretion of the pancreas and bile. In the more distant sections of the intestine, where the reaction is normally alkaline, the acids have an irritant action, and cause diarrhœa. The excessive drinking of dilute acids for a long period diminishes appetite and weakens digestion, with poor nutrition and anæmia as secondary consequences.

The action on the **blood and tissues** is not very marked and is but little known as far as small quantities of acid are concerned. In the healthy human being, dilute acids, even in very large doses, have no effect upon *pulse* and *temperature*. In fever, according to many clinicians, they somewhat reduce the pulse-frequency, but the temperature very little. It is, of course, obvious that in conditions in which the production of acid is already increased they should be more active than in normal conditions.

In the living body the blood never becomes acid, as even a considerable decrease of its alkalinity is incompatible with the continuance of life. Salkowski and Schmiedeberg-Walther's fundamental investigations have shown that attempts to supersaturate the organism with acids by continued supply have different results according to whether the subjects of the experiments are herbivorous or carnivorous animals. In *herbivorous animals* (rabbits), the acids are excreted as salts of potassium and sodium. The blood is thus rapidly deprived of its fixed alkalies, and when a large amount is lost, the animal dies with symptoms of cardiac failure and dyspnœa, but up to the very last can be saved by intravenous injection of sodium carbonate. (Whether this is the case with all herbivorous animals is not known.) With *carnivorous animals* the circumstances are quite different, as these animals exhibit a marked immunity to acids. In dogs, even if the amount of acid taken, calculated according to body-weight, is double that which proves fatal to rabbits, there is no serious loss of fixed alkalies, these being saved by the excretion of the acids in combination with ammonia, probably at the expense of the urea.

This interesting difference between herbivorous and carnivorous animals is explained by the different character of their food. Vegetable food is always rich in potassium and sodium salts, and in that sense is alkaline food. In nature, herbivorous animals are, of course, never in the position of having to defend themselves against acids, but this is a necessity to carnivorous animals, whose food may be regarded as acid as it contains little fixed alkalies, and who form acid products of metabolism. Their organism must therefore be equipped with a means of defence against large quantities of acid, and so possesses this power to place ammonia at the disposal of the acids.

Man occupies an intermediate position between these two classes, but *stands nearer to the carnivora*—a weighty argument against vegetarianism if the tolerance to acids is not to be regarded as an acquired property. The acids are excreted both as ammonium salts and combined with fixed alkalies. A test of man's ability to render innocuous large quantities of acid is to be found in the serious forms of diabetes, in which β-oxybutyric acid and aceto-acetic acid are neutralised for a long time by the aid of ammonia, while at the same time the amount of urea is greatly decreased.

The acids are **excreted** in the urine as neutral or acid salts,

which have a slightly diuretic action. A small proportion remains free in the kidneys, and in carnivora and omnivora strengthens the acid reaction of the urine. In herbivorous animals the urine remains neutral or even alkaline.

In cases of **poisoning** the symptoms depend upon the concentration, and in the main are similar for all strong acids. The lips and the skin round the mouth show parchment-like streaks running from the corners of the mouth, and the mouth, throat, œsophagus and stomach are all more or less corroded. By the diffusion of the acids through the walls of the stomach, neighbouring organs, *e.g.* the pancreas and the liver, are affected. Perforation with diffuse peritonitis is rare. The clinical symptoms consist in intense pain and vomiting, in which the very acid contents of the stomach are first brought up and, later, shreds of bloody mucous membrane. In the most acute cases death may ensue in the course of a few hours, either as a consequence of perforation or from paralysis of the heart, which may follow any widespread corrosion of the intestinal mucous membrane. The great fall of blood-pressure arising from the dilatation of the large abdominal vessels, which contain a large proportion of the entire amount of blood in the body, also contributes to the fatal result. If the acid is volatile (hydrochloric acid), or if any of it, in being swallowed, has made its way into the larynx, there is dyspnœa, and acute œdema of the glottis may be the cause of death. Even when recovery is made from the immediate effects of the corrosion, the prognosis is still often doubtful, as swallowing is almost impossible and the alkalinity of the blood is reduced by the absorption of the acids. After several days have passed, moreover, the separation of sloughs may give rise to fatal hæmorrhages, and later contractures may once more endanger life. Nephritis and protracted gastritis with atrophy of the glands of the gastric mucous membrane often remain as sequelæ.

The above refers to the acids in general ; the peculiarities of the different acids will now be mentioned.

The intensely caustic action of **sulphuric acid** is due to its highly acid properties and its great affinity for water. In spite of its deterrent properties and the extreme suffering the poisoning entails, sulphuric acid is not infrequently employed in attempted suicide. A few grammes are generally fatal. Sulphuric acid is excreted in the urine, partly as alkaline sulphates, partly as aromatic sulphuric acids.

Dilute **nitric acid** precipitates albumin and is employed as a very delicate reagent for albuminuria. The concentrated acid dissolves albumin, and a nitration-product, *xanthogenic acid*, is formed, which gives a yellow colour to the slough and facilitates

the diagnosis of the poisoning. Inhalation of the vapour leads to inflammation of the bronchial mucous membrane, pneumonia and œdema of the lung. Nitric acid differs from other mineral acids in that internally, even when much diluted, it soon has a deleterious effect on the gastric digestion, and causes dyspeptic symptoms.

Hydrochloric acid, although chemically the strongest acid, does not dissolve tissues until after repeated application ; on account of its volatility it penetrates the skin, causing burning pain and producing erythema and vesicles. Inhalation of the vapour has the same consequences as inhalation of nitric acid. A mixture of hydrochloric acid and nitric acid, the so-called *aqua regia*, evolves free chlorine, which increases the corrosive action.

Among the organic acids **acetic acid,** in concentrated form, is comparable with the mineral acids in its corrosive action on unbroken skin, on account of the ease with which it dissolves horny tissue and epithelium. Excessive use internally induces gastric catarrh, loss of weight and anæmia. In the blood the acetates are oxidised to carbonates. **Formic acid** also acts strongly upon the skin.

Lactic acid has a corrosive action, especially on pathological tissue, far less on its healthy surroundings. The corrosion is accompanied by prolonged pain. In the stomach, where lactic acid occurs normally, it seems to be of the same value to pepsin digestion as hydrochloric acid. Introduced into the body in small quantities, the lactic acid undergoes complete combustion in the blood, and is excreted in the urine as alkaline carbonate ; larger quantities are excreted to some extent unchanged.

The fruit acids so widely distributed in the vegetable kingdom, **tartaric acid, citric acid** and **malic acid,** are almost without action on the epidermis, and are injurious to mucous membranes only in large quantities. Citric acid is oxidised almost completely in the body, tartaric acid less completely, and some is excreted unchanged. Malic acid, like tartaric acid, is changed by the pepsin of the gastric juice to succinic acid, which can be demonstrated in the urine.

Therapeutic Uses. *Internal Employment.* As a normal constituent of the gastric juice, hydrochloric acid is indicated in *anacidity of the stomach*, and is often of great benefit, although it must be left undecided whether it can altogether take the place of the physiological hydrochloric acid, which appears to be secreted not in the free state but in a loose chemical combination with pepsin. Besides co-operating in the protein digestion, hydrochloric acid is of great importance as a disinfectant of the stomach. It may therefore also be the right remedy for *hyperacidity* due to

fatty acids (ferment-acids), the formation of which is a symptom of a deficiency of hydrochloric acid. If the quantity of hydrochloric acid in the gastric juice is normal or augmented, its employment is contra-indicated. Various other acids have also been tried for hypo-acidity or anacidity, and are said to have the same effect ; but there is no necessity to take any other acid than the one with which the stomach is supplied by nature.

Hydrochloric acid is useful in *infantile diarrhœa*. As the acid is absorbed too quickly for a direct antiseptic action, the favourable influence must be a gastric action. Hydrochloric acid is especially indicated in cases in which previous gastric symptoms point to the arrival of the contents of the stomach in the intestine in a fermenting or insufficiently prepared condition. This also applies to lactic acid as a remedy for diarrhœa.

Of course the least corrosive acids are employed as antidotes in *poisoning with caustic alkalies, e.g.* citric acid or household vinegar.

The employment of the acids in *febrile diseases* rests upon a purely empirical foundation. The internal antiseptic action that is ascribed to the acids is more than doubtful, and the lowering of the temperature is only trifling. They are thus only to be regarded as mild adjuvants to other antipyretics ; they form, however, good thirst-quenching and refreshing drinks, and are useful digestives in the dyspepsia which always accompanies high fever. The acids most employed in fever are sulphuric, phosphoric, hydrochloric, tartaric and citric acids ; the last two are given as lemonades or as julep. When palpitation can be traced to flatulent dyspepsia associated with hypochlorhydria, the administration of hydrochloric acid is frequently attended by gratifying results.

When an acid is applied directly to a bleeding surface it acts as a hæmostatic, as the albumen coagulates and mechanically closes the open vessels. Sulphuric acid and acetic acid are also sometimes prescribed internally as hæmostatics, *e.g.* in *pulmonary* and *uterine hæmorrhages*, but with doubtful benefit. The only place in which a styptic action may perhaps be looked for is in the kidneys, the secretion of which is made more acid by mineral acids. For the same reason acids are employed in ammoniacal urine fermentation, but they do not dissolve the phosphate calculi formed in alkaline urine.

In rickets, osteomalacia and badly healing fractures phosphoric acid and phosphates were formerly employed, but have been superseded by dietetic measures and the use of preparations containing vitamin D. Nitric acid was at one time recommended for Bright's disease and diseases of the liver, but has now been abandoned.

External Employment. Concentrated and fuming nitric acid and glacial acetic acid serve as corrosives on *septic wounds*, *telangiectases*, *pigment spots* and small *epithelial formations*, such as warts and corns. Trichloracetic acid is now often recommended, as it is a strong corrosive, with the advantage that the action can be more easily confined and that the pain lasts for only a short time. Lactic acid is one of the numerous drugs tried for *lupus*, and is also used for painting *tuberculous ulcers in the larynx.*

Washing the skin with vinegar reduces the *secretion of sweat*, and the evaporation of the volatile acid has a cool, refreshing effect in fever. Formic acid, which occurs in the stinging-hairs of the nettle, and in the poison-weapons of various insects, *e.g.* the red wood-ant, *Formica rufa*, is an old popular remedy for *rheumatism* and *neuralgia* in the form of the so-called ant-baths, which are prepared from ant-hills with their occupants. The effect is due to the hot water combined with the skin-irritant properties of the formic acid and the turpentine oil from the pine-needles.

The addition of an acid (vinegar) to an enema increases the aperient action.

Treatment of Acid Poisoning. The natural antidotes are alkalies. Those most readily obtainable are soap and water, chalk, or lime scraped off a wall. The best remedy is calcined magnesia (several tablespoonfuls in water), which has the advantage over the carbonates of not evolving carbonic acid, which distends the stomach and may, with deep corrosion, carry the risk of rupture. In the further treatment, mucilaginous drinks and white of egg are given. The stomach-tube and emetics are contra-indicated. Œsophageal stricture is treated in the usual way with bougies; gastric strictures may necessitate operative procedure.

Preparations and Doses

Acidum Sulphuricum (B.P., U.S.P.), sulphuric acid, a heavy, oily liquid, containing about 95 per cent. of H_2SO_4. It is very hygroscopic, and mixes with water with explosive violence and great evolution of heat. The crude acid may be employed for disinfection, *e.g.* of typhus and cholera dejections.

Acidum Sulphuricum Dilutum (B.P., U.S.P.), 10 per cent. *Dose*, 0·3—4 mils, 5—60 mins. (B.P.); 1 mil, 15 mins. (U.S.P.).

Acidum Sulphuricum Aromaticum (U.S.P.), 20 per cent., an alcoholic solution of sulphuric acid, flavoured with cinnamon and ginger. *Dose*, as the above.

Acidum Nitricum (B.P., U.S.P.), nitric acid, containing about 70 per cent. of HNO_3. A corrosive used for warts and septic sores.

Acidum Hydrochloricum (B.P., U.S.P.), hydrochloric or muriatic acid, contains 32 per cent. of HCl.

Acidum Hydrochloricum Dilutum (B.P., U.S.P.). *Dose* (B.P.), as of Acid. Sulph. Dil.; 2 mils, 30 mins. (U.S.P.). Taken for dyspepsia in a

wineglassful of water 3 times a day after meals, for children in sugar and water or fruit syrup.

Acidum Phosphoricum (B.P., U.S.P.), contains about 86 per cent. of H_3PO_4.

Acidum Phosphoricum Dilutum (B.P., U.S.P.), 10 per cent. *Dose*, as of Acid. Sulph. Dil.

Acidum Hypophosphorosum dilutum (B.P.), *Acidum Hypophosphorosum* (U.S.P.), strength 10·5 per cent. and 32 per cent. respectively. An ingredient in hypophosphite preparations and in the syrup of ferrous iodide.

Acidum Aceticum Glaciale (B.P., U.S.P.), glacial acetic acid, containing 99 per cent. of $C_2H_4O_2$. Hardens at about 14° C. to an ice-like mass. Corrosive.

Acidum Aceticum (B.P., U.S.P.), 33—37 per cent.

Acidum Aceticum Dilutum (B.P., U.S.P.), 6 per cent. *Dose*, 2—4 mils, 30—60 mins.

Acetum, vinegar, corresponds in strength to the preceding preparation. Taken internally as an antidote to caustic alkalies. As an enema, 1 tablespoonful to a litre of water.

Acidum trichloraceticum (B.P., U.S.P.), trichloracetic acid, CCl_3COOH, deliquescent crystals with a slightly pungent odour, soluble in water. Used externally in solid form as a corrosive for condylomata, papillomata, and corns ; in a 1 per cent. solution for painting in rhinitis, ozæna, tonsillar hypertrophy and angina tonsillaris. For limited corrosion of mucous membrane, the pure acid may be used, with caution.

Acidum Lacticum (B.P., U.S.P.), lactic acid, a colourless or slightly yellow, syrupy fluid, containing 85—90 per cent. of $C_3H_6O_3$. *Dose*, 0·3—1·2 mils, 5—20 mins. (B.P.) ; 2 mils, 30 mins. (U.S.P.). Internally for diarrhœa in infants, a 2 per cent. solution with syrup to flavour, 1 teaspoonful every 2 hours ; for adults a tablespoonful of a 5 per cent. solution. For painting in tuberculosis of the larynx, beginning with a 20 per cent. solution and going on to the undiluted acid ; the great pain is relieved by cocaine.

Acidum Tartaricum (B.P., U.S.P.), tartaric acid, $C_4H_6O_6$, large colourless crystals, readily soluble in water. *Dose*, 0·3—2 grms., 5—30 grs. (B.P.) ; 0·5 grm., 8 grs. (U.S.P.).

Acidum Citricum (B.P., U.S.P.), citric acid, $C_6H_8O_7 + H_2O$, colourless crystals, dissolving very readily in water. *Dose*, 0·3—2 grms., 5—30 grs. (B.P.).

Syrupus Acidi Citrici (U.S.P.), used only as a flavour.

In small doses, *e.g.* 1 grm. several times a day, the citrates *Potassii Citras* (B.P., U.S.P.) and *Sodii Citras* (B.P., U.S.P.) are oxidised to carbonates and render the urine less acid or alkaline. *Doses*, 1—4 grms., 15—60 grs. (B.P.) ; 1 grm., 15 grs. (U.S.P.).

11. CARBON DIOXIDE (Carbonic Acid)

Carbonic acid occupies a peculiar position on account of its gaseous form, and because it is available combined with alkalies. It is one of the weakest of the acids, and accordingly exhibits only very mild acid effects upon the body. The activity of the respiratory-centre is regulated by the quantity of carbonic acid in the blood. A rise in the blood-CO_2 produces an increase in the rate

and depth of respiration, and, conversely, lack of an adequate amount of CO_2 in the blood leads to infrequent and shallow breathing. This association of the respiratory function and the carbonic acid content of the tissues is intimately concerned with the acid-base equilibrium of the body.

Action. On the unbroken skin carbonic acid first causes slight prickling, injection, heat, and finally numbness, a feeling of having gloves on, or distinct anæsthesia. In the mouth, for the first few seconds an almost painful stinging is noticed, and this soon passes into pronounced diminution of sensibility. If a strong stream of carbonic acid is directed against the pharyngeal mucous membrane, within a short time the membrane is completely anæsthetised. A corresponding action takes place in the stomach, first irritation of the sensory nerves (feeling of heat), and then local anæsthesia (suppression of nausea and pain). The secretion of hydrochloric acid is a little increased, an action which other acids lack (Pawlow). When large quantities are taken some are generally soon eructated and the rest of the gaseous acid very rapidly makes its way through the walls of the stomach into the blood, and accelerates the absorption of other substances. Sparkling wines are for this reason more quickly intoxicating than still wines of the same alcoholic strength ; and carbonic acid waters, being more quickly absorbed, are more diuretic than ordinary water. No amount, however great, of such waters, can produce poisoning, as the carbonic acid taken up by the blood is immediately excreted through the lungs.

It is a different matter when carbonic acid is inhaled under a pressure strong enough to increase the amount of carbonic acid in the body ; a number of toxic symptoms appear, varying with the concentration. Animals placed under a bell-glass filled with carbonic acid, give two or three gasps, drop down, and are dead in less than 1 minute. A death as sudden has been seen to overtake persons who have entered an atmosphere of almost pure carbonic acid. In these cases, however, both the lack of oxygen and the direct action of carbonic acid have to be considered. In order to see the latter effect alone, animals must be made to breathe a gas-mixture, which, besides carbonic acid, contains about 21 per cent. of oxygen like the atmospheric air. The following symptoms are then observed : with an amount of 20 per cent. of CO_2 in the air inspired, the respiration becomes quicker as a consequence of irritation of the respiratory centre, and the blood-pressure rises owing to vaso-constriction, also caused by central irritation. No other toxic action appears, even if the inhalation is continued for an hour. In an atmosphere with 30 per cent. of carbonic acid, these symptoms are masked by central paralysis ; the respiration becomes slow and weak, the blood-pressure falls, voluntary and reflex movements cease, general anæsthesia supervenes, and death takes place in the course of a few hours. With a still greater amount of carbonic acid the symptoms of stimulation are of short duration, the condition of the animal rapidly acquires a resemblance to a deep chloroform anæsthesia,

the respiratory movements become more and more shallow until they are scarcely visible and finally cease while the heart still beats. Carbonic acid is thus anæsthetic in its action, and has even been tried for that purpose in operations ; but for this it is not suitable, as a sufficiently deep narcosis is only obtained with a concentration that is dangerous for the respiration.

In man, serious cases of poisoning are very rare, as in circumstances in which much carbonic acid is evolved, much oxygen is also, as a rule, consumed. Man's tolerance seems to be somewhat less than that of animals ; but a concentration that seldom occurs in practice is required to call forth really serious symptoms. In an atmosphere with 8½ per cent. of CO_2, congestion is noticed after a few minutes, and commencing dyspnœa, which becomes unbearable after 15—20 minutes, but disappears at once on return to fresh air.

Therapeutic Uses. Inhalation of 7 per cent. carbon dioxide in oxygen is a reliable method of stimulating the respiratory centre. The mixture is obtainable in metal cylinders and is administered by means of a closely-fitting mask, such as is used for nitrous oxide anæsthesia. Impending respiratory failure due to depression of the centre in the medulla is the indication for treatment. Thus it is commonly employed in narcotic poisoning, *e.g.* from morphine, general anæsthetics and hypnotics, in blue asphyxia neonatorum, in carbon monoxide poisoning (coal-gas, etc.), and in cases of drowning. The increased pulmonary ventilation resulting from carbon dioxide administration may also be utilised to accelerate induction of anæsthesia with ether and as a post-anæsthetic measure to facilitate the excretion of volatile anæsthetics through the lungs. During convalescence after pleurisy or pneumonia, carbon-dioxide inhalations promote re-expansion of the affected lung. Beverages containing carbonic acid are employed in *febrile diseases*. For *nausea* and *cardialgia*, small doses of well-cooled sparkling waters are beneficial on account of their local anæsthetic action. For *diagnostic purposes* it was customary, before the time of X-ray photography, to fill the stomach with carbonic acid in order to demonstrate dilatation.

Carbonic acid is an important constituent of many *mineral waters*, as its sharp taste makes the salt solution, which otherwise is often insipid, easier to drink ; also, it increases the diuretic action of the water by promoting absorption. Waters containing carbonic acid are contra-indicated in diarrhœa and in diseases in which distension and movement of the intestinal canal are harmful, *e.g.* in meteorism, peritonitis, appendicitis, and also when there is liability to congestion and in heart-diseases, as distension of the stomach gives more work for the heart.

Carbonic acid baths have been much employed in *diseases of the heart* since 1870—80, when the doctors at the Nauheim baths discovered that rheumatic patients with heart-trouble were often greatly benefited by treatment with the carbonic acid waters of these baths. The effects are

of a peculiar and hitherto unexplained nature. The entire body is covered with gas-bubbles, which cause vaso-dilatation. After the bath the whole skin-surface is bright red, and the pulse-frequency, even in persons with normal heart, is generally decreased. With cardiac failure the effects are a decrease in the frequency of the pulse and the respiration, an increase in the amplitude of the pulse-wave, and, immediately after the bath, a distinct diminution in the size of a previously dilated heart. Where these favourable effects are obtained, dyspnœa and palpitations also cease, the flow of urine is increased, œdema disappears, etc. The action may thus be compared with the effect of a digitalis treatment, and the indications are in all essentials the same as those for digitalis, with the one difference that the more serious cases, requiring the greatest possible rest and confinement to bed, are less suited for hydropathic treatment. The late Sir James Mackenzie made a critical study of the results of the Nauheim treatment. He concluded that when due allowance was made for the benefits arising from the general régime, including *rest* and *hygiene*, there seemed to be very little reason to attribute special virtues to the carbonic acid baths.

Preparations

Carbonei Dioxidum (B.P., U.S.P.), carbon dioxide, CO_2. Compressed in metal cylinders. A heavy colourless gas.

For internal use, the ordinary artificial and natural waters, *soda water*, *Apollinaris*, etc., are usually employed. The curative treatment of cardiac diseases with baths is carried out on a very large scale at *Nauheim* in Oberhessen, where the waters of the Great Sprudel contain 1,340 c.c. of free CO_2 per litre. Similar results are now obtained at numerous places by " artificial Nauheim baths," which are prepared by introducing carbonic acid from cylinders containing the compressed gas, or by dissolving sodium carbonate in the water, and then adding about an equal amount of crude hydrochloric acid. As baths containing too much of the gas may aggravate the condition and produce dyspnœa and palpitations, the quantities are small to begin with (*e.g.* 100 grms. of each of the chemicals named), and gradually increased (*e.g.* to 1 kilo of the salt and the same amount of the acid). It is best to use sea-water, or water to which 3 per cent. of common salt has been added, as this increases the irritant action on the skin. A local use of carbonic acid is made, in the form of carbonic acid snow, on lupus, pigmentation-spots, etc. The treatment leaves smooth scars or a pale atrophic skin. The compressed carbonic acid in a cylinder is allowed to escape into a bag, where it condenses into snow, which is cut into suitable pieces and pressed upon the skin. The application may be repeated several times, but must not last for more than a minute each time.

12. OXALIC ACID

Oxalic acid is found in numerous plants, especially species of rhubarb, sorrel and wood-sorrel, sometimes in considerable amounts; it exists partly free, partly combined with potassium and calcium. These salts are harmless to man, however, as he consumes only small quantities of these plants; but acute poisoning has been observed in grazing animals. Oxalic acid does not seem to be formed in the human body in normal conditions; the 2 centigrms. that are excreted daily in the urine is supposed to come from the vegetable food.

Oxalic acid and its salts have no medicinal uses, but are of *toxicological interest* owing to the occurrence of suicide by means of oxalic acid, and to the fact that the acid or the acid potassium salt (which is employed technically under the name of salt of lemon or sorrel) is sometimes mistaken for tartaric acid or Epsom salts. After large doses, especially of the free acid, the specific effects are of secondary importance compared with the corrosion of the stomach, which takes place in the same violent manner as in poisoning with the strong mineral acids. Death may occur in a very short time, even after doses of 4 or 5 grms. The specific symptoms consist of "lock-jaw," tetanus and convulsions, cyanosis and general weakness, and while the symptoms of paralysis become more and more pronounced, the pulse grows very feeble, and death occurs in deep coma. In the lighter cases these symptoms may be slight, but death may, nevertheless, take place after several days from anuria and uræmia caused by the blocking of the renal tubules with oxalate of lime. In some cases there is glycosuria. The diagnosis is based upon this and the abundant secretion of the above-named salt, which, at the autopsy, is found to fill the renal tubules (not the glomeruli) in such quantities that they can even be seen macroscopically as white lines running from the base to the apex of the pyramids. Under the microscope, hour-glass-shaped and flat, round crystals arranged in stars and rosettes are seen, but few of the ordinary octahedra. In explanation of this action the theory that oxalic acid injures protoplasm by precipitating its dissolved calcium salts has been put forward, and is supported by the fact that even very advanced poisoning in the frog may be arrested by intravenous injection of calcium chloride.

Treatment. After washing out the stomach (if this is not prevented by convulsions), chalk is given, milk of lime, or better still, saccharated solution of lime. The ordinary alkalies, *e.g.* bicarbonate of soda, assist in the absorption of oxalic acid, and must not be employed. In accordance with what has been said above there is every reason for trying intravenous injection of calcium chloride when there are dangerous specific symptoms. Later in the poisoning it will probably be good to give water and diuretics to wash the oxalate of lime out of the urinary tubules.

13. BORACIC ACID AND BORAX

Boracic acid is less antiseptic than the majority of the mineral acids in corresponding concentration. Most bacteria are not destroyed in the ordinarily employed solutions of 1—4 per cent. strength, but only cease growing as long as they are in contact with the solution.

On raw surfaces boracic acid has only a slightly irritant action, being a weak acid, which even in a concentrated solution has no strong acid reaction and does not precipitate albumin. Taken internally, boracic acid solutions as a rule only produce some gastric and intestinal irritation (pain in the epigastrium, vomiting, diarrhœa). This also applies to borax, which, although no specific action on the uterus is known, has the reputation of being an abortifacient, and for this purpose is sometimes taken in large doses. Cases of serious poisoning, several ending fatally, have

been observed after the washing out of serous cavities, the bladder, the rectum, or the stomach, with large quantities of boracic acid solution, which subsequently were only imperfectly removed.

The chief symptoms of poisoning are diarrhœa, faintness and headache, vomiting, irritation of the kidneys (pain, albuminuria and hæmaturia), psychical excitation, sometimes a soporific condition lasting several days, and finally prostration and collapse. In most cases peculiar skin-affections are also seen, appearing in the form of pustular and papular eruptions, nettle-rash or psoriasis (psoriasis borica), and lasting for a long time. Animal experiments show that the cause of death is ascending central paralysis.

Formerly boracic acid was far more used as a *perservative* than medicinally. As its presence is not revealed by any taste or smell, and it is inexpensive, its use increased to such an extent that boracic acid or borax was to be found in almost every possible kind of food—meat, sausage, fish, milk, butter, tinned provisions, etc. Boracic acid is also a natural constituent of many kinds of fruit, *e.g.* apples, pears, plums and cherries, and is present in grapes and consequently in wine. This natural occurrence of boracic acid is so small, however (1—2 milligrammes per 100 grammes in apples and pears, 1·5—40 milligrammes in 1 litre of wine), that it has no significance. It is a different matter with regard to preserved foods, for in order to secure the protective action, boracic acid or borax must be used abundantly, *e.g.* ½—3 per cent. Boracic acid penetrates deeply into the meat and cannot be thoroughly washed out; even after twelve hours' washing in running water, more than half the acid may still remain. The amount that may be consumed in this way is considerable, and may easily mount up to from 1 to 3 grammes daily, or in exceptional cases even more. The question whether these doses are deleterious or not has consequently acquired great interest. The principal results of comprehensive experiments made by Forster, Rubner and Rost, on man, are as follows:—

Daily doses of 0·5—1 gramme of boracic acid diminish the absorption of food in the intestine; this is shown by the increase in the weight of the fæces and the fact that they contain more nitrogen. Experiments with persons enclosed in an apparatus for measuring gaseous metabolism, showed an augmented excretion of carbonic acid, indicating increased combustion of carbon compounds, especially fat. The flow of urine also increased somewhat. As a consequence of these disturbances of nutrition, the body-weight may be reduced. Rost found, for instance, in three healthy experiment-subjects, a loss of weight amounting to 600—1,650 grammes from the consumption of 3 grammes of boracic acid daily for 5 to 12 days. There is also significance in the fact that boracic acid is easily absorbed, but is excreted so slowly that it may accumulate in the body; after a single dose of ½—1 gramme, the acid may be demonstrated in the urine for from 4 to 6 days, and in disease of the kidneys the excretion takes several weeks. All this, in spite of numerous reports of prolonged consumption without injury, goes to show that the *prohibition* existing in many countries *of the employment of boracic acid (and borax) for the preservation of articles of food is justified.*

Borax, like boracic acid, is feebly antiseptic, but has an alkaline reaction, and, therefore, a cleansing action upon the skin

very much like soap. Internally, borax behaves as a weak alkali; it is readily absorbed, and is excreted in part in the saliva, but mainly in the urine, where to some extent it prevents acid deposits (uric acid, biurates, oxalates). Regarding its use as a preservative, the same may be said as of boracic acid.

Therapeutic Uses. **Boracic acid,** dissolved in water, or as an ointment, is a much used remedy for wounds, and boracic wool for dressings. As it possesses very little antiseptic action, boracic acid is best adapted for *fresh and more or less clean wounds*, and is less suitable for infected ulceration with profuse secretion, which requires more powerful remedies. As it causes little irritation, it is also used as an *eye-wash, mouth-wash*, for *washing out the stomach in fermentation* (dilatation), *the bladder in cystitis*, and *the vagina in leucorrhœa*, and for insufflation in *diseases of the ear and nose*. Upon gonococci, according to Welander, it has no effect.

Boracic acid was formerly regarded as an emmenagogue and as a sedative (*Sal Sedativum Hombergi*), and was tried some years ago for *epilepsy*, but now seems to have been discarded. It has been suggested as a *remedy for obesity*, but has not been sufficiently tested.

Borax is employed similarly, especially as an antiparasitic for *dermatomycoses* (*herpes tonsurans* and *favus*), and for *aphthous stomatitis*, and is the principal remedy for *thrush*. As an internal antacid and uric acid solvent it has been superseded by the alkaline carbonates.

Preparations and Doses

Acidum Boricum (B.P., U.S.P.), boric acid, boracic acid, H_3BO_3, white, glistening scales that feel greasy to the touch, soluble in 25 parts of cold water, very soluble in hot water and in glycerin. *Dose*, 3—10 decigrms., 5—15 grs. (B.P.); 0·5 grm., 8 grs. (U.S.P.). For poulticing wounds and for washing out the vagina, 2 per cent.; for washing out the stomach (no great quantity must be left) and the bladder, and for an eye-wash, 1 per cent. solution. As a cure for obesity, 3 grms. a day may be tried, but the more rational methods of restriction of food, and the administration of thyroid are to be recommended.

Glycerinum Acidi Borici (B.P.), *Glyceritum Boroglycerini* (U.S.P.), 30 per cent. *Dose*, 0·6—2 mils, 10—30 mins. (B.P.). For external use, diluted ten times.

Unguentum Acidi Borici (B.P., U.S.P.), 10 per cent.

Borax (B.P.), **Sodii Boras** (U.S.P.), $Na_2B_4O_7 + 10H_2O$, colourless crystals, transparent or with a rough surface, soluble in 17 parts of cold water, very readily soluble in hot water and in glycerin. *Dose*, 3—10 decigrms., 5—15 grs. (B.P.); 0·75 grm., 12 grs. (U.S.P.).

Glycerinum Boracis (B.P.), 20 per cent.

Mel Boracis (B.P.), 10 per cent. For painting the mouth in thrush in children.

14. CHLORATES

Chlorate of potassium, when heated, gives off oxygen and oxidises very combustible substances, *e.g.* coal, sulphur, starch or sugar, with such energy that even on gentle trituration of such mixtures in a mortar, they may explode with violence. It was introduced into therapeutics upon the assumption that also within the organism it would act as a powerful oxidiser, and in that way have an antiseptic influence. This assumption has proved to be erroneous, for, in solution and at an ordinary temperature, it scarcely oxidises organic substances at all, passes through the body unchanged (90—95 per cent. is found in the urine), and even in strong concentration (1 in 30) does not arrest the growth of bacteria.

Action. Chlorate of potassium has a slightly bitter, cool taste, resembling that of saltpetre, and when taken in large quantities causes vomiting and diarrhœa, and during its excretion through the kidneys, increased flow of urine—in other words, the ordinary salt-action. The absorption of larger quantities may produce fatal poisoning, which, in the first place, is due to the influence of the chlorate upon the **red blood-cells.** When blood is mixed in a test-tube with a solution of potassium chlorate, the red colour gives place to a dark chocolate brown, and spectroscopic examination shows, instead of the normal hæmoglobin absorption bands, the lines belonging to methæmoglobin and hæmatin. The same reaction takes place in the living organism in man, dogs and cats, while rabbits and guinea-pigs are immune. Some of the hæmoglobin is transformed into methæmoglobin and hæmatin, which are dissolved in the serum and excreted through the kidneys. The changed blood-corpuscles fall to pieces or swell up, when their colour is completely gone, into gelatinous lumps which cohere to one another in large masses that are unable to pass through the smallest blood-vessels, and therefore cause thrombi, infarcts and extravasation of blood in all kinds of places.

Poisoning often occurs (swallowing a gargle, mistaking for other salts), and runs a course differing according to the size of the dose. If a very large proportion of the blood-cells are changed in the way described, death occurs with cyanosis and "internal asphyxia," because the methæmoglobin gives off no oxygen to the tissues. The most *acute* cases may end fatally in the course of a few hours from this cause in combination with gastric symptoms and, perhaps, potassium action on the heart. *Subacute* poisoning is the result of several doses, each in itself not fatal. In such cases there is a smaller amount of methæmoglobin formed and death by asphyxia does not take place, but in the course of

a few days symptoms of thrombosis occur and emboli form in various organs. There is nose-bleeding, diarrhœa, vomiting of dark green masses, enlargement of liver and spleen, in which the abnormal products of the blood are gathered, cardiac weakness and often dyspnœa. The skin is mottled grey, or icteric ; the scanty urine is of a reddish brown or almost black colour and contains albumin and the *débris* of red blood-cells, either in amorphous fragments or in the form of brown casts. The blocking of the renal tubules and swelling of the epithelium at last completely prevents the passage of the urine, and death follows from uræmia. In adults, 10 grammes elicits symptoms of poisoning, and 15—20 grammes is generally fatal.

Childhood predisposes to poisoning, and also all factors that induce a decrease in the alkalinity of the blood, such as fever and dyspnœa.

Potassium bromate, according to Santesson, is far more poisonous to frogs and rabbits than potassium chlorate.

Therapeutic Uses. Chlorate of potassium is prescribed very frequently as a gargle for *sore throat*, and often seems to have an almost specific action. Of what nature the local influence is in this complaint is not known, as the antiseptic action is very slight. It is used as a mouth-wash for *stomatitis*, especially for the mercurial mouth affection. It is doubtful whether its effect is different from, or better than, ordinary cleansing of the teeth and mucous membrane of the mouth, for the mercurial stomatitis is also prevented and cured by ordinary cleansing of the mouth with pure water.

Internally, chlorate of potash is given for *pyelitis* and *cystitis*, but with no very apparent benefit. The internal employment in *diphtheria* is objectionable, and carries all the more risk of poisoning from the fact that nephritis (with consequent slow excretion) is a frequent complication.

Treatment of Poisoning. The stomach is first washed out and the intestine emptied by large enemata. After this attempts are made to prevent the blocking of the renal tubules by an abundant supply of liquid and diuretics. Blood-letting, with subsequent saline infusion, is also recommended. The most important prophylaxis consists in never prescribing potassium chlorate as a gargle for children, as they are apt to swallow it.

Preparations

Potassii Chloras (B.P., U.S.P.), potassium chlorate, $KClO_3$, lustrous, colourless crystals, soluble in 16 parts of water. *Dose*, 3—6 decigrms., 5—10 grs. (B.P.); 0·25 grm., 4 grs. (U.S.P.). Externally, as a gargle for sore throat, 3 per cent.; as a dressing for burns, 1 per cent. solution.

Internally, for pyelitis and cystitis, 0·5—1 grm. a few times a day, up to 5 grms. daily. Must not be prescribed as a powder together with organic substances (explosion).

Trochisci Potassii Chloratis (not official), each containing 0·15 grm.

15. NITRATES

The nitrate of potassium is a salt that has passed through many vicissitudes. Some 60 or 70 years ago it had a great reputation as an antipyretic and a sedative to morbidly increased cardiac action, and as an antiphlogistic was very widely prescribed in acute febrile diseases attended with high temperature.

Potassium nitrate is now believed to act as a readily soluble and easily absorbed neutral alkaline salt, and to have only a general salt-action ; it is somewhat more irritant than other neutral salts, and when the doses are very large the potash-action on the heart may occur. In the doses formerly employed in medicine, ½—1 gramme, it exerts no specific action. It is very easily absorbed, and in the process of excretion by the kidney, the salt prevents the re-absorption of water which normally occurs in the renal tubules and therefore acts as a diuretic. As the potassium requirements of the tissues are very small the potassium ions are excreted rapidly and this enhances the value of this salt as a diuretic. The reason why it was formerly considered to be a cooling remedy is perhaps that it has a cool taste, and on solution in water uses heat (employed in freezing-mixtures).

Cases of acute poisoning have often occurred through mistaking the nitrate for salts of similar appearance, *e.g.* Epsom salts or Glauber's salt. The symptoms after large quantities of nitre (10—30 grms.) are intense pain in the epigastrium and abdomen, profuse vomiting and diarrhœa, the vomited matter and stools sometimes containing blood, a small, soft pulse, attacks of syncope, convulsions, and finally arrest of the heart, probably as a consequence partly of the gastro-intestinal affection, and partly of potassium action on the heart. The course the poisoning takes depends very much upon whether the salt is taken in solid form or in solution ; in the first case the local effects are much more prominent.

Potassium nitrate is entirely absorbed in the intestine, but only part is found again in the urine as nitrates. The remainder disappears, *i.e.* undergoes some change in the body, the nature of which is not known. It has been supposed (Binz) that the nitrate, which is a powerful oxidiser, is reduced, perhaps to nitrous acid or to ammonia.

Therapeutic Uses. Nitrate of potash is scarcely ever given now as a febrifuge. In the form of nitrated paper it is used for asthma, the paper being lighted and the fumes inhaled. In burning, ammonium carbonate, empyreumatic compounds and pyridin are formed, the last-named being probably the component that sometimes relaxes bronchial spasm. Potassium nitrate is occasionally employed as a saline diuretic.

Preparation

Potassii Nitras (B.P., U.S.P.), potassium nitrate, nitre, saltpetre, KNO_3, transparent prisms or a white powder with a cool taste, readily soluble in water. *Dose*, 3—10 decigrms, 5—15 grs. (B.P.) ; 0·3 grm., 5 grs. (U.S.P.).

16. SULPHUROUS ACID AND SULPHITES

Sulphurous Acid, SO_2, which comes from the burning of sulphur in the air, is a gas with a suffocating, pungent odour, with which we are acquainted from the old-fashioned lucifer match. Sulphurous acid is exceedingly irritating to all mucous membranes, and gives an unpleasant feeling, even in a dilution of 1 in 100,000. When present in the air in the proportion of 1 in 30,000, it causes tingling in the nose and inclination to cough. Greater concentration produces in animals severe inflammation of the mucous membrane of the entire respiratory tract, and a speedy death. On micro-organisms SO_2 has a poisonous effect, and was employed for some time, in the form of sulphur fumigation, for the disinfection of sick-rooms (16 grms. of sulphur per cubic metre). The method is now almost abandoned, since it was found by Koch to be unreliable.

A good many years ago the **sulphites** were recommended as internal disinfectants in typhoid fever, puerperal fever, pyæmia, malaria, etc., but were soon discarded, as they proved to be useless and often irritated the gastric mucous membrane; they induced the evolution of SO_2 in the stomach.

These salts have now once more come to the fore, as sodium sulphite is the principal constituent of numerous preparations which have been widely employed under various names (such as preserving-salt, meat-preserver, sozolith), and often also contain boracic acid, for the preservation of food and beverages, or to improve their appearance. There has been a difference of opinion as to the advisability of this. The result of the careful investigations of the last few years (Rost) is that sodium sulphite, in the quantities used for the above purposes, has no specific toxic action, as it is quickly oxidised in the blood to sulphate. From this it does not follow, however, that it is quite harmless, for if food containing sodium sulphite is eaten daily, the sulphurous acid liberated by the hydrochloric acid of the stomach may cause irritation of the mucous membrane.

Modern sanitary legislation in most countries allows a certain low percentage of sulphurous acid in food and beverages, with the exception of meat and meat foods. The reason of this very legitimate prohibition is that in meat that is beginning to putrefy, the disagreeable odour can be removed by treatment with sodium sulphite and the fresh, red appearance restored, thus concealing its condition.

The former therapeutic employment of the sulphites for fermentation in the stomach is now seldom made.

Preparations and Doses

Sodii Sulphis (B.P.C.), sodium sulphite, $Na_2SO_3 + 7H_2O$, colourless, transparent crystals, efflorescent in dry air and readily soluble in water. *Dose,* 3—12 decigrms., 5—20 grs.

Sodii Sulphis Exsiccatus, Na_2SO_3, a white, easily soluble powder. *Dose,* 1 grm., 15 grs.

Sodii Thiosulphas (B.P., U.S.P.), sodium hyposulphite, $Na_2S_2O_3 + 5H_2O$, colourless, easily soluble crystals. *Dose,* by subcutaneous, intramuscular or intravenous injection, 0·3—1 grm., 5—15 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). Used occasionally as an aperient. Externally in a 5—10 per cent. solution for itching of the skin, and as an ointment or paste of the same concentration for psoriasis, lupus and parasitic skin-affections. It is a valuable antidote in arsenical poisoning, doses of about 0·5 grm.

being injected intravenously in 10 per cent. solution. Also, if a dose of neoarsphenamine has "leaked" into the tissues around a vein, local infiltration with a 10 per cent. solution of sodium thiosulphate should be carried out immediately to prevent necrosis.

17. HYPOPHOSPHITES

The hypophosphites were introduced into medicine by Churchill in 1858, in the belief that tuberculosis was due to a deficiency of phosphorus in the body. Although no special action has ever been shown, either in man, healthy or otherwise, or in animals, vague ideas of the benefit of the hypophosphites continue to be held, and a certain amount of trust is placed in them in tuberculosis and in anæmic and cachectic conditions. Almost the whole of the hypophosphites can be recovered unchanged from the urine, only a very small proportion being oxidised, probably to phosphates.

18. HALOGENS

The halogens are elements with very strong affinities. They combine with almost all other elements, and destroy organic compounds. In the presence of water they combine with the hydrogen while the oxygen is liberated, and in its nascent state is a powerful oxidiser. On account of these properties, the free halogens are protoplasmic poisons and strong antiseptics, and they are on the whole destructive of all living tissue.

Chlorine

The very smallest amount of free chlorine in the air causes irritation of the eyes and the mucous membrane of the nose. If the air contain larger quantities, there is a feeling of suffocation and dyspnœa, and soon after bronchitis or pneumonia, with bloody expectoration, occurs. In an atmosphere containing 1 per cent. of chlorine, mammals become drowsy and succumb with symptoms of inflammation of the respiratory passages. Binz has shown, by experiments with frogs, that inhalation of chlorine, as of the vapour of bromine and of iodine, has a paralysing action on the cerebrum. In the chapter on the narcotics of the fatty series there is an account of the strengthening of the narcotic effect by the entrance of halogens into these compounds.

Chlorinated lime, which, under the influence of the carbonic acid of the air, or by the addition of mineral acids, gives off free chlorine, is used as a disinfectant. In practice its employment is very limited, however, owing to the fact that it destroys textile fabrics and wall-papers, bleaches colours, etc. It can only be used, therefore, where there is nothing of this kind to be considered, as in the disinfection of refuse, water-closets, etc.; and

it must always be employed in abundance, as chlorine is fixed by all the organic substances present.

The internal employment of *chlorine water* as an intestinal disinfectant in cholera and typhoid fever has now been abandoned, as the chlorine dissolved in water is fixed long before it reaches the distant sections of the intestinal canal, and, moreover, is quite as injurious to the mucous membranes as to the bacteria. The same drawback is encountered in the use of a solution of sodium hypochlorite as an antiseptic for wounds. Although many of the bacteria are immediately killed by the union of the free chlorine with the amine group of the bacterial protein, the action is fleeting and incomplete because the same combination occurs between the chlorine and the products of inflammation—serum, pus and cellular *débris*. To be effective, therefore, it is essential that the wound should be flooded with fresh solution at frequent intervals. This is best accomplished by the Carrel-Dakin technique whereby the antiseptic reaches the wound by means of glass tubes inserted into the dressings, thus making it unnecessary to disturb the bandages. Other uses of sodium hypochlorite solution are mentioned under Preparations and Doses. Chloramine differs from chlorinated lime and Dakin's solution in that it parts with its chlorine more slowly and produces a relatively weak but sustained action.

In *chlorine poisoning* the symptoms of irritation of the respiratory passages are relieved by the inhalation of aqueous vapour and dilute ammonia. Atropine injections are recommended for the profuse secretion in the bronchial tubes. In cases of poisoning by the mouth, dilute alkalies or magnesia are given.

Bromine

Chemically and toxicologically, bromine behaves like chlorine, and inhalation of the vapour produces the same violent irritation of the lungs. Cases of poisoning are best treated by inhalation of dilute carbolic acid, which forms with bromine insoluble tribromphenol. Bromine has been tried, dissolved in water, as an external disinfectant in diphtheria and for septic sores, but is now hardly ever used. Its narcotic action is apparent in the alkali compounds which are discussed on p. 428.

Iodine

Iodine has the same strong affinity for the tissues as the two other halogens mentioned above, but has a far greater therapeutic value, as, unlike chlorine and bromine, it is a stable solid, the effect of which is more lasting and can easily be restricted.

Action. When the *skin* is painted with a fairly strong solution of iodine, *e.g.* the official liquor, it is dyed a dark brown ; this is followed by a burning, pricking sensation, and an erysipelatous

rash; after repeated applications the skin peels off in large pieces. A few hours after painting, serous exudation and a wholesale emigration of leucocytes occur, not only in the skin, but also in the subcutaneous and intramuscular tissues and in the periosteum of the adjacent bone, and this to a considerable depth. After a few days a further change is observed, the leucocytes and the surrounding tissues undergo fatty degeneration, and are absorbed. In this way the absorption of morbid products that lie within the reach of these changes is brought about.

The effect is more violent on *mucous membranes*. Iodine has an exceedingly unpleasant caustic taste and affects the teeth; internally in small doses it produces pain, in larger doses gastro-enteritis. Injected into *serous cavities* or *cysts*, solutions of iodine cause adhesive inflammation, which, after the absorption of the liquid, ends in adhesion of the walls and the obliteration of the cavity.

Iodine is *absorbed* very easily both through the skin and from all mucous membranes and wounded surfaces; it passes into the blood and is excreted, principally as sodium iodide, in the urine, where it is found 1 hour after painting with iodine; traces are excreted by the stomach, the bronchial tubes (odour of iodine in the breath), and by all secretions. A part of the absorbed iodine is stored up by the thyroid gland as thyroxine.

In acute *poisoning* from taking tincture of iodine, the most marked symptoms are due to corrosion of the mucous membranes. Recovery has been seen after 10 and 20 grammes, and death in 36 hours after 30 grammes. The greater number of fatal cases of poisoning are the result of the injection of too large quantities into serous cavities or cysts, especially ovarian cysts. In a well-known case described by Rose, in which 150 grammes of tincture of iodine were used, intense vaso-constriction occurred during the first few days, with a small, hard radial pulse, very scanty urine, drowsiness and delirium; subsequently there was hyperæmia of the skin, kidneys, and uterus, obstinate vomiting (the vomited matter containing iodine), fever, papular exanthema and on the 10th day sudden collapse.

Iodine is a very powerful antiseptic for *micro-organisms*, but statements as to the concentration that kills them or hinders their development vary.

Therapeutic Uses. In surgery iodine is now much used for *disinfecting the skin and small wounds*. Painting once is sufficient to disinfect not only the surface, but also the deeper layers of the epithelium. Previous washing with soap is unnecessary or even objectionable, since inert alkaline iodides are formed if the soap is not thoroughly removed.

Painting the skin with tincture of iodine is a favourite means of promoting the dispersion and absorption of exudates, inflammation, and inflammatory products of all kinds, such as *swollen glands, inflammation of the subcutaneous tissue, lymphangitis, phlebitis, periostitis, tendo-vaginitis, synovitis, inflammation and accumulation in serous membranes*, etc., etc. Painting with iodine is especially effectual in such complaints when the inflammation or exudate is superficial ; but it must not be resorted to in more serious diseases which ought without loss of time to be treated surgically, nor in cases which are more suited for massage, as this treatment is prevented for some time when the skin has been destroyed by iodine. In various *affections of the mucous membranes*, such as *ozœna, chronic pharyngitis* and *laryngitis*, in *inflammation of the gums* in mercurial poisoning, in *alveolar periostitis and chronic catarrh of the vagina and uterus*, the local treatment with tincture of iodine or Lugol's solution is much employed. A good effect may also be seen in *parasitic skin-diseases*, such as pityriasis versicolor.

Injections of tincture of iodine, or solution of iodine in potassium iodide, are employed in *hydrocele* or *cysts*, in order to cause absorption and subsequent adhesion of the walls of the cavity. The injections are very painful, and the first result is an increased accumulation of fluid. Iodine has the advantage over solutions of irritant salts of metals (also employed for the same purpose) of having a strongly antiseptic action, and of soon disappearing without leaving, like the salts of metals, a crust that is long in being absorbed. For *ovarian cysts* injections of iodine are objectionable, as they have frequently caused peritonitis, and are not very efficacious, because the cysts are generally multilocular.

Iodine is prescribed, although rarely, internally for *obstinate vomiting*, *e.g.* during pregnancy.

Treatment of Iodine Poisoning. For poisoning with tincture of iodine, white of egg or large quantities of dilute alkalies are given to fix the iodine. Starch has also been recommended, but is less reliable ; it combines with the iodine, but so loosely that it is very easily given off once more to albumins (gastric mucous membrane). If the poisoning is a consequence of injections into cysts, hydrocele, etc., there is little to be done ; large doses of bicarbonate of soda may be tried, and for great pain morphine should be given.

Fluorine

The fourth of the halogens, *fluorine*, a greenish yellow gas that is extremely irritating to the respiratory organs, is only with much difficulty obtained in a free state, as it has the greatest chemical affinity of all hitherto known elements. It is physiologically important, as it is found in considerable quantities in bone-tissue and teeth, but has no medicinal importance.

The action of its compounds is quite different from that of the other halogens. *Sodium fluoride*, unlike the chloride, bromide and iodide of sodium, is poisonous. In mammals it causes increased salivation, epileptiform convulsions, slight narcosis, and paralysis of the respiratory and vasomotor centres; it is strongly antiseptic in a ½ per cent. solution. It is excreted in the urine, and preserves it for a long time from putrefaction.

Hydrofluoric acid, HF, a colourless gas fuming in the air, is exceedingly corrosive, and in glass-factories, where it is employed for etching on glass, produces deep, indolent ulcers among the workers.

Preparations and Doses

Calx Chlorinata (B.P.), chlorinated lime, bleaching powder, a white or greyish white powder with the odour of chlorine, partially soluble in water. It is obtained by exposing slaked lime to the action of chlorine, and consists mainly of a mixture or weak compound of calcium hypochlorite and calcium chloride. Externally, as a dusting powder or in a 1—5 per cent. solution on gangrenous and foul sores, and for injection in fistulas and wound cavities. For gonorrhœa, a ¼—½ per cent. solution. For disinfecting purposes, crude hydrochloric acid is added (0·25 kilo of chlorinated lime and 0·35 kilo of hydrochloric acid per cubic metre).

Liquor Sodæ Chlorinatæ Chirurgicalis (B.P.), **Liquor Sodii Hypochloritis Dilutus** (U.S.P.), prepared from *Liquor Sodii Hypochloritis* (U.S.P.). Dakin's solution. Chiefly sodium hypochlorite and sodium chloride, and contains 0·5 per cent. of available chlorine. Externally, as a mouth-wash and gargle, and for leucorrhœa, 5 per cent.; as a dressing for foul sores, a 10 per cent. mixture with water. The well-known *Eau de Javelle* contains the corresponding potassium compound. There are several prescriptions, including that for *Eusol*.

Chloramina (B.P.), **Chloramina-T** (U.S.P.), sodium p-toluenesulphonchloroamide. White crystals or a crystalline powder, odour of chlorine, taste unpleasant and bitter. Decomposes in air, losing chlorine and assuming a yellow colour. Soluble in 7 parts of cold water and in 2 parts of boiling water. Action like that of the solution of sodium hypochlorite. For the Carrel-Dakin technique 2 per cent. strength is used. As a mouth-wash and for urethral irrigation 0·5 per cent.

Dichloramina-T (U.S.P.), appearances and uses similar to those of chloramine, but solutions, *e.g.* 5 per cent., are more irritant and also their effects are more prolonged. It is sometimes employed in solution in paraffin; this must be freshly prepared.

In recent years chlorinated xylenols have been largely used as general surgical antiseptics, *e.g. Dettol*. They are very effective and can be applied extensively without fear of injury to the tissues. Unlike most antiseptics in common use, they are non-poisonous on absorption, and even when taken by mouth there is no constitutional upset. Dettol is an amber-coloured solution, soapy to the touch, and should be suitably diluted with water before use. When applied to the skin undiluted, it affects the superficial tissues in the same way as strongly alkaline soaps.

Iodum (B.P., U.S.P.), iodine, dark grey laminæ with a metallic lustre, giving a violet vapour when heated. It is almost insoluble in water and volatilises in an ordinary temperature, with the odour of chlorine. *Dose*, 0·01 grm., ⅙ gr. (U.S.P.). For painting the throat, etc., iodine, 0·20; potassium iodide, 2; glycerin, 20; or stronger solutions.

Liquor Iodi Fortis (B.P.), 10 per cent. of iodine in potassium iodide, water and alcohol. For external use.

Liquor Iodi Mitis (B.P.), 2½ per cent. of iodine in potassium iodide, water and alcohol. *Dose*, 0·3—2 mils, 5—30 mins. Given in milk. The same doses for injection in hydrocele, etc., diluted by not previously entirely emptying the tumour.

Liquor Iodi Simplex (B.P.), 9 per cent. in 95 per cent. alcohol. *Dose*, 0·2—1 mil, 3—15 mins.

Tinctura Iodi (U.S.P.), 7 per cent. *Dose*, 0·1 mil, 1½ mins.

Tinctura Iodi Mitis (U.S.P.), contains about 2 per cent. of iodine in sodium iodide, water and alcohol. Used externally as a disinfectant.

Liquor Iodi Aquosus (B.P.), *Liquor Iodi Compositus* (U.S.P.), Lugol's solution, 5 per cent., dissolved in a 10 per cent. potassium iodide solution. *Dose*, 0·3—1 mil, 5—15 mins. (B.P.); 0·2 mil, 3 mins. (U.S.P.). For injection into cysts, etc.

Unguentum Iodi (U.S.P.), 4 per cent.

Oleum Iodisatum (B.P.), *Oleum Iodatum* (U.S.P.), an iodine addition product of poppy-seed oil. Contains about 40 per cent. of combined iodine. Colourless or pale yellow oily liquid. It is sterilised before use. Iodised oil is introduced into various body passages and cavities, *e.g.* the bronchi, bile-ducts, Fallopian tubes, fistulæ and sinuses. This preparation is also used in the localisation of spinal tumours. After withdrawing an equal quantity of cerebro-spinal fluid about 10 mils of this iodine preparation are injected into the cisterna magna. The iodised oil, being relatively heavy, falls down within the spinal theca and its gradual descent can be watched by radiographic examination at intervals of a few hours. In the presence of a spinal tumour, however, there may be a hold-up of the oil indicating the level of the neoplasm. Alternatively, a relatively light iodine-oil may be injected into the cerebro-spinal fluid by lumbar puncture and observations made as the oil ascends towards the base of the brain.

19. IODOFORM

Many of the modern antiseptics consist of organic combinations of iodine, of which *iodoform* may be regarded as the type. Iodoform has been known since 1832, but its antiseptic properties were not discovered until 1879—80.

Action. The great use made of iodoform as soon as it was introduced into the treatment of wounds is due, not to any specially strong bactericidal power, but to a combination of other effects. Although iodoform has now lost much of its importance, these effects will be described here, as they are found in some measure in the various allied remedies that have taken its place. Pure, dry iodoform remains unchanged for an unlimited time, and is not antiseptic. In solutions, iodoform is very unstable: an ethereal solution soon becomes brown, and on wound-surfaces, where iodoform is gradually dissolved by the fat of the secretion, a slow but constant liberation of iodine takes place. The iodine is liberated in an amount which does not perceptibly irritate the wound, but is sufficient to prevent the growth of micro-organisms.

Iodoform and various similar compounds also diminish secretion ; they keep a clean wound-surface dry, and in an infected one tend to lessen or arrest the secretion, and thus make it possible for the same dressing to remain for a long time without changing. Iodoform has also a slight analgesic effect.

The *specific effects* have not been fully explained. The liberated iodine is absorbed as an albuminate or alkaline salt, and is excreted in the urine as sodium iodide and sodium iodate. It may be doubted whether unchanged iodoform is absorbed, as the characteristic odour has never been found in the blood or secretions ; but some is absorbed in a form other than as salts or albuminates, for in acute iodoform poisoning there are two series of symptoms, only one of which belongs to the real iodine action.

Acute Iodoform Poisoning. For some days the patient suffers from indefinite, slight symptoms, such as anxiety, restlessness, sleeplessness, headache and general indisposition, though in the more serious cases a sudden acute confusion of mind occurs. His mood is generally melancholy ; he has hallucinations, refuses nourishment, and is in fear of persecution. This is followed by violent delirium, sometimes convulsions and mania. The pulse is often frequent, and the temperature sometimes raised. In a few days or weeks death may occur, with heart-weakness and œdema of the lungs. In rarer cases great drowsiness is seen, which, without symptoms of cerebral excitement, passes into heavy slumber and coma, and is thus more like plain narcosis. Permanent insanity is also sometimes a result. In the slighter cases there are only the above-mentioned prodromal symptoms, vomiting, and complaints that everything tastes and smells of iodoform. In addition to all these symptoms, which are considered to be the result of absorption of unchanged iodoform or some other organic compound of iodine, there are the well-known iodine symptoms, nasal catarrh and acne.

High fever, disturbances of circulation, and disease of the kidneys, which diminish the excretion, predispose to poisoning. The nature of the wound-surface also has some influence, for the greater the amount of fat in it, the more easily does the solution and absorption take place ; for example, cases of poisoning in operations on the mammæ are remarkably numerous. Finely powdered iodoform is taken up far more quickly than the crystalline preparation.

Therapeutic Uses. The internal employment of iodoform as an anti-syphilitic remedy has had no success.

It was at first much used externally as a *dry antiseptic in operations*, on *wounds* and *ulcers* of various kinds, in *wound-cavities*, in diseases of the *female genital organs* (tampons with

iodoform gauze), etc., but has now been abandoned by most on account of its extremely disagreeable and persistent odour. It is still largely employed for tuberculous processes, *e.g. tuberculous laryngitis, empyœma, abscess cavities, articular affections*, injections being given in the last-mentioned ; inhalations have been tried for *tuberculosis of the lungs.* It has not yet been determined whether iodoform affects the bacilli, but injections into tuberculous joints or foci in the bone-tissue frequently cause such signal benefit that a specific action is probable.

Treatment of Iodoform Poisoning. The slighter symptoms disappear when the iodoform is removed. In the more serious forms the prognosis is doubtful, as the first toxic signs appear so late that a fatal result is not always averted by the removal of the poison from the wound. Sodium bicarbonate ($\frac{1}{2}$—1 gramme every hour) is recommended for restricting the formation of free iodine, and saline infusions are also employed. As a maximal external dose 8 grammes has been suggested.

Preparations and Doses

Iodoformum (B.P., U.S.P.), iodoform, triiodomethane, CHI_3, small, glistening, lemon-coloured crystals, or yellow powder, with a disagreeable smell, almost insoluble in water, sparingly soluble in alcohol and fixed oils, and readily so in ether. *Dose*, 3—20 centigrms., $\frac{1}{2}$—3 grs. (B.P.) ; 0·25 grm., 4 grs. (U.S.P.). Used externally, as a dusting powder for insufflation in the nose, ear, larynx, etc. ; for hermetic closing of small wounds as iodoform collodion (1 in 15) ; for injection into abscesses and joints, a 10 per cent. emulsion in glycerine or oil ; iodoform gauze or wool for tampons and drainage of fistulas and wound-cavities. For inhalation, 1 tablespoonful of a 2 per cent. alcohol solution in 2 tablespoonfuls of water ; this forms a fine emulsion, which is inhaled by means of one of the ordinary spray apparatuses.

Suppositoria Iodoformi (B.P.), each contains 20 centigrms., 3 grs., unless otherwise prescribed.

Oculentum Iodoformi (B.P.), contains 4 per cent. of iodoform.

Iodoform is also an ingredient in *Pasta Bismuthi et Iodoformi* (B.P.C.). This preparation, also known as "BIPP" (Bismuth Iodoform Paraffin Paste), is a potent antiseptic and is used in surgical practice for wounds and sinuses. Application to a large surface may result in toxic absorption.

The disagreeable odour that iodoform possesses has caused a great many attempts to be made to find remedies to replace it. Most of these, however, have proved far less valuable and have been discarded. Probably the best is bismuth tribromphenolate, which will be mentioned in the chapter on bismuth. Among others may be mentioned aristol (see p. 247) and iodol.

20. IODIDES

The employment of *alkaline iodides* is based upon a purely empirical foundation. Long before iodine was known to exist,

the ash of certain species of sea-weed and sea-sponge which contained iodine was prescribed for scrofula ; even now, notwithstanding numerous investigations and the fact that iodide of potassium is one of the most important of drugs, our knowledge of its influence upon the organism is defective on many points.

Action. This is partly the ordinary salt action and partly to be ascribed to the iodine ions of the dissociated salt.

The small quantities of iodine salts present in mineral waters have no influence on the **skin.** *Pure* potassium iodide, even in large doses, does not generally exert any deleterious action on the **gastric mucous membrane** when the precaution is taken of not administering on an empty stomach such concentrated solutions as will subject the mucous membrane to the irritation that any strong hypertonic saline solution will cause. If it is contaminated with potassium iodate, on the other hand, iodic acid and free iodine are soon formed.

In the **blood** and the **tissues** potassium iodide is changed with sodium chloride into sodium iodide and potassium chloride, and in consequence of the formation of the two new salts, the osmotic or *salt action* becomes very marked, which partly explains its influence in promoting the absorption of morbid deposits and exudates. Sodium iodide circulates unchanged in the blood, and has the same specific action as potassium iodide.

Since potassium iodide became a frequently employed remedy for arterio-sclerosis, its effect on the **circulation** has acquired great interest, but is still imperfectly understood. Several French writers, who class potassium iodide, like the nitrites, among vaso-dilators, ascribe a vaso-dilator action to the iodides, but this is denied by more recent investigators. Even in experiment-animals which gradually received doses so large that the percentage of iodine in the blood was at last 0·7, no pronounced changes in the blood-pressure and pulse were to be found. According to Müller and Inada, the viscosity of the blood is diminished after the employment of from 1 to 1½ grammes of iodine daily for 10—14 days, and they ascribe a favourable influence on the circulation to the reduced friction in the capillaries. Others, again, find the viscosity unaltered. The principal importance of the iodine is probably that it is employed for the synthesis of the thyroid hormone, which, as will be shown later, has a great influence on the circulation.

Various **secretions** are increased by potassium iodide. The *bronchial secretion* becomes more abundant and more fluid. The *amount of urine* is augmented as a consequence of the salt action. *Menstruation* is increased or may be produced, while the *secretion*

of milk decreases after large doses. The same unfortunate influence upon lactation has been seen in animals (cows and goats) to which potassium iodide has been given with the intention of using the milk as a medicine. The thyroid gland is reduced only in certain cases of pathological enlargement. Early records exist of atrophy of the mammæ and testes after prolonged use of potassium iodide, and it has been stated that with children it carries the risk of causing permanent sterility. It is, therefore, wise, in the case of young people, to be somewhat cautious as regards its prolonged use. In adults, notwithstanding the extensive employment of the drug, sterility never seems to have been observed.

Potassium iodide is absorbed very easily from wound-surfaces and all mucous membranes, and in a very short time makes its appearance in the urine as sodium iodide. The quickest instance of **absorption and excretion** is recorded by Roux, who, in the case of a man suffering from ectopion vesicæ, found iodine in the urine oozing from the ureters $1\frac{3}{4}$ minutes after the administration of 1 gramme of potassium iodide. Others state that iodine can be demonstrated in the urine in from 7 to 18 minutes after administration. The excretion takes a long time as compared with the interval between the administration of the drug and its first appearance. After 3 doses of $\frac{1}{2}$ gramme taken in the course of 10 hours, the urine, according to Anten, gave an iodine reaction for 3 days. After repeated large doses it only disappeared at the end of 11 days, and after continued use for some time, the urine was still giving an iodine reaction when 8 weeks had passed. After a few large doses, 65 to 85 per cent. was excreted through the kidneys in the course of some days. A little is retained by the thyroid gland, and small quantities leave the body through the respiratory and genital mucous membranes and in secretions of all kinds—saliva, tears, the intestinal secretion, the bile and the milk, through which it passes into the child. Iodine has been found in the child's urine 20 minutes after the mother had received potassium iodide. The treatment of syphilitic children by giving potassium iodide to the mother or wet-nurse has been suggested, but this would be a very uncertain way of dosing. In diseases of the kidneys the excretion through the kidneys is imperfect, and in serious cases of nephritis the urine may even be entirely free from iodine. The greatest caution in the employment of potassium iodide is therefore necessary. In watery solutions (baths), potassium iodide is not taken up at all through the *unbroken skin ;* but after the employment of potassium iodide ointment, the urine gives an iodine reaction, because the peroxide of hydrogen, which is formed from the water and the fat of the ointment, decomposes

the salt and thus causes the appearance of free iodine, which is readily absorbed.

Distribution in the Body. When a foreign substance is introduced into the body it does not, in the majority of cases, distribute itself equally among all the tissues, but keeps especially to those organs or cells for which it has the greatest affinity. In general, the circumstances cannot be accurately followed, for want of sufficiently delicate methods of demonstration. With regard to iodine, however, minute traces can be demonstrated and the quantity determined. It has thus been found that potassium iodide distributes itself in a definite manner. The highest percentage of iodine is found in the thyroid gland, less in the blood and skin, while in the bone-tissue, the adipose tissue, and the brain and spinal cord there is none. It is an interesting fact that this distribution may be altered by pathological conditions, to the benefit of the diseased organs. O. Loeb, Jacobi and van den Velden have found, for instance, that with suppuration, syphilis, cancer and tuberculosis, there is 2 or 3 times as much iodine in the diseased tissue as in the corresponding normal tissue. This storing up is probably of therapeutic value, even if it does not indicate any special affinity between these diseases and iodine, but only that the drug is more easily fixed by diseased than by healthy tissue. The affinity of iodine for the thyroid gland is of great interest. Investigations by Marine, Feiss and Rogoff show that the excised, living gland, when perfused with blood containing potassium iodide, takes up a definite amount of iodine irrespective of the concentration of potassium iodide in the blood and of the duration of the perfusion, as the fixing (storing) takes place in the course of a few minutes. The same thing is found in living animals on the intravenous injection of potassium iodide. The iodine taken up into the gland, however, is, for a time, physiologically inert (has not the effect on tadpoles mentioned in the next chapter), as the synthesis of the hormone requires a certain time. In analogous experiments with other excised organs (liver, spleen), no storing up of iodine was found.

Idiosyncrasy and Poisoning. After prolonged use of potassium iodide troublesome *symptoms of irritation* may appear *in various mucous membranes and in the skin ;* these are called *iodism.* The first signs of intolerance are swelling, injection and profuse secretion from the nasal (*iodine catarrh*) and adjacent mucous membranes, œdema of the eyelids and conjunctiva, flow of tears, secretion in the frontal sinuses with frontal headache, swelling of the laryngeal mucous membrane, in certain cases serious œdema of the glottis, and, finally, mucous bronchial secretion (*iodine cough*). More rarely there is irritation of the mucous membranes

of the mouth and throat, salivation and swelling of the tonsils. Sometimes the only symptom of iodine idiosyncrasy is parotitis. The patient may also complain of unpleasant sensations in the chest and of loss of appetite. After the above-mentioned affections of the mucous membrane, eruptions generally appear on the skin, most frequently in the form of papules and pustules (*iodine acne*), more rarely exceedingly polymorphous skin-complaints, such as purpura, small areas of œdema, phlegmonous, vesicular and bullous eruptions (*iodine pemphigus*), attended with pyrexia.

There is great irregularity in the appearance of all the above symptoms, and tolerance and intolerance alternate in the same person, irrespective of the size of the dose. By giving very small doses for some time a resistance develops, so that amounts which originally produced nasal catarrh or acne can be taken with impunity.

After long, steady employment of potassium iodide, emaciation has been observed (*iodine cachexia*), and a peculiar condition which expresses itself in restlessness, anxiety, irritability, sleeplessness, palpitation, and a very quick, irregular pulse. In the more serious cases hyperæsthesia and paræsthesia occur, with uncertainty of movement and gait, paralysis and dulness.

Some of these symptoms, it will be seen, are similar to those of Basedow's disease, and are perhaps due to an over-production of iodothyrine. The formation of free iodine which is supposed to take place on the nasal and oral mucous membranes is considered to be the cause of the irritation of the skin and mucous membranes. As a rule the toxic symptoms disappear very quickly when the employment of potassium iodide ceases, but may assume a serious character when the excretion is prevented by renal disease.

Sodium iodide acts very similarly to potassium iodide. **Ammonium iodide,** on account of its large percentage of iodine, is considered to be more efficacious (KI contains 76·5 per cent. of iodine, NaI, 84·7, and NH_4I, about 88), but as it gives off free iodine much more easily, it produces nasal catarrh, acne, etc., more quickly than do the sodium and potassium compounds.

Therapeutic Uses. Potassium iodide was introduced into the therapeutics of *syphilis* in 1836 by the Irish physician, Wallace, and has acquired great importance in the treatment of this disease. Its action is especially marked on gummatous ulcers, which often heal in an astonishingly short time. It has also frequently a good effect in the later stages of secondary syphilis, but has no influence on primary sores. In the earlier part of the secondary period, potassium iodide is, as a rule, superfluous, but some of the early symptoms, *e.g.* the syphilitic pyrexia and violent night headaches, may yield to a few large doses. In many of the later cases the

simultaneous employment of potassium iodide and mercury may be beneficial, but it is wrong to make potassium iodide systematically follow the mercury cure, as the former promotes the excretion of the metal, whereas the disease requires its presence in the body as long as possible. It is important in syphilis that potassium iodide should be given in sufficiently large doses—at least 1 or 2 grammes a day—and that if these do not act, trial be made of larger quantities, *e.g.* 10—20 grammes daily. If the large doses are used, the kidneys must be sound, the patient kept under constant observation, and the excretion maintained by the aid of a mild diuretic, *e.g.* an abundance of milk. For fear of idiosyncrasy a few trial doses are first given ; but as a rule the larger doses are tolerated well and elicit no digestive troubles when given in sufficiently dilute solution. Notwithstanding all the excellent properties of potassium iodide, it must not be forgotten that it is only a symptomatic remedy. It has no specific action in the sense of destroying the spirochætes, has no distinct influence upon the Wassermann reaction, and the early occurrence of relapse is not infrequent. Even the most brilliant immediate results of a potassium iodide cure do not therefore remove the necessity of a treatment with the true specific remedies, mercury and arsenic.

The employment of potassium iodide as a remedy for *tuberculosis of the lungs* has now been generally abandoned. In latent catarrh of the apex, the administration of iodides causes, after a few days, moist râles to appear, or the sputum may contain bacilli. The interpretation of these occurrences is that iodine induces a softening or autolysis of the diseased tissue. It will be easily understood that this involves a risk of spreading the infection. Nature, as we know, heals in the opposite way, namely, by the encapsulation of the bacilli. The wisdom of the employment of potassium iodide in *glandular tuberculosis* (scrofulous) is less doubtful. If open suppuration results, some, at any rate, of the offending matter is removed.

For non-tuberculous *bronchitis*, with scanty, viscid secretion, potassium iodide is one of the best expectorants, but is contra-indicated by abundant secretion. It often proves to be a valuable remedy in *asthma*, as the attacks cease as long as the drug is used ; but the treatment must be continued without interruption, as a cessation of only a few days or a week may be sufficient to cause the disease to reappear with unabated violence. The action is thus only symptomatic.

Potassium iodide is prescribed as a *specific remedy* in conditions in which there are assumed to be remains of inflammation, *e.g.* in *pelvic exudation in women* and in *exudation from serous membranes*, especially the pleura, and also in all kinds of peripheral and

central *nervous diseases*, particularly where there has been syphilis. *Neuralgia* may be benefited also in cases in which there seems to be no question of syphilis. In chronic poisoning, especially *lead* and *mercury* poisoning, it aids in the excretion of the metals. In *psoriasis* the effect is often good when large doses are employed. *Actinomycosis* is also benefited by iodine remedies, which cannot, however, take the place of surgical treatment.

Hyperplastic *goitre* may be interpreted as a compensatory hypertrophy elicited by diminished internal secretion. The disease indicates potassium iodide, which supplements the lack of iodine in the gland by increasing its amount of thyroxine. When this takes place, the proliferation of glandular tissue that contains little iodine and colloids becomes unnecessary and decreases. With regard to their thyrotropic properties, it has been shown by Hunt and Seidell's interesting investigations that there is a great difference in the behaviour of the various iodine compounds, and potassium iodide is far surpassed by the iodic substance in the sea-weed *Fucus vesiculosus*.

Potassium iodide has been extensively employed of late years in cardiac and vascular diseases such as fibrous and fatty *degeneration of the heart and coronary sclerosis with attacks of angina pectoris*, and for *aneurysms* and *arterio-sclerosis* where hæmorrhage is feared. In these diseases it is employed for years in small doses.

Where there is idiosyncrasy against potassium iodide, attempts are first made to induce tolerance by employing small doses for some time, or by prescribing potassium iodide together with bicarbonate of soda in order to make the mucous membrane secretions more alkaline, and thereby prevent the formation of free iodine. Nasal catarrh and other hypersecretions are often combated successfully by the addition of $\frac{1}{2}$ milligramme of atropine sulphate to each dose (1—$1\frac{1}{2}$ milligrammes a day).

There are many recent remedies (calcium iodobehenate, lipo-iodin, etc.) that are combinations of *iodine with fatty acids*. They differ from potassium iodide in being more slowly absorbed and only gradually decomposed in the organism, so that the iodine remains in the body for a longer time than after corresponding doses of an inorganic iodide. They are, moreover, insoluble in water, but soluble in lipoids ; and they are distributed differently in the body, the largest percentage of iodine being found in the fatty and nerve tissues. They are thus "lipotropic" and "neurotropic." Whether this has any therapeutic advantage is a question that can only be decided by wide clinical experience ; and, in the meantime, it may be advisable to try the preparations of the new type in cases in which a mild and prolonged iodine action is desired. When a quick, strong effect is required, potas-

sium iodide should be used, regardless of the fact that it far more frequently causes nasal catarrh, acne, etc., than do the fatty acid compounds, which contain considerably less iodine. The recommendation so often given of new preparations, that they have "no unpleasant after-effects," not infrequently means that they have little efficacy of any kind.

Compounds containing iodine combined with albumin, peptone, etc., behave as the inorganic iodates, and probably have no special advantages.

Local treatment with calomel, e.g. dusting into the eyes, or insufflation in the larynx, is *strictly contra-indicated* during the internal employment of iodine remedies, as it may cause inflammation and ulceration, probably in consequence of the formation of corrosive iodide of mercury.

Preparations and Doses

Potassii Iodidum (B.P., U.S.P.), potassium iodide, KI, colourless, bitterly saline cubical cystals, soluble in 0·75 part of water. *Dose*, 3—20 decigrms., 5—30 grs. (B.P.); 0·3 grm., 5 grs., antiluetic, 2 grms., 30 grs. (U.S.P.); given in an aqueous solution after food, often with the addition of a little bicarbonate of soda. In grave syphilis large doses are sometimes required, *e.g.* 10—20 grms. a day; for psoriasis and actinomycosis, 10—40 grms. a day; for arterio-sclerosis, 0·10—0·25 grm. a day for years.

Sodii Iodidum (B.P., U.S.P.), sodium iodide, NaI, colourless, cubical crystals or a white powder, soluble in 0·6 part of water. *Dose*, as of the potassium iodide; but this drug is less suitable, as it is hygroscopic.

Acidum Hydriodicum Dilutum (U.S.P.), an unnecessary preparation.

Chiniofonum (B.P., U.S.P.), a mixture of 4 parts of 7-iodo-8-hydroxyquinoline-5-sulphonic acid and 1 part of sodium bicarbonate. Contains about 29 per cent. iodine. A light yellow powder, bitter taste with a sweetish after-taste. Soluble in 25 parts of water. Insoluble in alcohol. *Doses*, 0·06—0·5 grm., 1—8 grs. (B.P.); 1 grm., 15 grs. (U.S.P.). *Per rectum*, 1—5 grms., 15—75 grs. (B.P.). Used in the treatment of amœbic dysentery where it is supplementary to emetine hydrochloride. Good results have also been reported following its use in ulcerative colitis. It is administered in the form of pills, *e.g.* 5 grs. three or four times daily; enemata are also recommended—200 to 500 mils of 2 per cent. aqueous solution. The proprietary preparation, Yatren, is closely related chemically to chiniofon.

Calcii Iodobehenas (U.S.P.), calcium iodobehenate. White or slightly yellow powder, odourless and tasteless. Insoluble in water and alcohol. Contains about 24 per cent. of iodine. Used as a substitute for the iodides of sodium and potassium. *Dose*, 0·5 grm., 8 grs. It is dispensed in powders.

Lipoiodinum (not official), di-iodobrassidine ethyl ester, colourless crystals, containing 41 per cent. of iodine. *Dose*, 2—5 grms. daily.

Uroselectan or *Iopax* is a non-official preparation which is chemically iodopyridone sodium acetate. It contains 40 per cent. of iodine. Injected intravenously, it is excreted unchanged by the kidneys and the renal tract then becomes radio-opaque. It is therefore of considerable value in the

diagnosis of surgical abnormalities of the urinary tract. The drug is contra-indicated in the presence of acute nephritis and when liver function is impaired. *Dose*, 30 grms. in 100 mils water injected slowly intravenously.

Other preparations of this type are available.

21. BROMIDES

It was only two or three years after Balard had discovered bromine in the water of the Mediterranean at Montpellier, in 1826, that potassium bromide was taken into use as a medicine. On the ground of the new element's relationship to iodine it was assumed that potassium bromide acted in a manner similar to potassium iodide, and it was given for glandular swellings, syphilis, and scrofula, in quantities of up to 30 grammes a day. The expectations of a cure of these diseases were disappointed, but on the other hand these large doses of the salt revealed in the clearest manner a peculiar narcotic action, which has since given it a place among the most important drugs.

Action. The small doses of 1 to 2 grammes of potassium bromide that are often used in medicine have no noticeable specific action on a healthy person. Larger doses, *e.g.* 4—8 grammes, have a narcotic effect, and weaken the reflexes. A feeling of rest and relaxation is induced, a disinclination for mental or physical work, slight drowsiness and inclination to sleep. Bromide of potassium is not directly hypnotic in the same way as morphine or chloral ; it only favours the advent of sleep by producing a condition of dulness which prevents the ordinary impressions from without from exerting a disturbing influence. The sleep after large doses is not refreshing, but, on account of the slow excretion, is followed by drowsiness and weariness. Doses of 10—15 grammes cause in healthy adults pressure and feeling of heat in the epigastrium, salivation and slight indisposition, frontal headache, a difficulty of comprehension and thought, slowness of speech and misplacing of words and syllables, apathy and dulness regarding impressions of all kinds, but no immediate sleep.

All these symptoms arise from decreased irritability of the **central nervous system,** especially the *brain.* Such an action has been directly demonstrated by Albertoni, who found, by experiments with dogs, that the electrical stimulation of certain parts of the cerebral cortex, which in normal animals produces violent epileptic fits, had no effect after 2 or 3 weeks' treatment with bromide of potassium, an experiment that has its analogy in the treatment of epilepsy with that drug. Some time after the bromide was stopped—the length of time varying with the dose—electrical stimulation once more elicited fits. A prolonged after-effect was

most pronounced in those experiments in which the animals had had potassium bromide so long that they began to show " saturation " in the form of uncertain movements and constant drowsiness. The *spinal cord reflexes* are also so weakened in animals that larger doses of strychnine than usual are required to elicit convulsions. The action on the central nervous system is further shown by the cessation or diminution of the *irritability of the mucous membranes*, earliest and most marked in the throat, which can be touched and examined without eliciting the ordinary reflex movements. The sensitiveness of the genital mucous membrane is also reduced, as well as that of the skin, as demonstrated by Weber's compasses ; after very large doses the sensitiveness of the conjunctiva and cornea is so reduced that reflexes disappear.

No other effects are very pronounced. The **heart** is not affected by the ordinary doses, and it is only after exceedingly large single doses, *e.g.* 10—15 grammes, that the pulse becomes slow and somewhat soft and irregular, and the temperature falls 0·5—1·2° C.

There is increased **secretion** from various mucous membranes, that of the bronchi among others, but not to the same extent as after iodide of potassium. The secretion of milk decreases. The statements regarding menstruation vary ; according to some the discharge is scanty, according to others more abundant and of longer duration. There is a lessening of **sexual desire**, to which both the psychical dulness and the weakening of the local reflexes contribute.

The **amount of urine** is increased a little by large doses. In a few cases the amount of phosphate in the urine has been found to decrease, and a connection has been assumed between this condition and the diminished activity of the cerebral substance with its abundance of organically fixed phosphorus.

The only **local action** that potassium bromide has upon mucous membranes is in its character of a readily soluble hygroscopic salt. In solid form or in too concentrated a solution it causes, like common salt, gastric pains, eructations, and in very large doses vomiting and diarrhœa, but is indifferent when properly diluted.

Absorption, Distribution and **Excretion.** Potassium bromide is absorbed from the alimentary canal as readily as iodide of potassium, and makes its appearance as quickly in the urine and saliva ; but the complete excretion is accomplished much more slowly. After prolonged potassium bromide medication, 1 or 2 months, or even more, pass before the urine is bromine-free. The reason why it remains so long in the organism is that bromine expels chlorine. An exchange with sodium chloride goes on in the blood—$KBr + NaCl = KCl + NaBr$—the potassium chloride

formed being rapidly eliminated, while the bromine is retained as sodium bromide, and in secretions may take the place of chlorine. Thus Nencki found that the gastric hydrochloric acid in a dog during the use of potassium bromide was partly replaced by hydrobromic acid, and that the gastric juice sometimes contained even more of the latter acid than of the former. As soon as the supply of bromine ceases the reaction is once more reduced, and the greater the amount of sodium chloride present the more rapidly does this take place. According to Ellinger's experiments the greater percentage of bromine is found in the blood and but little in the brain. The excretion is principally in the urine, although bromine is also found in many other secretions—in the tears, sweat, milk, in acne pustules, and in the urine of new-born infants whose mothers have been treated with bromide.

Poisoning (bromism). Cases of *acute poisoning* are very rare, but may occur, especially when disease of the kidneys is the cause of imperfect excretion. *Chronic potassium bromide poisoning* is of more importance. It is seen during the prolonged use of large doses in epileptic patients, and may either appear gradually, or suddenly, after the treatment has long been borne without unpleasant results. The commonest and nearly always the first symptom is skin-eruptions, especially " bromide acne," in which scattered pustules appear first at the roots of the hair and on the face, associated with urticaria or erythema. In malignant cases the pustules may coalesce and form the starting-point for ulceration and phlegmonous inflammation. Another series of toxic symptoms which almost regularly follows a long treatment with potassium bromide is due to *cerebral depression*, consisting in loss of memory, apathy, dulness, diminution or extinction of sexual desire, hesitating or faltering speech, uncertain, slow gait, intention tremor, cessation of mucous membrane reflexes, and drowsiness. The *bronchial secretion*, especially in previously established bronchitis, is worthy of much attention, as the cough reflex is greatly lessened. In the worst cases—" bromide cachexia "—there is anæmia, emaciation and diarrhœa. Death, with symptoms of cardiac weakness, loose stools, or broncho-pneumonia, is of rare occurrence. As a rule, the toxic symptoms disappear when the bromide of potassium is stopped or the dose diminished ; but experience has shown that the enfeebled patient has little power of resistance to intercurrent diseases for a long time afterwards.

Sodium bromide, which contains more bromine (77·7 per cent.) than the bromide of potassium (66·4 per cent.), has the same sedative action and causes the same toxic symptoms with continued use ; and the same is true of **lithium bromide. Ammonium bromide** (containing 81·7 per cent. of bromine) is considered to be

the most powerful of the alkaline bromides, but it is also the least stable. It readily gives off free bromine, becomes yellow on exposure to air, and therefore more frequently gives rise to dyspeptic symptoms and poisoning.

Therapeutic Uses. Bromide of potassium was first recommended for *epilepsy* by the English physician, Locock, in 1853, a memorable year in the treatment of this most intractable disease. In the great majority (90—95 per cent.) of sufferers from epilepsy the effect of the bromide treatment is to cause the attacks either to cease entirely or, in any case, to become milder and less frequent, and, even after the conclusion of the treatment, to appear at longer intervals than formerly. Complete recovery is as exceptional as the absence of favourable results. The anti-epileptic action commences simultaneously with the first symptoms of poisoning, which indicate saturation of the organism with bromide, that is to say, that a certain amount is stored up. This at first takes place quickly; thus, in a case in which 80 grammes of potassium bromide was given, 41 grammes was excreted in 8 days and the rest retained in the body; afterwards excretion is slower, until the amount taken balances the amount excreted. In a patient who received 7—8 grammes a day equilibrium was reached about the 18th or 20th day. The degree of saturation varies in each case, and a suitable dose must, therefore, be determined experimentally for each patient. For this purpose a definite plan is followed, although individual conditions may necessitate many deviations from it. In general, 3 grammes a day is given during the 1st week, 4 grammes a day during the 2nd week, and so on, with an increase of 1 gramme a day each week, until in the 8th week 10 grammes a day is reached. If necessary, and provided that the treatment is well borne, this is continued until, in the 13th week, 15 grammes is given daily, larger doses being rarely employed; after this the doses are reduced in the same way. If the attacks return, the treatment is begun again, and may be continued in this manner for years. If it appears that a smaller quantity, *e.g.* 5 or 6 grammes a day, can keep off the attacks, a halt is made at that amount or a slightly larger daily dose. The principle is to keep the patient sufficiently saturated with bromide; and since the storage, as already mentioned, is effected by the conversion of the sodium chloride of the body into sodium bromide, the action is strengthened by simultaneously restricting the consumption of common salt. Experience will then often show that a very good effect is obtained with doses that were almost ineffectual with a free consumption of salt. The degree of energy with which the treatment is carried out must depend upon the reaction of the

patient and the gravity of the disease. Even in the rare cases in which the disease appears to be cured after a single period of treatment it is repeated now and again during the few following years to prevent a relapse. If serious symptoms of bromism appear, the doses must quickly be reduced ; but sudden cessation should be avoided as far as possible, as a relapse follows more quickly. Slight symptoms of intolerance, such as scattered acne pustules, do not necessitate an interruption of the treatment. In old and poorly-nourished persons even daily doses of 4—6 grammes may induce such marked symptoms of depression that the treatment has to be discontinued.

Among other spastic diseases, *chorea minor* and *convulsions in children* are often benefited by potassium bromide, but traumatic tetanus, strychnine poisoning and eclampsia demand more powerful remedies, such as chloral hydrate or, better still, barbiturates. In *whooping-cough* the violence of the attacks can be subdued, but the course of the disease is not shortened. The palpitations and other cardiac symptoms in *exophthalmic goitre* are greatly relieved.

The bromides are frequently prescribed in *neurasthenia* and *nervousness*, for symptoms of cerebral excitement and sleeplessness, and are of much value. As previously stated, they exert no marked hypnotic action, but only a sedative effect, and thus induce a natural sleep.

For obstinate *vomiting*, even the *hyperemesis of pregnancy*, large doses of potassium bromide are sometimes useful ; and *sea-sickness* is not infrequently prevented by doses of 4 or 5 grammes taken daily for several consecutive days before the voyage.

In cases of poisoning with potassium bromide the patient is given saline waters to promote the excretion. Bromide acne quickly disappears, but serious skin-complaints and the psychical symptoms disappear more slowly.

Several new preparations of bromine, two or three of which are mentioned below, are analogous with the iodine and fatty acid compounds mentioned in Chapter 20 ; these are intended either to exert a more lasting action than the alkaline bromides, or to influence epilepsy by using smaller quantities of bromine. All may be satisfactory in slight cases, but in more serious cases it is best to keep to the alkaline bromides.

Preparations and Doses

Potassii Bromidum (B.P., U.S.P.), potassium bromide, KBr, colourless, cubical crystals with a saline taste, readily soluble in water. *Dose*, 3—20 decigrms., 5—30 grs. (B.P.) ; 1 grm. 15 grs. (U.S.P.). The ordinary dose in neurasthenia, etc., is 1 grm. 3 times a day, dissolved, if desired, in a 10

per cent. infusion of valerian. The doses in epilepsy for adults are given above; for infants the dose is 25—50 centigrms., for older children (5—10 years) up to 3 or 4 grms. a day.

Sodii Bromidum (B.P., U.S.P.) and *Ammonii Bromidum* (U.S.P.). Characters and doses as above.

Calcii Bromidum (U.S.P.), calcium bromide, $CaBr_2$, a white, deliquescent salt. *Dose* as above. Its purpose is to combine the actions of bromine and calcium upon the nervous system, and it is recommended for tetany and laryngospasm in children.

Acidum Hydrobromicum Dilutum (B.P.) is superfluous.

22. THE OXYGEN GROUP (OXIDISERS)

Oxygen is essential for the continuance of the normal metabolic changes in the tissues. It is derived from the blood-plasma, which contains 0·3 per cent. of the gas in solution. The concentration of oxygen in the plasma is maintained at the expense of the oxyhæmoglobin; increased metabolism tends to reduce the amount of oxygen in the plasma and leads to more rapid dissociation of oxyhæmoglobin. In ordinary respiration nearly all the hæmoglobin that passes through the lungs is saturated; inhalation of pure oxygen cannot therefore increase appreciably the amount of oxyhæmoglobin. On the other hand, the amount of oxygen in the *plasma* may be increased ten-fold by this means and is the sole justification for oxygen therapy in the great majority of cases of anoxæmia.

A variety of circumstances may lead to lack of oxygen in the tissues, the most obvious being life at high altitudes. A diminution in the extent of the effective absorbing surface occurs in pulmonary diseases, such as pneumonia, acute œdema of the lungs, and advanced emphysema. Sudden reduction in the quantity of hæmoglobin available for the purpose of respiration may also produce symptoms of oxygen-lack, *e.g.* profuse hæmorrhage, carbon monoxide poisoning and methæmoglobinæmia. Thirdly, despite an adequate supply of oxygen and an ample supply of hæmoglobin to carry it, the tissues may suffer from anoxæmia owing to circulatory insufficiency, *e.g.* in congestive cardiac failure and in shock.

In the anoxæmia of cardiac failure the results of oxygen therapy are often disappointing owing to stagnation in the circulation. Treatment should therefore be given *early* and as efficiently as circumstances permit; failure to observe these requirements frequently brings the treatment into discredit. The oxygen-tent is the ideal method of administration, but on account of expense and the need for expert supervision it is not widely used by practising physicians. The most practicable

method consists of delivering the oxygen to the patient through a wide soft rubber catheter introduced into the nasopharynx. Alternatively, a large cardboard hat-box suitably cut, may be placed over the patient's head ; oxygen is then allowed to flow into the box and a high concentration of the gas can thus be obtained. In cases of coal-gas poisoning, etc., oxygen mixed with 7 per cent. of carbon dioxide is usually administered by means of a mask similar to that used for induction of nitrous oxide anæsthesia. This is a very effective method of treatment and it is unfortunate that conscious patients suffering from such conditions as pneumonia and cardiac failure are nearly always unable to tolerate the application of the mask. The practice of holding in front of the patient's face a funnel and tube from which oxygen is flowing should be abandoned ; it has little or no therapeutic value. In recent years the intravenous route for oxygen administration has been advocated and good results have been claimed. The danger of gas-embolism is obvious, but it is said that this can be avoided by suitable technique.

Increased pulmonary ventilation may cause excessive elimination of carbon dioxide from the blood ; the body is thus robbed of the natural stimulus to the respiratory centre and a temporary state of apnœa occurs. Furthermore, the disappearance of the volatile acid of the tissues results in a tendency to alkalosis which hinders the normal dissociation of oxyhæmoglobin. The combined effects of these events is to produce a state of anoxæmia in the body accompanied by a grey or "ashen" facies instead of ordinary cyanosis. This condition of "grey cyanosis," as it is sometimes called, is not characterised by dyspnœa. Under these conditions a mixture of oxygen and carbon dioxide should be given.

When oxygen is administered by inhalation, most patients should receive not less than two litres per minute. The gas should be brought to a suitable temperature by bubbling it through warm water.

The classical researches of Paul Bert established the fact that oxygen under more than atmospheric pressure is actually toxic to the organism and experimental animals succumb rapidly in these circumstances.

The oxygen of the air consists of O_2 molecules. In this condition it is comparatively inert, and at an ordinary temperature has no very great oxidising power, as the molecule $O = O$ behaves as a compound, the atoms of which fix one another. Many other compounds far more easily give off oxygen in a nascent form (atoms). This nascent oxygen cannot be collected or preserved, as it is immediately changed to O_2 ; it is supposed to exist only at the moment of generation, when it acts with great energy, and

oxidises many bodies that are not affected by molecular oxygen. A few such compounds, the so-called oxidisers, are employed in medicine, and will be mentioned here.

Potassium Permanganate

Potassium permanganate, $KMnO_4$, in solution is antiseptic, not as an entire molecule, but because it very readily gives off oxygen to organic substances, whereby it is itself reduced to manganese oxides, which occur as a brown precipitate and may colour the skin. As potassium permanganate is immediately reduced by albumin, it cannot penetrate deeply. Unstable organic substances, such as the malodorous products of decomposition, are first oxidised, so that permanganate of potash is often more a deodorant than a true antiseptic. Concentrated solutions (1 per cent. on mucous membranes) have a corrosive action on places from which the epithelium has been removed, forming, with a considerable amount of pain, a black eschar, while the healthy skin is not affected. Potassium permanganate is not absorbed from the alimentary canal, and appears to be poisonous only inasmuch as it causes corrosion.

Permanganate of potash is used as a deodorant and disinfectant in the washing of *foul and fœtid sores*, as a mouth-wash in *fœtor oris*, for nasal insufflation in *ozœna*, for *sweating feet*, and as a wash in *leucorrhœa*. In *gonorrhœa*, injections of dilute solutions are often beneficial. Potassium permanganate is used as an antidote to *phosphorus* (oxidation), *prussic acid* and *cyanide of potassium* (formation of potassium cyanate), and in cases of poisoning with *opium* and *morphine*, which are rapidly oxidised to non-poisonous products ; its action on strychnine is too slow to be of any use. It is, of course, only in the stomach that the poisons can be acted upon, not after absorption. For *snake-bites* injections quickly made in and around the bite are effectual ; but there, too, only the poison with which the oxidiser comes in immediate contact is affected, not that which has been absorbed.

Hydrogen Peroxide

Peroxide of hydrogen, H_2O_2, is present in the atmosphere, especially after thunder and heavy rain, being almost always found in rain and snow, though only in the proportion of 0·04—1 milligramme to a kilogramme of air. It is formed in many processes of oxidation when water is present, and it is remarkable for the

ease with which it is decomposed into water and oxygen. The decomposition is elicited by many inorganic bodies which act as ferments, such as finely-divided platinum, gold, silver, etc., apparently without causing changes in them (catalysis, contact-action), and also by all kinds of ferments or enzymes containing organic substances, such as pus, blood, infusoria, bacteria, yeasts, etc., which immediately cause a watery solution of peroxide of hydrogen to effervesce with the escape of oxygen. The nascent oxygen gives to peroxide of hydrogen antiseptic properties that are almost equal to those of corrosive sublimate. It is not much used, however, notwithstanding its powerful action. The effect lasts only for the few moments whilst the evolution of gas takes place, and is quite superficial. It is necessary, moreover, for the gas to have free egress. When hydrogen peroxide is injected into the blood of animals, the oxygen evolved forms gas-emboli, which cause instant death. The occurrence of a sudden death on washing out an empyæma with peroxide of hydrogen is probably caused by the *rapid* shifting of the mediastinal structures to accommodate the gas in the pleural sac. In other cases hemiplegia has been observed, but this has not been satisfactorily explained. Nor should hydrogen peroxide be injected into the tissues hypodermically, as the explosive evolution of gas may cause gangrene. On the other hand, it is useful as a mouth-wash and gargle, as a poultice on gangrenous or foul sores, and as a deodorant for foul discharges, *e.g.*, on tampons in cancer of the uterus. It has a wide technical employment as a bleaching agent.

Peroxide of hydrogen has been suggested as a preservative for milk, but is objectionable for this purpose. By its use milk remains sweet for a long time even in hot weather, but its enzymes are destroyed and perhaps its vitamins, which are of great importance.

Ozone

In addition to O_2, the atmosphere contains O_3, which is called *ozone* on account of its odour ; it is a polymeric form of oxygen, originating under almost the same conditions as hydrogen peroxide. When changing into ordinary oxygen, ozone gives off oxygen more easily than hydrogen peroxide, and is the most powerful of all oxidisers. It oxidises at an ordinary temperature many bodies that are only affected by ordinary oxygen when heated, and it is irritating to the respiratory mucous membrane. Medicinally, ozone is of little interest. The advertised " ozone air " of health resorts does not exist. The minute quantities (at most only a

few milligrammes in 50,000 litres of air) that may be present have no significance ; and even if the air really contained an abundance of ozone, it would not cause any increase of the oxygen in the blood. The only significance of an ozone reaction in air is that it serves to a certain extent as an indicator of the purity of the air. If the air contains many oxidisable substances, they consume the ozone, which thus disappears in large towns. The " ozone water " advocated as an antiseptic is also an illusion, for ozone is almost insoluble in water, and in it soon changes into ordinary oxygen.

Preparations and Doses

Oxygenium (B.P., U.S.P.), a colourless gas, odourless and tasteless. One volume dissolves in about 43 volumes of water. For convenience it is compressed in metal cylinders.

Potassii Permanganas (B.P., U.S.P.), potassium permanganate, $KMnO_4$, dark purple, iridescent, prismatic crystals, soluble in 16 parts of water. *Dose*, 6—20 centigrms., 1—3 grs. (B.P.) ; 0·06 grm., 1 gr. (U.S.P.). Externally, for washing and disinfection, $\frac{1}{10}$—1 per cent. solution (the brown spots left can be removed with dilute acids, *e.g.* vinegar) ; on mucous membrane always very dilute solutions ; for washing out the stomach in cases of poisoning, 1 in 1,000 to 1 in 500 ; for the urethra, 1 in 4,000 to 1 in 1,000 ; as a mouth-wash, 1 teaspoonful of a 1 per cent. solution to a tumblerful of water.

Liquor Hydrogenii Peroxidi (B.P., U.S.P.), a 3 per cent. aqueous solution of H_2O_2, yielding ten times its volume of oxygen. *Dose*, 2—8 mils, $\frac{1}{2}$—2 fl. drs. (B.P.) ; 4 mils, 1 fl. dr. (U.S.P.). Externally, as an antiseptic, mixed with water or undiluted ; for a mouth-wash or gargle, 1 or 2 teaspoonfuls to a tumblerful of water. *Perhydrol* is a very pure and more concentrated preparation, containing 30 per cent. of H_2O_2, and yielding 100 times its volume of oxygen.

Sodii Perboras (U.S.P.), sodium perborate, $NaBO_3 + 4H_2O$, a white powder containing about 9 per cent. of available oxygen, which is evolved slowly when the powder is dissolved in cold water, more quickly in hot water. *Dose*, 0·06 grm., 1 gr. Used as a disinfectant, dry or in solution.

Several peroxides of metals have been tried as oxygen-yielding antiseptics. Of these *Magnesium Peroxidatum*, MgO_2, is a white powder, insoluble in water, and evolving oxygen when brought in contact with acids. It is said to be useful as a gastric and intestinal disinfectant. *Dose*, 25—50 centigrms., 4—8 grs., 3 times a day. *Zincum Peroxidatum*, ZnO_2, is a yellow, insoluble powder. It is used externally as an antiseptic in the form of a dusting-powder or a 10 per cent. ointment.

Addendum

Charcoal

When a suspension of finely-divided particles of, for instance, kaolin, talc, or charcoal is mixed with solutions of salts, colouring

matter, alkaloids, colloids, or with fine emulsions, a border-layer appears upon the surface of all the small particles, where the concentration is greater than in the surrounding medium. This physical fixation is called *adsorption*, and being a surface-action is therefore greatest when the surface is very large (*i.e.* the particles very small), or is made greater by porosity (animal charcoal). The adsorption can be very firm (irreversible). When an albumin solution, for instance, is shaken up with charcoal, the charcoal fixes a considerable amount of albumin, and does not give it off again to water. Although adsorption is a purely physical process, it may also be accompanied by chemical changes. Many salts are dissociated in such a manner that the filtrate contains free acid, while part of the base is left behind. From a copper sulphate solution, for instance, more Cu than SO_4 is adsorbed ; if a potassium iodide solution be passed through a charcoal filter, the iodine is left behind, and so forth. In many cases the oxygen collected in the pores causes oxidation. Thus sulphuretted hydrogen is oxidised to sulphurous acid, and even at 32° oxalic acid is oxidised to carbonic acid and water. Charcoal, although it does not itself contain oxygen, acts as a carrier of oxygen, and may thus be reckoned as an oxidiser. Dry, freshly-charred charcoal, like spongy platinum and other porous bodies, also possesses the property of adsorbing large quantities of other kinds of gas. Charcoal can thus take up 55 times its own volume of carbonic acid, and 90 times its volume of ammonia. Putrefying water loses its odour and taste when passed through a charcoal filter.

On account of its ability to absorb colouring matter, colloidal impurities, etc., charcoal has long been employed in the chemical industry as a purifying agent. In medicine, before the introduction of the modern treatment of wounds, charcoal was used as a deodorant for *profusely-secreting, foul sores*. Internally it is employed for *meteorism*, but the power of absorbing gases is weakened when the charcoal is moist. The internal treatment with charcoal has gained ground of late, after it had been demonstrated that well-prepared animal charcoal is remarkable for its far greater power of adsorption than the hitherto employed charcoal of the pharmacopœias. In cases of *poisoning* in animals (with phenol, strychnine, phosphorus or fungi) it was found that the toxic symptoms, if any, were only slight when animal charcoal was given ; and subsequent clinical experience has confirmed the efficacy of the treatment. It must be remembered, however, that the service it renders is only that of considerably delaying the absorption, and that the poison may again become free during its slow passage through the intestine. An aperient is therefore also given, preferably a saline purgative. Good results have been

reported of its use for *summer* and *infantile diarrhœa*, *dysentery* and even *cholera*. Its action is probably due partly to the fact that the charcoal fixes the micro-organisms, and partly that the colloid bacteria-poisons are adsorbed even better than crystalline substances (alkaloids, metal salts, etc.).

Preparations and Doses

Carbo Activatus (U.S.P.), wood charcoal, a fine black power. *Dose*, internally, from a teaspoonful to a dessertspoonful; official *dose*, 1 grm., 15 grs.

Carbo Animalis, animal charcoal, prepared from bone and containing 85 per cent. of mineral ash. Is not more efficacious than wood charcoal, and is highly adsorptive only after being boiled with hydrochloric acid and thoroughly washed with water (*Carbo Animalis Purificatus*). *Dose*, as of wood charcoal.

Kaolinum (B.P.), kaolin, bolus alba, fullers' earth, a native aluminium silicate, forming a whitish powder, which feels greasy to the touch. Like ordinary clay it forms a plastic dough when mixed with water (excipient for pills). *Cataplasma Kaolini* (B.P.), is now employed externally as a poultice for *rheumatism*, etc., and after careful sterilisation (tetanus bacilli) as an astringent for *wounds*, and in the vagina for *leucorrhœa*; kaolin is given internally in large doses (50—100 grms.), stirred into water, for *diarrhœa*, *dysentery* and *cholera*; official *dose*, 15—60 grms., ½—2 oz.

Talcum Purificatum (U.S.P.), a purified native magnesium silicate, forming a very fine, white powder, which is slippery to the touch and adheres to the skin. Is employed as an indifferent dusting powder on *excoriations*, etc.

Terra Silicea Purificata (U.S.P.), purified kieselguhr, purified infusorial earth, a very bulky, fine powder, consisting of fragments of diatoms. Employed as the above.

IV.—THE HEAVY METALS AND METALLOIDS

1. GENERAL PROPERTIES

THE heavy metals form a special, fairly well-defined group of drugs ; certain common features are found to prevail with regard both to their local and general action and to their absorption and excretion. In order to avoid repetition, these features will be mentioned in this introductory chapter.

The **local action** of the heavy metals is dependent upon their affinity for albumin. In the test-tube, as we know, neutral albuminous solutions are precipitated by metallic salts ; a white sediment is deposited of metallic albuminate. These albuminates differ from ordinary salts in not being constituted according to definite proportions, so that the amount of metal they contain may vary considerably. The same process takes place when a soluble metallic salt or oxide comes in contact with the living, moist tissue. All protein that is reached by the metal compound is precipitated as metallic albuminate, and is thereby rendered lifeless. If the albumin precipitate is only superficial, the action is called astringent, but if it goes deeper it is corrosive. The nature of the action depends on both the metal and the acid of the salt ; when the metal unites with albumin, the acid is set free and sets up an action of its own. The two components must, therefore, be considered separately.

Most metals precipitate albumin as an insoluble compound, which coats the tissue and thus confines the action to the surface. A few albuminates are of a looser consistency, or are soluble in excess of protein and in salts (chloride of sodium). These do not protect the underlying tissue, nor prevent the action from penetrating deeper. The type of the first class of metals is lead, that of the second mercury, and between these two extremes lie the rest in about the following order (beginning from lead) : iron, aluminium, copper, zinc, and silver, all, however, more closely partaking of the action of lead than of mercury (Schmiedeberg).

As a rule the acid is more important to the local action than the metal. Those salts which are most easily dissociated into ions, namely, chlorides and nitrates, have the most powerful action, that is to say, the most corrosive. Next come the sulphates, and the weakest of action are the slowly-dissociated salts of organic acids, acetic acid, tartaric acid and citric acid. The

combination of lead with the weakest acid gives the most gently-acting, simple astringent salt, lead acetate ; the combination of the strongest acid with the corrosive mercury gives the most caustic of all salts, corrosive sublimate. This is the case, however, only as long as the salt is soluble ; if it is insoluble, it cannot exert a chemical reaction and does not become corrosive, even if its components are two of the most strongly acting (*e.g.* calomel). A few salts that are insoluble in water are soluble in albumin, and are thereby able to acquire considerable activity (mercuric iodide).

From the above it will be easily understood that the metal salts may possess every degree of local action from the purely astringent to the purely caustic, according to the varying combination of metal and acid. The chemical nature is not the only determining factor, however, for the time and the concentration in which a compound is employed are also of importance. A substance that is a strong corrosive in concentrated solution may be an astringent when used in a dilute solution. The affinity for water also plays a great *rôle*, and a hygroscopic salt has a stronger local action than one that is not hygroscopic.

Specific Action. All the heavy metals are poisonous, but as most of them are absorbed through the alimentary mucous membrane in only extremely small quantities (see below), acute specific effects are very rare. What is called acute metal poisoning is generally only gastro-enteritis and thus a local action. Chronic metal poisoning occurs when absorption of small quantities has been going on for a long time ; and if the elimination takes place even more slowly than the absorption, as is generally the case, cumulation occurs. The general action of the metals is studied experimentally by injecting subcutaneously or intravenously compounds which are not precipitated by albumin or by the alkaline carbonates of the body. The ordinary salts cannot be employed, as they cause coagulation of the blood and widespread disturbance of the circulation.

To a casual observer the general action of the metals presents a very heterogeneous character, but on closer inspection a certain uniformity is apparent in the almost constant occurrence of a few fundamental features. In cases of poisoning, paralysis of various sections of the *central nervous system*, often preceded by convulsions, is one of the regular symptoms. Many metals cause—if the patient lives long enough—*destruction of the red blood-corpuscles* (jaundice, hæmorrhage) and *fatty degeneration* of various organs, *e.g.* the heart. Many of them produce a *peripheral vascular paralysis*, which is probably of a nature similar to that caused by arsenic. Finally, *inflammation of the intestinal canal* (injection,

ulceration, vomiting and diarrhœa) and of the *kidneys* (nephritis, albuminuria) forms an important series of symptoms which will be frequently mentioned in the descriptions of metal poisoning. The fact that the inflammation affects just those places where the principal excretion takes place argues a causal condition, although both the intestinal and the renal affections may arise from vascular changes.

A necessary condition for specific action is that in the body the metal shall be in such compounds as are dissociated into ions. Metallic-organic compounds which are dissociated slowly at first show only the action of the molecule, not that of the metal. The immediate action of lead triethyl is thus narcosis, and the action of the lead ion does not appear until, after several hours in the body, it is converted into dissociable compounds. If a firm compound such as this remains unchanged in the body, there is no symptom that reveals the metal.

Absorption and Excretion. Mercury is the only metal that is very readily absorbed in the intestinal canal; all the others are either absorbed very slightly or not at all. In what manner the intestinal epithelium prevents the passage of the metals into the body is not known; it may, perhaps, have something to do with the solubility of the albuminates. Other mucous membranes (such as the vagina) seem to behave in the same way as the intestine. From wound-surfaces, on the contrary, the metals are generally absorbed readily. It must therefore be remembered when, in the following chapters, there is frequent mention of slow absorption from the intestinal canal, that this only refers to uninjured mucous membrane covered with epithelium. If the salts are given in such a way as to cause corrosion, absorption takes place as from any other wound-surface. The absorbed metals soon leave the blood and are deposited in various organs, where they remain for a long time. The greatest amount is nearly always found in the liver, less in the spleen and kidneys, and small quantities in many other organs, the brain being one of them. Excretion takes place principally in the intestinal canal, partly through the bile, partly through the mucous membrane all the way from the stomach to the large intestine. Only a little is found in the urine, and still less in other secretions, such as the milk and the saliva.

The heavy metals have hitherto been employed in medicine either in their pure, metallic condition (iron, mercury) or in the form of the ordinary inorganic and organic salts, oxides and other well-known compounds. The so-called **colloid metal solutions** are now being tried as drugs—new forms which exhibit many features that do not fit in with our accustomed ideas of the properties of

heavy metals. Colloid silver, gold, mercury, platinum, etc., are apparently readily dissolved in water, which acquires a dark, generally brown colour. The liquid is in reality not a solution at all, however, but a pseudo-solution, a suspension of exceedingly fine, solid particles, which may be so minute that they are not visible even to ultramicroscopical observation. These colloid solutions have a catalytic action and resemble ferments. Like diastase, emulsin, yeast, and organ-fluid with its enzymes, they assist in infinitely small amounts in chemical processes, *e.g.* the splitting up of hydrogen peroxide into water and oxygen. As an example of their activity it may be mentioned that solutions containing $\frac{1}{3000000}$ milligramme of platinum per cubic centimetre still have a distinct catalytic action. The colloid metals bear, moreover, an interesting resemblance to several ferments in that they are paralysed by many poisons, *e.g.* prussic acid, but may survive the poisoning and regain their activity. When kept long their activity is weakened, because they generally begin to coagulate into large, insoluble particles. Even slight friction of the dry colloid mercury, which forms resin-like pieces, is sufficient to cause the excretion of drops of mercury. A greater durability is attained by the addition of gum, white of egg, or similar substances (" protection colloids "). It is not known with certainty whether the colloid metals retain their properties and exert special actions within the body. When injected directly into the blood, they do not produce in mammals the typical metal poisoning, but pyrexia and hyperleucocytosis, which probably indicate that the organism, with the aid of the leucocytes, is endeavouring to free itself from the foreign colloids. It has further been found that the activity of poisons and bacterial toxins is weakened when they are injected together with colloid metal solutions. This is interpreted as an adsorption phenomenon due to their large surface. It is possible, however, that all this is not characteristic of the metals, but that any strange colloids introduced into the blood have a similar action.

2. ARSENIC

Arsenic is one of the most widely-distributed elements. It occurs, not only in the true arsenical ores, but also in many other minerals, and in mineral springs; and in many places it has been demonstrated in the soil, whence it is taken up by numerous plants. It was thought to be non-existent in the animal organism until Gautier, in 1899, found arsenic as a constant constituent of the thyroid gland and other organs in various mammals and in man

especially in the skin and hair. It was subsequently also demonstrated by Bertrand in many marine animals, *e.g.* seals, starfish, sea-slugs, etc., and it seems always to occur in dried fish. Gautier puts the total arsenic in the human body at 0·43 milligramme, of which 0·17 milligramme is in the thyroid gland. It is very doubtful whether these extremely small quantities are of any physiological importance; the occurrence is probably to be regarded as that of an "impurity" taken into the body with food, or in the case of the marine animals, from the sea-water.

All the inorganic compounds of arsenic are very poisonous. Whether their activity is due to the arsenic itself, or to an oxygen compound appearing as an ion, is not known, but the latter is the more probable. The most important preparations are *arsenious anhydride*, As_2O_3 or As_4O_6, best known by the name of *arsenic*, and *arsenic anhydride*, As_2O_5. The organic compounds in which the arsenic is combined with carbon behave somewhat differently from the inorganic, and, as long as they are present in unchanged condition in the body, do not exhibit the ordinary arsenic action. With the introduction of arsenobenzol (salvarsan) and related compounds into therapeutics, they have now acquired great interest, and will be considered separately.

Inorganic Arsenic Compounds

The only interest that arsenic has for therapeutics lies in the **action of very small doses.** In *healthy persons* this is neither very distinct nor characteristic. The result of treatment with a few milligrammes daily for a long period is stated to be a peculiar sensation like hunger in the epigastrium, increased appetite and thirst, an indefinable impression of well-being and inclination for work, and an increase in weight. The gastric digestion is neither hastened nor retarded, nor is artificial digestion in the test-tube.

The effect of small doses on animals has been carefully studied by Gies. Of the same litter of young rabbits some were given arsenic with their food and others none. Gies found that the arsenic-fed rabbits in the course of a few weeks had gained considerably in weight, looked more vigorous, and had a finer coat than the controls. The subcutaneous fat and that surrounding the intestine and kidneys was greatly developed, and the long bones were of greater length than in the control animals. Examination of the bone-tissue showed changes similar to those described by Wegner after small doses of phosphorus, and a layer of dense tissue was deposited on the epiphyses which was altogether lacking

in the normal animals. When both parents were treated with arsenic, the fœtuses were abnormally large, but were all still-born, perhaps because their size prolonged parturition. Stockman, however, was unable to confirm these observations.

Large doses of arsenic or other inorganic arsenic compounds produce **acute poisoning,** which has long been known in history. During the Middle Ages, and in more recent times until some 50 or 60 years ago, arsenic was the poison most frequently used for murder on account of the absence in it of any strong taste that could arouse suspicion. It now no longer plays this prominent part, as the choice of poisons is greater, and it seems to be generally known that chemical examination nearly always reveals this cause of death. There are two distinct forms of acute arsenic poisoning, the *paralytic* and the *gastro-intestinal.* These sometimes occur alone, sometimes together, so that symptoms belonging to each form appear in the same person.

In the rarer *paralytic form,* which more often appears when very large quantities of the poison have been absorbed in a short time, the symptoms are weakness, anxiety, tremor and painful twitchings in various groups of muscles, convulsions, and, finally, delirium, unconsciousness and coma. The respiration stops before the heart (arsenic asphyxia). Death ensues after the lapse of from 1 to 12 hours.

The more ordinary *gastro-intestinal form* runs a very different course. From half an hour to several hours after the poison has been taken, a strong metallic taste is observed, with dryness, tickling and burning in the throat and œsophagus, soon followed by vomiting, during which severe pain spreads over the epigastrium and abdomen. The vomiting is incessant, the vomited matter being after a time coloured with bile and generally streaked with blood, but never containing large quantities of blood. The vomiting, as a rule, becomes less frequent after a few hours, but the violent abdominal pain, intolerable thirst, and constricted feeling in the œsophagus continue, and after a period of varying length, from 4—24 hours, the pathognomonic symptom, *choleraic diarrhœa,* begins, with incessant evacuations. At first this consists largely of bile-stained mucus, but later resembles rice-water. The resemblance to Asiatic cholera is made more complete by the symptoms of the drying-up of the body produced by the great loss of fluid, namely, diminished secretion of urine or anuria, hollow cheeks and sunken eyes, dry, inelastic skin, hoarse voice or aphonia, cramp in the calves of the legs, and cyanosis. During a cholera epidemic the differential diagnosis may be difficult; but the burning in the throat, the violent abdominal pain and tenesmus, and the commencement of the vomiting several hours before the diarrhœa, are symptoms that point to arsenic poisoning.

In the gastro-intestinal form of poisoning the patient dies, in the most acute cases, in from 12—18 hours, but, as a rule, death occurs after 2 or 3 days. If a longer time elapses, there often appears on the 3rd or 4th day a new series of symptoms that are of great diagnostic value, namely, *skin* eruptions of the most varied appearance—roseola, papules, vesicles, itching pustules, or urticaria accompanied by fever—which disappear with desquamation and falling of the hair.

The *post-mortem* shows no typical changes in the paralytic form. In the gastro-intestinal form the gastric mucous membrane is found to be injected, swollen and covered with a glassy, ropy mucus, in which little grains of arsenic may often be found ; in the fundus and on the posterior wall, especially wherever the particles of arsenic have attached themselves, hæmorrhagic inflammation and lesions of the epithelium may be seen, but no very deep corrosion. In the abdominal cavity the mesenteric vessels are filled with dark, viscid blood. The swollen intestinal walls are injected, and the surface of the mucous membrane is covered with a pseudo-membrane formed of shed epithelium stuck together by a viscid transudate. The contents of the intestine are of the same nature as the rice-water evacuations. In the intestine there is also extravasation of blood and even ulceration. When the course of the poisoning is protracted, fatty degeneration of the intestinal glands, liver, heart and arteries occurs.

As little as 0·10 gramme may constitute a *fatal dose of arsenic*, but when the poison is taken dry and the vomiting begins early there may be recovery after far larger doses. The prognosis is less favourable with solutions, as they are more quickly absorbed.

Chronic arsenic poisoning may originate in an acute poisoning from which the patient has recovered, but is more generally a consequence of long-continued absorption of small quantities of arsenic inhaled in the form of dust from wall-papers and textile fabrics, in smelting-works, in rooms containing stuffed animals of which the skins are preserved with arsenic, etc., etc., or it may be taken with food or beverages, *e.g.* milk, wine, beer, in which case the poisoning may appear as an epidemic, of which the cause is discovered too late.

From facts gathered from a large number of cases (400 cases, due to wines containing arsenic), Brouardel and Pouchet describe four distinct, separate phases, in which various organs suffer. 1. First the *alimentary canal* is affected. The symptoms resemble the acute gastro-intestinal poisoning in a milder form, with anorexia, frequently nausea, vomiting, irregular evacuations alternating between diarrhœa and constipation. The diagnosis, which at this stage is difficult, acquires certainty by the demonstration of arsenic in the urine. 2. In the second phase the characteristic *mucous membrane and skin symptoms* appear. Dry conjunctivitis is most usual, with smarting and redness, especially of the lower eyelid (probably owing to deficient lacrymal secretion), dryness of the nose and throat, or the reverse, namely, coryza with viscid, mucous secretion, hoarseness and bronchial catarrh. In medicinal poisoning these are generally the initial symptoms. The cutaneous affections are of the same polymorphous nature as in acute poisoning, the most characteristic being hyper-keratosis on the palms of the hands and the soles of the feet, a peculiar pigmentation (arsenic melanosis) produced by the deposit in the

skin of a product of the decomposition of hæmoglobin, and vesicles arranged as in herpes, but occurring only on the face and the extremities, not on the back and chest. There may also be jaundice and enlarged liver. 3. In the third stage the *central nervous system* is attacked, and there are disturbances of sensation and motion. They are preceded by persistent headache, diminished working-power and cerebral depression. Heralded by paræsthesia (formication), anæsthesia or hyperæsthesia, arsenic paralysis then appears. This characteristic motor paralysis may affect both the upper and the lower extremities, but is most frequent in the extensor muscles of the foot and calf of the leg (thus differing from lead paralysis, which especially affects the forearm muscles). The vocal cords may also be affected (arsenic aphonia). Arsenic paralysis may be accompanied by rapid muscular atrophy. Sexual desire may become extinct (arsenic anaphrodisia), or be greatly increased. Extensive anæsthesia of the lower extremities may produce uncertainty of gait and ataxy (arsenic tabes). 4. In the fourth and final stage death ensues, after repeated attacks of dyspnœa, from paralysis of the heart or from dropsy and *marasma* as a consequence of fatty degeneration of internal organs, especially the liver, kidneys and heart. It is not always, however, that the entire series is observed. In the last wholesale poisoning in the North of England (1900) from beer containing arsenic, the disease appeared in the great majority of cases in the form of peripheral neuritis, to which the abuse of alcohol seems to predispose.

It is probable that all the above-described symptoms have their common origin in one and the same *fundamental action*. Various theories have been advanced as to the nature of this action.

The original view held was that arsenic was a corrosive poison, and that the severe gastric and intestinal symptoms of the acute poisoning were due to a local action on the mucous membranes similar to that produced by the mineral acids and the caustic metallic salts. This view is now abandoned for several reasons. Arsenic has a caustic action, it is true, but of a different kind from that of the typical corrosives. When applied to mucous membranes or wound-surfaces, it produces inflammation with considerable pain, and finally deep necrosis, but the action is very slow ; that the process is of a different nature is also shown by the fact that arsenic, unlike acids and metallic salts, does not precipitate albumin. Another reason for not regarding the gastro-intestinal symptoms of arsenic poisoning as an ordinary corrosion is that the same gastro-enteritis appears when arsenic is injected subcutaneously or intravenously.

A more recent theory regards the **capillaries** as the real point of attack of arsenic. A few minutes after an intravenous injection of arsenic in animals there is a great fall of blood-pressure. This is partly caused by a somewhat weakened heart-action and by paralysis of the medulla oblongata, but above all by a peripheral paralysis of the capillaries and smallest arteries of the splanchnic area, which so completely lose their tone that electrical stimulation of the splanchnic nerve no longer elicits their contraction. The action probably affects all the capillaries of the body, but first and most strongly the splanchnic vessels, and, as a result of the hyperæmia, secretion of a coagulating transudate occurs which induces watery diarrhœa, the casting of epithelium, the formation of pseudo-membranes, and all the other anatomical changes described. Direct contact of the arsenious acid with the mucous membrane contributes to the intensity of the symptoms, but is not their first cause.

The Nervous System. In the gastro-intestinal form of arsenic poisoning in man, the nerve symptoms are not very marked. The paralysis must be ascribed to a direct action on the central nervous system, although it may be partially explained by the disturbances of nutrition which are presumably caused by the capillary action. The limited areas of paralysis appearing in chronic poisoning generally give the impression of being due to peripheral neuritis, and in many cases the nerve-trunks are affected. Pathological changes in the spinal cord have also been described.

Large doses depress the **heart,** but the muscle is not completely paralysed, and may retain its irritability long after death. In fatal cases of poisoning, the respiration always ceases before the heart-movements.

Arsenic stimulates the hæmopoietic tissues of the bone-marrow and increases the output of red blood-corpuscles where these are deficient. A definite but temporary inprovement is produced in pernicious anæmia by the administration of arsenic, and prior to the introduction of liver therapy in this disease arsenic was the drug mainly employed.

Little is known of the effect of small doses upon the **metabolism.** Toxic quantities act in the same way as phosphorus, but less strongly ; the nitrogenous elimination increases, and, as in phosphorus poisoning, considerable quantities of lactic acid are found in the urine, and in some cases sugar.

It has been already mentioned that arsenic corrodes mucous membranes. On unbroken, dry **skin** it has no effect, but when moisture is present and the action is much prolonged, suppurating ulcers are formed. Wound-surfaces and patches of lupus are corroded deeply but slowly ; and after the lapse of a few days,

cavities separated by ridges of the resistant healthy skin are seen. Subcutaneous injection of arsenites produces pain and infiltration, more rarely suppuration. When taken internally in small doses for a long period, arsenic appears to promote the nutrition of the skin and the development of the subcutaneous fat.

Absorption and Excretion. Arsenic, in solution, is absorbed readily from all sites of application, with the exception of the unbroken skin. It is deposited most abundantly in the liver, spleen and kidneys, but is also found again in all organs, even in the bone-tissue, and in all secretions and excretions, the milk among others, in the placenta and in the fœtus. A fatal case of a child poisoned by the milk of its mother, who was suffering from acute poisoning, is on record. According to Bertrand, eggs always contain arsenic. Excretion takes place principally in the urine, which 2 months after the poisoning may still give an arsenic reaction.

The much-discussed **tolerance** of arsenic forms a remarkable contrast to the chronic poisoning. It is known principally from Steyermark's famous arsenic-eaters. They begin taking the drug when young, with the object of gaining great powers of endurance under physical exertion, using at first small doses, *e.g.* 1—2 centigrammes of dry arsenic once or twice a week, and, according to accounts given, may in time increase these without exhibiting symptoms of intoxication until they can take with impunity amounts (0·4 gramme) many times greater than those that are fatal to ordinary mortals. Arsenic-eaters are described as strong, healthy men, who generally live to a great age. It is not known what means of protection their organism adopts.

Arsenic is highly poisonous to most **micro-organisms.** Exceptions to this are formed by several moulds, which show luxuriant growth in a 1 per cent. solution of arsenite of potassium. The activity of the unorganised ferments is not checked even by considerable quantities. Certain mould-fungi, especially *Penicillium brevicaule,* have the property of evolving, on a soil containing arsenic, a gas—according to Klason, tetra-ethyl-diarsinoxide—with so strong an odour of garlic that the presence of even $\frac{1}{1000}$ milligramme of arsenic is thereby revealed (the "biological arsenic test"). Many protozoa are extremely sensitive to arsenic, but when the concentration is not sufficiently strong to kill them, may acquire a certain power of resistance. If an animal infected with trypanosomes be treated with an insufficient dose, the parasites disappear from its blood only for a short time; renewed treatment has a still briefer result on the trypanosomes, and the increased resistance is handed down from generation to generation of the parasites. In this way

arsenic-resistant tribes arise which, in the animals infected by them, are no longer susceptible to arsenic treatment. These conditions are probably of practical importance in the treatment of protozoal diseases with preparations of arsenic.

Therapeutic Uses. *Malaria.* In the sequelæ and cachexia after malignant forms or repeated attacks of intermittent fever, arsenic is generally superior to quinine. In the acute disease it is said to have some beneficial effect, and it has also been recommended as a prophylactic against infection.

Skin-diseases. In the treatment of *lichen ruber*, arsenic in most cases effects a cure; for *psoriasis* it is the only internal medicine that has a decided effect, although, as with other remedies, relapses occur. Both these diseases require large doses, and the improvement does not generally begin until several weeks have passed. Obstinate *chronic eczema* sometimes disappears under arsenic, though no definite indications can be laid down. In many other skin-diseases it is continually tried, but with doubtful benefit.

Nervous Diseases. Arsenic is an invaluable drug in obstinate cases of *chorea*, in *nervous asthma*, and in various forms of *neurasthenia*, *e.g.* in nervous dyspepsia, especially in anæmic persons. In *neuralgia* which resists other treatment, a trial of arsenic is indicated; it is said to be efficient in the recurrent forms.

Arsenic is, further, employed in a number of general diseases and the cachectic conditions resulting therefrom, such as *hypochromic anæmia* to accelerate the response to iron-therapy, although this is only occasionally necessary, *leucæmia* and *pseudo-leucæmia*, for *multiple sarcomata* (both internally and as parenchymatous injections into the tumours), for *syphilitic anæmia*, together with the specific remedies and iron, for *bronchitis* and *pulmonary tuberculosis* in its first stage, when it acts by improving the nutrition without possessing any specific influence. The reason for its former employment in *rickets* is that its action upon bone-tissue resembles that of phosphorus, but the use of these drugs for this purpose has been abandoned. Arsenic has often been recommended for diabetes, but has proved to be entirely without effect.

Externally, arsenic is employed as a corrosive for *cancer* and *lupus*, where it is practical, as it only affects the diseased tissue. It has now, however, been generally superseded by other, less dangerous drugs. In dentistry it is employed to destroy the pulp and nerves of *decayed teeth*.

A *general rule for the prescription* of arsenic is that it shall be taken immediately after meals, as otherwise gastric irritation is liable to occur. When the employment is to be of long duration,

the doses must at first be small and be increased gradually, as in the reverse case there is a risk of early inducing toxic symptoms. If conjunctivitis, dryness of the throat, dyspepsia or exanthemata appear, the drug must be discontinued ; it is generally said that this must take place gradually, but patients very often suddenly break off the cure of their own accord without deleterious consequences. Persons who are subject to anomalies of digestion can often take mineral waters containing arsenic better than the ordinary preparations.

Arsenic acid, the salts of which are used in some countries, acts similarly to arsenic, but is less poisonous.

Treatment of Arsenic Poisoning. In acute poisoning the stomach is emptied as quickly as possible with the stomach-tube or, when this is not obtainable, by an emetic (apomorphine). The washing-out must be repeated several times, even if the vomiting has begun, as the latter does not sufficiently cleanse the stomach (in a recent case in this country [Norway], notwithstanding repeated violent vomiting, 0·1 gramme of arsenic was found in the stomach after death). After this, as chemical antidotes, are given bases that form with arsenic sparingly soluble arsenites. Such are the previously-mentioned (p. 364) magnesium hydrate and freshly precipitated ferric hydrate. Both these antidotes are given by the tablespoonful, at first every 5 to 10 minutes, then less frequently, as long as the gastro-intestinal symptoms continue. Milk is also given, white of egg and mucilaginous drinks, which act as a poultice to the mucous membranes. Collapse is treated with the ordinary stimulants, cardiac weakness with caffeine. In chronic poisoning, when the cause has been found and removed, the elimination is assisted by baths and diuretics.

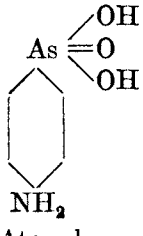
Organic Arsenic Compounds

Micro-organisms that have found their way into the body and caused disease can only be destroyed by substances that have a special affinity for the particular micro-organism in question. Such substances are called *parasitotropes*. All parasiticide drugs, however, are also *organotropes*, *i.e.* they also have an affinity for vital organs, and are therefore poisonous. It will thus be seen that only those substances in which these properties bear the right proportion to one another can be thought of as remedies for parasitic diseases. It is necessary that the affinity for the parasites shall be much stronger than that for the organs, a requirement which it has been found very difficult to fulfil. All the well-known, strong antiseptics injure the host quite as much as, or

even more than, the parasites. All kinds of experiments have been made in the treatment of the ordinary infectious diseases caused by bacteria, bacilli or cocci, with the internal, subcutaneous or intravenous employment of antiseptics, but all in vain. The doses that would be required to sterilise the body would far exceed those that would be fatal to the patient (this does not apply to the effect of salicylic acid on articular rheumatism, of which the cause is not known). Fortunately, in the case of a few bacterial diseases, another means has been found in the serum treatment.

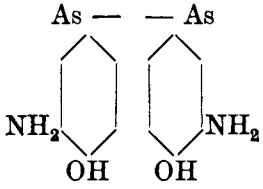
Different conditions prevail in another important group of diseases, namely, that which includes malaria, sleeping-sickness, syphilis, etc., which are caused by parasites (plasmodia, trypanosomes and spirilla or spirochætes) that are more nearly allied to the animal than to the vegetable kingdom, and are considered to be protozoa. These respond better to specifically-acting chemical substances. The ideal parasitotrope for malaria has long since been found in quinine empirically; this alkaloid kills the plasmodia without injury to their host. Empiricism has also gone far with syphilis. There is much that favours the belief that the hitherto principal remedy, mercury, is taken up by, and destroys, the *Spirochæta pallida;* but complete destruction of the parasites cannot be counted upon, because mercury, in the compounds at present at our disposal, has too powerful organotropic properties and elicits the well-known toxic action which limits the doses.

Arsenic has long been employed for malaria and syphilis without exhibiting any marked specific effect. Animal experiments have shown, as already mentioned, that even inorganic arsenic has protozoa-destroying properties, but these are of little practical use, because the toxic action on the host is too powerful. Leveran and Mesnil succeeded, by intramuscular injections of arsenic in rats that were infected with *Trypanosoma Brucei*, in causing the disappearance of the parasites; but after a few days they reappeared, and a complete cure could not be attained, as the animals died of arsenic poisoning. Some years ago arsenical compounds were found which had a pronounced effect upon syphilis and sleeping-sickness, and were far less poisonous than arsenic; but these, too, were not sufficiently harmless to be used without danger in the large doses necessary. One of these compounds, *atoxyl*, formed the starting-point of Ehrlich's investigations, the object of which was to find the

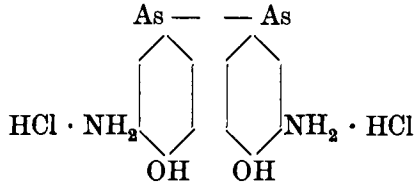


Atoxyl
(sodium aminophenylarsonate).

connection between constitution and action, in order, if possible, to separate the antiparasitic from the toxic properties. By a multiplicity of changes and syntheses, and by experiments with thousands of infected animals, Ehrlich endeavoured to find out which atoms or groups of atoms, and what grouping in the molecule, most increased the affinity for the parasites and most reduced the toxicity. He found that these requirements were best fulfilled by dihydroxy-diamino-arsenobenzol, the hydrochloride of which, arsenobenzol (salvarsan), became one of the most important of drugs.

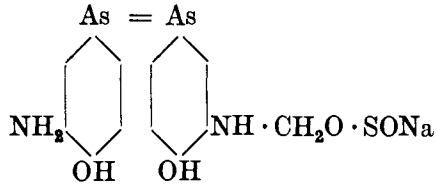


Dihydroxydiamino-arsenobenzol.



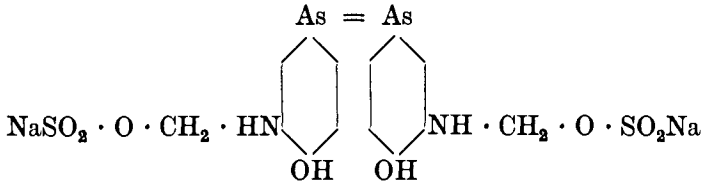
Salvarsan (Arsenobenzol), *Arsphenamina* (U.S.P.).

Further substitution in the amino group resulted in the formation of the following compounds which have displaced salvarsan for therapeutic purposes :



(Sodium diaminodihydroxyarsenobenzene methylene sulphoxylate).

This is known as Neoarsphenamine or " 914 " and it is administered intravenously.



(Sodium diaminodihydroxyarsenobenzene dimethylene bisulphite).

The official name of this compound is Sulpharsphenamine. It is injected subcutaneously or intramuscularly.

Action and Indications. In diseases due to spirochætes arsenobenzol has shown properties which surpass everything that has

been seen in the way of specific action. It must be a transformation-product originating in the body, which destroys the parasites or prevents the development of new generations, for in the test-tube arsenobenzol kills cultures of *Spirochæta pallida* only in a comparatively strong concentration (1 in 1,000). The toxicity is increased by the addition of extract of liver or still more by blood. This is probably on account of enzymes, for the toxicity is not augmented by boiled organs.

Relapsing fever. The effect of this treatment in an epidemic of relapsing fever was as follows: Some hours after injection of 0·2 to 0·3 gramme of neoarsphenamine, a sudden fall of temperature took place, the spirilla disappeared from the blood, and in 92 per cent. of the cases the patient was definitely cured. The cure was effected by a single injection. The fall of temperature was generally immediately preceded by rigor and great rise of temperature, probably caused by the endotoxins of the dead parasites. Salvarsan has a similar effect upon the tropical disease, *frambœsia*, which is caused by *Spirochæta pertenuis*, and had previously defied all treatment. By a single injection (in exceptional cases only were two injections required) about 700 frambœsia patients were cured in a short time, and it was possible for the hospital to be closed and the staff dismissed.

In *sleeping-sickness* the trypanosomes have been seen to disappear after injections of 0·5—0·6 gramme of neoarsphenamine; but judgment of the ultimate result can only be pronounced when greater experience has been gathered. The ordinary forms of *malaria* are acted upon so favourably and without danger by quinine, that there is no necessity to use any other remedy. In forms that resist quinine, organic arsenicals sometimes bring about recovery. Specific action is seen, further, in various diseases of the oral cavity with which species of *spirochæta* are probably connected, especially *Vincent's angina.* In early *gangrene of the lung* neoarsphenamine not infrequently (probably in cases in which spirochætes are the cause) effects a rapid cure. In the disease following rat-bite, seen especially in Japan, and characterised by relapsing pyrexia usually of several months' duration, neoarsphenamine is curative after one or at most two injections. In veterinary medicine it has become a very important specific remedy for *contagious disease of the lungs in horses.*

The organic arsenicals have also been tried in diseases in which protozoa are not known to play any part. It has been found that large intravenous injections may save animals from an otherwise fatal *anthrax infection.* Accounts are given of favourable effects on *chorea* and *anæmia.* It is obvious that in these cases the ordinary arsenic treatment will first be tried.

Externally, neoarsphenamine is used for painting the throat in Vincent's angina. The ulcers are cured as a rule in 3 or 4 days.

In a disease so protracted and so irregular in its course as **syphilis** no reliable judgment as to the value of a remedy can be pronounced without a long and close acquaintance with the subsequent fate of the persons treated. The results obtained up to the present are that in the majority of cases of primary, secondary and tertiary syphilis and in malignant syphilis, arsenobenzol and its more recent derivatives have a powerful action which is much more rapid than that of mercury and iodide. The primary affections, with their abundance of spirochætes, and condylomata, are free from parasites in the course of 1 or 2 days, and healing takes place with astonishing rapidity. Complete destruction of the parasites, however, is much more difficult to obtain in syphilis than in relapsing fever and frambœsia, as the relapses show. This is especially the case in the later stages of the disease, where the parasites, like the bacilli in tuberculosis, must either be encapsuled or lie in foci with poor blood-supply and therefore relatively inaccessible. At the commencement of the disease, the conditions are far more favourable. Many cases have been described in which a few intravenous injections immediately after the appearance of the hard chancre have resulted in a complete cure, a fact which can hardly be doubted since numbers of such patients have been under observation for years, and reinfection has frequently been described. Experienced clinicians reckon that in at least 90 per cent. of cases constitutional syphilis is prevented when the treatment is begun early enough and is carried out correctly. Among other things, the Wassermann reaction is a valuable guide to the patient's progress while under treatment (see also Preparations and Doses).

Noguchi and Akotsu transferred pure cultures of *Spirochæta pallida* every 14 days to a new medium which contained increasing concentrations of arsenobenzol, and found that they gradually acquired five times their original resistance to the drug. Applied to therapeutics, this means that primary syphilis, in which the reactions mentioned below need not be considered, should be treated with large doses. It is not improbable that in the employment of small but repeated doses there is a risk of producing the arsenic-resistant races feared by Ehrlich (*cf.* p. 449). Even if the resistance should be only temporary, valuable time is lost.

Neoarsphenamine is thus especially indicated in primary syphilis. It is also of great value in the later stages, but its use is not without danger on account of the reactions (see later) that may occur when the body is inundated with spirochætes or specific products of disease. In the metasyphilitic diseases, tabes and

general paralysis, the effect of neoarsphenamine often seems slight, but a trial may be made. A sufficiently long treatment during pregnancy, and better still also before conception, ensures, in the majority of cases, a healthy offspring, whereas with syphilitic mothers not under treatment, whether the disease is latent or manifest, an infection or mortality in early infancy of 80 per cent. must be expected.

Secondary Effects and Contra-Indications. Neoarsphenamine is now almost exclusively employed intravenously, care being taken that none of the solution leaks into the surrounding tissues where it might result in painful sloughing. For subcutaneous or intramuscular injection sulpharsphenamine is used. Intravenous injection is also not without disagreeable consequences, but, assuming correct procedure and the employment of freshly-distilled water, these are slight. Sometimes soon after the injection diarrhœa, nausea, indisposition, and slight rigors may occur, and in nearly every case the blood-pressure sinks a little and the pulse becomes quick and rather irregular. Vaso-motor effects sometimes occur, shown by congestion in the face, œdema of the lips and eyelids, and cough (œdema of the larynx). These symptoms last only for a few minutes. Pyrexia is often observed, either immediately after the injection or some hours later. Greater increase of temperature seems especially to occur in cases in which the Wassermann reaction is positive, and where spirochætes or their products occur in great abundance, and probably has the same origin as the analogous symptoms in relapsing fever (p. 454). A rise in temperature may also occur some days after the injection.

Skin reactions are seen immediately after injections of organic arsenicals, even more frequently than after treatment with mercury. Formerly-existing exanthemata may reappear, or maculous or papular eruptions may occur (the Herxheimer reaction). The urticaria, herpes and polymorphous erythema, which recall the cutaneous symptoms in arsenic poisoning, are of a different nature and far less frequently seen. They must be regarded as toxic exanthemata, perhaps not produced by the arsenic compound itself, but by the products of its decomposition. Various other secondary effects should be regarded as due to the disease. Such are jaundice in syphilis of the liver, epileptiform convulsions in syphilis of the brain, and neuritis which principally affects the optic, auditory and facial nerves. These were at first taken to be toxic effects of arsenic, but this interpretation has been abandoned since it was found that they can be cured by further injections of that drug, or by persistent treatment with mercury.

Formerly, the salvarsan treatment was not devoid of danger, but this has been almost entirely eliminated with increasing experience and the discovery of less toxic preparations. The majority of the deaths that occurred appear to have been due to specific reaction in vital organs analogous with the Herxheimer reaction on the skin. This also explains why the treatment may be regarded as almost free from danger in the first stage of the disease, before the entire organism has become infected.

Several deaths have been due, however (especially when arsenobenzol was first employed and the doses were larger than now), to drug poisoning, although it is not known whether the blame lay with the arsenobenzol molecule or with the products of its decomposition. After intravenous injections animals die with dyspnœa and convulsions; the dose fatal to rabbits is about 20 centigrammes per kilogramme of body-weight. Examination reveals nephritis, inflammation of the gastro-intestinal tract, hæmorrhagic inflammation of the large intestine, and œdema and hæmorrhage in the brain. In man the same parts are affected by the poison. The greatest danger lies in the action on the central nervous system. A few days after the injection vomiting begins, consciousness becomes clouded, the pupil does not react, and finally convulsions and coma supervene, followed by death. Lumbar puncture shows increased cerebrospinal pressure, and the *post-mortem* œdema and hæmorrhage in the brain. Attempts have been made to connect this affection of the brain also with the syphilitic process, and it has been interpreted as a Herxheimer reaction that was particularly dangerous because of the importance of the organ. The analogous conditions in animals, however, rather indicate the purely toxic nature of this group of symptoms. The *treatment* consists in the persistent employment of intravenous injections of adrenaline. According to Milian, this has several times saved apparently hopeless cases.

Contra-indications are given by all conditions of great weakness, advanced age, degeneration of the central nervous system, serious diseases of the circulation (vascular degeneration, aneurysm, heart-disease), severe albuminuria, fœtid bronchitis, advanced pulmonary tuberculosis, gastric ulcer, non-syphilitic dyscrasia such as untreated diabetes, and chronic intoxications, *e.g.* alcoholism. Pregnancy has been named as a contra-indication, but quite wrongly; the regular course of pregnancy is not disturbed, and the treatment, as already stated, is of decided significance to the fœtus.

Fate in the Body and Excretion. Arsenobenzol derivatives pass in part through the body unchanged, appearing in the urine from 5 to 30 minutes after intravenous or intramuscular injection, and in part are converted into unknown compounds. Most of the drug is excreted in the course of the first week, the remainder leaving the body more slowly, so that the urine gives an arsenic reaction for several weeks.

Dosage in Syphilis. Innumerable schemes have been devised

for the treatment of syphilis, using the organic arsenicals either alone or in combination with bismuth preparations. The following is an example of one of these and it has the virtue of being comparatively simple. A *course* of treatment means—

(*a*) Ten weekly injections of Neoarsphenamine (N.A.P.); doses increasing from 0·45 gramme to 0·75 gramme. Total, 6 grammes.

(*b*) Ten weekly injections of Bismuth; doses 0·3 or 0·4 gramme. Total, 3 or 4 grammes.

Standard Courses. (*a*) Primary syphilis with negative Wassermann reaction: Two courses of treatment; two months' interval between them, during which potassium iodide is given (gr. 10 thrice daily).

(*b*) Primary syphilis with positive Wassermann reaction: At least a third course; further courses if Wassermann reaction remains positive at the end of the first course.

(*c*) Secondary syphilis: As in (*b*).

(*d*) Tertiary syphilis: Number of courses depends on clinical condition and the Wassermann reaction tested periodically. Iodides are given from the beginning. In the presence of tertiary lesions of the central nervous system and/or cardiovascular system smaller doses of N.A.P. are given, but these are administered more frequently, *e.g.* twice weekly.

A patient is not to be regarded as cured until the Wassermann has remained persistently negative for two years.

The precursor of **arsenobenzol** sodium arsanilate or **atoxyl**, has a specific action both in syphilis and sleeping-sickness, but is a two-edged weapon, since it causes serious poisoning (gastro-intestinal symptoms, general weakness and drowsiness, cardiac irregularities, retention of urine, deafness, and above all, weakness of vision, or even optic atrophy and blindness). The large doses recommended for syphilis are therefore far too risky. Atoxyl is still employed for sleeping-sickness.

Among other organic preparations, **Cacodylic Acid**, $(CH_3)_2AsOOH$, has some claim to interest, having been warmly recommended by French clinicians, especially in tuberculosis, because large doses of arsenic can be given without danger in this form. It would appear that the intact cacodylic acid molecule, or its ion, $(CH_3)_2AsO_2$, is not poisonous, but that in the body it is to some extent oxidised to arsenic or arsenic acid, which acts in the usual way. How much, however, of the absorbed cacodylic acid passes through the body without being decomposed, and how much is oxidised, is not known. Heffter found varying conditions of the urine in psoriasis patients who had been treated with sodium cacodylate. Until, therefore, its superiority has been proved clinically, it seems better to keep to arsenic, which can be given in exact doses. Another drawback is that when given internally (not hypodermically), cacodylic acid, which when pure is odourless, is partially reduced to cacodyle oxide, $(CH_3)_4As_2O$, and perhaps even to cacodyle, $(CH_3)_4As_2$, which is excreted through the lungs and imparts a penetrating and very offensive odour to the breath.

Preparations and Doses

Arseni Trioxidum (B.P., U.S.P.), As_2O_3, arsenious (or arsenous) acid arsenic trioxide, arsenic, white arsenic, ratsbane, forms white, glassy or porcelain-like pieces, or a white powder, sparingly soluble in water, easily soluble in alkalies. *Dose*, 1—5 milligrms., $\frac{1}{64}$—$\frac{1}{12}$ gr. (B.P.); 0·002 grm., $\frac{1}{30}$ gr. (U.S.P.). Generally given as Fowler's solution, or in pills containing 1 milligrm. (Granula Dioscoridis). A dosage often used to begin with is, 3 milligrms. a day, increasing with 1 milligrm. every 3rd day until it reaches 15 milligrms. a day, which is continued for a few weeks. In lichen ruber it is often necessary to go to daily doses of 30 milligrms. Hebra gave, for psoriasis, 72 milligrms. a day for several months without eliciting toxic symptoms.

Liquor Acidi Arsenosi (U.S.P.), contains 1 per cent. of arsenious acid and a little hydrochloric acid. *Dose*, 0·2 mil, 3 mins.

Liquor Arsenicalis (B.P.), **Liquor Potassii Arsenitis** (U.S.P.), Fowler's solution, contains 1 per cent. of arsenious acid. It is prepared by dissolving arsenic trioxide in a solution of potassium hydroxide, diluting with water, and rendering neutral to litmus with dilute hydrochloric acid. *Dose*, 12—50 centimils, 2—8 mins. (B.P.); 0·2 mil, 3 mins. (U.S.P.). A much-used preparation. Like all arsenic preparations, taken after meals.

Arseni Triiodum (B.P.), *Arsenii Triiodum* (U.S.P.), arsenious iodide, AsI_3. Orange-red crystals or powder, soluble in about 12 parts of water. *Dose*, 4—16 milligrms., $\frac{1}{16}$—$\frac{1}{4}$ gr. (B.P.); 0·005 grm., $\frac{1}{12}$ gr. (U.S.P.).

Liquor Arsenii et Hydrargyri Iodidi (B.P.), Donovan's solution. 1 per cent. solution of arsenic triiodide and 1 per cent. of red mercuric iodide. *Dose*, 0·3—1 mil, 5—15 mins.

Sodii Cacodylas (U.S.P.), $Na(CH_3)_2AsO_2$, sodium cacodylate, a white powder or crystals, very soluble in water. *Dose*, 0·06 grm., 1 gr. May be increased to 0·3—0·4 grm. daily. For subcutaneous injection, half these doses.

Arsphenamina (U.S.P.) (for formula, see p. 453), a pale yellow powder, soluble in water, supplied in glass tubes containing 10—90 centigrms., the free space being filled with an inert gas. Oxidises on exposure to the air, turning brown and becoming much more poisonous; only freshly-opened tubes, therefore, should be used, and any that remains be thrown away. Given intravenously in an alkaline solution diluted with 0·5 per cent. of saline solution. With regard to the administration—which must above all be strictly antiseptic, the water being freshly distilled and sterilised—and the preparation of the solution, the reader is referred to the special literature and the instructions accompanying each tube. *Dose*, by intravenous injection, 0·4 grm., 10 grs.

Neoarsphenamina (B.P., U.S.P.), Novarsenobenzol. A dry yellow powder, odourless, soluble in water, neutral or slightly alkaline. Distributed in hermetically sealed glass phials from which the air has been evacuated or replaced by an inert gas. Should not be used if it becomes dark in colour. Prepared for injection by dissolving the contents of a phial in the requisite amount of sterilised water. Contains approximately 20 per cent. of arsenic. *Dose*, by intravenous injection, 0·15—0·9 grm., $2\frac{1}{2}$—14 grs. (B.P.); 0·6 grm., 10 grs. (U.S.P.).

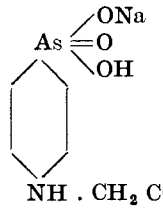
Sulpharsphenamina (B.P.), Sulpharsenobenzene. A yellow powder,

not hygroscopic, no odour, soluble in water. Kept, etc., as with neo-arsphenamine. Contains approximately 20 per cent. arsenic.

Silver Salvarsan Sodium, silver arsphenamine sodium, a brown powder, readily soluble in water, with neutral reaction. This preparation, which contains only $\frac{2}{3}$ as much arsenic as salvarsan, has proved itself effective. The treatment is begun with intravenous injections of 10 centigrms., and increased at intervals of not less than 4 days to a maximum dose of 20 centigrms. for women, and 25 centigrms. for men. The condition for giving the larger doses is that the smaller are tolerated well. With enfeebled persons, begin with 5 centigrms.

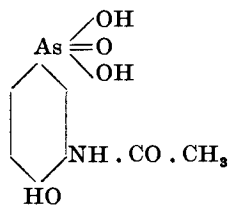
Atoxylum, $NH_2.C_6H_4.AsO_3HNa + 4H_2O$, sodium arsanilate, a white powder, soluble in 6 parts of water. Subcutaneously, 4—20 centigrms., $\frac{2}{3}$—3 grs., of a 10 per cent. solution. There must be an interval of at least 2 days between the injections. Of historic interest only; its use has been abandoned on account of the danger of optic atrophy. The English preparation, *Soamin*, is closely allied to atoxyl.

Tryparsamidum (B.P., U.S.P.), colourless, crystalline powder, odourless, soluble in water, insoluble in alcohol. Contains approximately 25 per cent. of arsenic. Particularly suitable for the treatment of sleeping-sickness; early administration is often curative. In neuro-syphilis, *e.g.* general paralysis and some cases of tabes dorsalis, it is of more value than other organic arsenicals. It has been tried in disseminated sclerosis apparently with some success. Blindness occasionally results from the administration of tryparsamide. This complication is usually temporary, but may be permanent. *Dose*, by subcutaneous, intramuscular or intravenous injection, 1—2 grms., 15—30 grs. (B.P.); 2 grms., 30 grs. (U.S.P.).



Tryparsamide
(sodium phenyl glycinamide arsonate)

Acetarsol (B.P.), Acetarsone. A white crystalline powder, insoluble in cold water, moderately soluble in boiling water. *Dose*, 0·06—0·25 grm., 1—4 grs. Clinical value not definitely established; effective doses liable to produce signs of arsenical poisoning (one-sixth of patients). More suitable for use in amœbic dysentery and in lamblia infection. It is also of value in Vincent's angina and in yaws. Oral route of administration an advantage. Contains approximately 27 per cent. of arsenic.



Acetarsol
(acetylaminohydroxyphenyl arsonic acid)

Carbarsone, 4-carbaminophenyl-arsonic acid is one of the more recent substitutes for acetarsone in the treatment of amœbic dysentery. It is said to be a more potent parasiticide than acetarsone and at the same time much less toxic. Carbarsone is a white powder, almost insoluble in water. It is administered in capsules in doses of 4 grs. twice daily for about 10 days. The drug is also administered as an enema (200 mils of 1 per cent. strength in 2 per cent. sodium bicarbonate solution). Five such enemata are given in one course of treatment, *i.e.* one on alternate days for 10 days. When an enema of carbarsone is given the oral dose of the drug is omitted.

3. BISMUTH

The therapeutic importance possessed by the bismuth compounds is, in part, due to their **local action.** One of the most important compounds, the basic subnitrate, *Bismuthi Subnitras* (U.S.P.), has an astringent and antiseptic action upon raw surfaces and mucous membranes, partly because minute amounts are dissolved in the secretion, partly in a purely mechanical way by the adsorbent action of the fine powder (*cf.* animal charcoal, p. 438). In the intestine it neutralises the alkaline and hydrogen sulphides which produce peristalsis.

When bismuth subnitrate is shaken up with water, a slight hydrolytic decomposition takes place, and the water acquires a feebly acid reaction. Free acid detracts from this decomposition, so that at an acidity corresponding with that of the gastric juice it quite ceases, the acidity remaining unchanged. Above this limit bismuth fixes acids, but only to a very small extent. Even with an acidity of 0·5 or 0·6 per cent., only about 10 per cent. of the free acid is fixed. The reputation that the subnitrate enjoys of being an antacid for counteracting hyperacidity is thus undeserved and probably comes from its often being given with bicarbonate of soda.

Specific Action. Considerable absorption may take place from fresh—not granulating—wound-surfaces, and serious poisoning has often been seen after incautious use, such as on large burns. The symptoms, which are very similar to those of sub-acute mercury poisoning, consist in a dark line, resembling the lead line, on the gums, salivation, loosening of the teeth, ulcerative stomatitis, diarrhœa, and finally nephritis. As a rule the prognosis is favourable if the drug is quickly removed from the sore, but the issue has sometimes been fatal. In a case described by Kocher, death occurred after 2 weeks' illness, and the *post-mortem* showed the walls of the entire intestinal canal, especially of the large intestine, to be stained black with bismuth sulphide.

These symptoms occurring in man are due to the gradual absorption of the metal, and thus represent a sub-acute or chronic poisoning. In mammals which are given subcutaneously a large amount of a soluble bismuth salt, the effect is different from the beginning. The medulla oblongata is first affected, and symptoms of stimulation appear (periodical convulsions, rapid respiration, vomiting), which are soon followed by motor paralysis and incoördination, fall of blood-pressure and respiratory weakness. If the animal does not die in the course of a few hours under these symptoms, the action on other organs slowly appears, and the condition becomes analogous to that of the poisoning in man, with nephritis and affections of the mouth and the large intestine, where there is ulceration and necrosis.

Taken internally, only a minute amount of bismuth, if any, is absorbed through the gastro-intestinal mucous membrane; this is shown by the fact that poisoning from the internal use of the subnitrate is of very rare occurrence. Traces of the metal have been demonstrated in the urine, but usually the whole of it leaves the body with the fæces, which are coloured black by bismuth sulphide. The sulphide may form crystals that have all the appearance of hematin crystals.

The above remarks refer only to the usual medicinal doses. After the far larger quantities used some time ago for X-ray examination of stomach and intestine, very serious cases of poisoning were several times seen. Here, however, the acid, not the metal, was to blame, for the symptoms (cyanosis and collapse) were the same as those after large doses of amyl nitrite or other nitrites, and arose from the reduction of the bismuth nitrate to nitrite by certain bacteria that are sometimes present in the intestine. For diagnostic purposes, therefore, the carbonate or oxychloride are preferable to the subnitrate, but in recent years barium sulphate has been employed almost exclusively in radiography. Bismuth carbonate is a very fine white powder which exerts a protective and sedative action upon the skin and mucous membranes. Taken internally, it is a very weak antacid, but it is mainly valuable for its mechanical effects. Bismuth oxychloride and bismuth salicylate are both inert in the stomach and act simply as gastric sedatives. In the intestine the sedative action of the bismuth salts continues, but in the case of the salicylate partial decomposition occurs, yielding salicylic acid which is an antiseptic.

Therapeutic Uses. The insoluble *Bismuthi Carbonas* and *Bismuthi Oxychloridum* are included in dusting-powders on account of their protective and sedative actions on the skin. The oxychloride is also frequently prescribed with starch and zinc oxide in bland ointment bases, *e.g.* benzoinated lard and wool-fat. These preparations are used extensively by dermatologists and as cosmetics by the lay public. Bismuth subnitrate is a very valuable drug in the treatment of *gastric ulcer*. Its beneficial action is to be found in its astringent property and in its being held (as experiments on animals with artificial gastric ulcer show) in the wound and forming a protective covering. It should be given in large doses and on an empty stomach; if the site of the ulcer can be to some extent determined, the patient, after taking the powder, should lie in such a position as will allow it to fall upon the desired spot. The subnitrate is further employed in acute and chronic *diarrhœa* and in *ulcerative affections of the intestine*. Externally it is used as a dry antiseptic, especially for

burns; but it is not altogether an innocent drug, as absorption and poisoning, as mentioned above, have often been observed. It should, therefore, be used with caution. Latterly, the subnitrate has fallen somewhat into disfavour and the carbonate, salicylate and oxychloride of bismuth are more commonly employed as gastro-intestinal sedatives in ulceration and inflammation of the alimentary tract. These salts are often prescribed along with antacids such as magnesia, chalk and sodium bicarbonate, or combined with opium which intensifies the astringent and sedative effects.

The last few years have brought a flood of new bismuth preparations of which the purpose is to unite with the astringent properties of bismuth the antiseptic action of various benzol derivatives. The most important of these preparations are the *subsalicylate* and the *subcarbonate*, the *subgallate*, and the *tribromphenolate*. The action of the first two is in all essentials the same as that of the subnitrate, and they are used for *diarrhœa*. The subgallate (dermatol) is employed for *sores* and *skin-diseases*. It is highly desiccating and but slightly irritant, but is not suitable for foul or profusely-secreting sores, as it forms with the secretion a hard crust which prevents the escape of the pus. The tribromphenolate (xeroform) is, perhaps, the best of all the substitutes for iodoform, and is largely used in the dry treatment of sores as an almost odourless, desiccating and non-poisonous antiseptic.

The introduction of bismuth in the treatment of syphilis was the result of work by Sazerac and Levaditi, who stated (1921) that they had discovered an efficacious anti-syphilitic remedy in sodium potassium bismuth tartrate. It is now established that the manifestations in all three stages of the disease are quickly brought under control: the chancre, roseola, plaques and gummata disappear, as also the spirochætes. With regard to the relative merits of the antisyphilitic metals, it would appear that bismuth occupies an intermediate position between mercury and arsenic, being more efficacious and less toxic than mercury but less potent than the organic arsenicals. It should especially be noted that a longer time elapses before the Wassermann reaction becomes negative. Hence it follows that bismuth is not the ideal remedy for the treatment of primary syphilis. The best results are obtained by a combination of intravenous injections of the organic arsenicals and intramuscular injections of bismuth preparations (see p. 458). Thus bismuth serves to produce a relatively mild but sustained antispecific action. The combined treatment is now a matter of routine for primary and secondary syphilis. In tertiary syphilis, where the ordinary doses of organic arsenic may be contra-indicated, intramuscular injections of

bismuth are of special value. Many preparations have been proposed including suspensions of metallic bismuth in 5 per cent. aqueous solution of dextrose, and oily suspensions of certain bismuth salts, *e.g.* the salicylate, oxychloride and hydroxide. Intramuscular injections of the metal in isotonic dextrose are the least painful of all the preparations.

Among the effects of over-dosage may be mentioned a greyish discolouration of the gums (precipitation of bismuth sulphide) resembling the blue line of lead-poisoning, more rarely stomatitis, and sometimes temporary albuminuria.

Preparations and Doses

Bismuthi Subnitras (U.S.P.), bismuth, subnitrate or oxynitrate, white bismuth, Magisterium Bismuthi, a white, odourless, and almost tasteless powder, insoluble in water. Like the basic salts below, its composition is of a varying character. *Dose*, 1 grm., 15 grs. For gastric ulcer, ½—1 teaspoonful finely divided and suspended in water, 3 times a day on an empty stomach; for diarrhœa, 1—2 grms. or larger doses, often with opium. For infants, 20—30 centigrms. 3 times a day. Bismuth subnitrate is an ingredient in *Pasta Bismuthi et Iodoformi* (B.P.C.). This compound is mentioned on p. 420.

Bismuthi Carbonas (B.P.), bismuth carbonate, bismuth oxycarbonate. A basic salt of varying composition. A white or creamy white powder, insoluble in water. *Dose*, 0·6—2 grms., 10—30 grs.

Bismuthi Salicylas (B.P.), bismuth salicylate, a basic salt of varying composition. A white or nearly white powder, insoluble in water. *Dose*, 0·6—2 grms., 10—30 grs.

Trochiscus Bismuthi Compositus (B.P.), contains 0·15 grm. of bismuth carbonate, together with the magnesium and calcium carbonates.

Magma Bismuthi (N.F.), milk of bismuth, a thick white liquid containing bismuth hydroxide and bismuth carbonate in suspension in water. *Dose*, 4 mils, 1 fl. dr.

Bismuthi Subcarbonas (U.S.P.) and **Bismuthi Subsalicylas** (U.S.P.) are basic preparations with physical properties similar to those of bismuth subnitrate. They are used in doses of 1 grm. (15 grs.) as gastro-intestinal sedatives and are *preferable to the subnitrate.*

Bismuthi Subgallas (U.S.P.), bismuth subgallate, dermatol, a yellow, odourless, insoluble powder. *Dose*, 0·5 grm., 8 grs. Internally, for diarrhœa in tuberculosis, typhoid fever, dysentery, etc. Externally, as a dusting-powder, either alone or mixed with starch or talc (1 to 5), as an ointment (1 to 5), or in collodion (1 to 10).

Bismuthi Tribromphenolas (not official), xeroform, a yellow powder, almost odourless. Externally, as a dusting-powder, xeroform gauze, etc.

Among other preparations may be mentioned *Bismuth dithiosalicylate* (thioform), used internally and externally as dermatol; *Bismuth oxyiodide gallate* (airol), an antiseptic dusting-powder; *Bismuth bitannate* (tannismuth), 0·5 grm. 3—5 times a day for diarrhœa; *Bismon*, colloid bismuth oxide, a yellow powder, readily soluble in water, used as an intestinal astringent for children, 1 teaspoonful of a 10 per cent. solution, 3 times a day.

The following preparations are used in the treatment of syphilis :—

Bismuthi Precipitatum (B.P.), precipitated bismuth, a dull grey powder, insoluble but easily diffusible in water. *Dose*, by intramuscular injection, 0·1—0·2 grm., 1½—3 grs.

Injectio Bismuthi (B.P.), 20 per cent. of precipitated bismuth, 5 per cent. of dextrose, ½ per cent. of cresol, in water. *Dose*, by intramuscular injection, 0·5—1 mil. 8—15 mins.

Injectio Bismuthi Salicylatis (B.P.), 10 per cent. of bismuth salicylate, 1 per cent. of camphor, 1 per cent. of phenol, in olive oil. *Dose*, by intramuscular injection, 0·6—1·2 mils, 10—20 mins.

Bismuthi Subsalicylas (U.S.P.). *Dose*, by intramuscular injection, 0·125 grm., 2 grs.

Bismuthi et Sodii Tartras (B.P.), sodium bismuthyl tartrate.

Bismuthi et Potassii Tartras (U.S.P.), potassium bismuthyl tartrate. Both are white powders darkening on exposure to light. Freely soluble in water. *Dose*, by intramuscular injection, 0·06—0·2 grm., 1—3 grs. (B.P.) ; 0·15 grm., 2½ grs. (U.S.P.).

Injectio Bismuthi Oxychloridi (B.P.), 10 per cent. of bismuth oxychloride, 5 per cent. dextrose, ½ per cent. phenol, in water. *Dose*, by intramuscular injection, 1—2 mils, 15—30 mins. The official dose of bismuth oxychloride for intramuscular injection is 0·1—0·2 grm., 1½—3 grs.

Non-official compounds for the treatment of syphilis include *Bicreol*, *Bismostab*, *Bisglucol*, and *Quinine Iodobismuthate*. *Bismarsen* (Bismuth Arsphenamine Sulphonate) incorporates two antisyphilitic remedies and is recommended in early cases.

4. MERCURY

Mercury and iron are the two most important metals in medicine, and mercury, on account of its healing action upon syphilis, is one of the most valuable and indispensable of all drugs.

Action. Mercury is a powerful *protoplasm poison*. Its great toxicity for **micro-organisms** is dependent on the Hg ions, and the soluble and dissociable compounds, such as corrosive sublimate, exert the typical mercurial action.

The growth of most micro-organisms is arrested by corrosive sublimate solutions of 1 in 30,000—20,000, while solutions of 1 in 2,000 or 1 in 1,000 definitely destroy them. It has been stated, however, that tubercle bacilli are still alive after 24 hours in a $\frac{1}{10}$ per cent. solution. The cholera bacillus is one of the micro-organisms which is most easily overcome ; its growth is distinctly retarded in a solution of 1 in 1,000,000, and ceases when the concentration reaches 1 in 300,000. The activity of mercury salts is inhibited by all substances that fix Hg, and is therefore weaker on wound-surfaces, where the mercury is fixed by albumin.

Of the mercurial compounds, corrosive sublimate is the most toxic to the cells of higher organisms. Even the weak solutions

employed in surgery often cause irritation of the **skin** ("corrosive sublimate eczema"), and greater concentrations—1—5 per cent., in ointments, liniments, or poultices—produce in a few hours inflammation and vesicles on the unbroken skin, and, on places where there is no epidermis, deep sores with necrosis. The frequently-employed hypodermic injections of a 1 per cent. solution are painful and precipitate albumin locally. Even metallic mercury, when it comes into close contact with the skin in a finely-divided condition, may cause inflammation, and when injected into the tissues, abscesses.

Mucous membranes are extraordinarily sensitive to dissociable mercurial salts. Taken internally, corrosive sublimate is one of the strongest caustic poisons, especially in an empty stomach, where it finds only the albumin of the mucous membrane. If the contents of the stomach are abundant, the metal combines with them, and the local action is moderated. Clinically, the symptoms exactly resemble those of poisoning with concentrated mineral acids (pain, vomiting, the vomit containing blood, and collapse), and in the most rapid cases death is mainly due to the corrosion. If the latter does not kill within 24 hours, there is also absorption and general poisoning, the symptoms of which will be mentioned later. The smallest fatal dose is said to be 0·18 gramme. After corrosive sublimate come the other mercury compounds in a descending series. The local action is weakened with decreasing solubility and dissociation, all grades being represented down to calomel, which can be introduced into the eye without injury to the tender epithelium. The action is not dependent, however, only upon the nature of the compound itself, but also upon that of the seat of application. Calomel, for instance, is quickly converted in the intestine into compounds that are sufficiently irritant to elicit peristalsis.

Specific Action. The small therapeutic doses, that exert a powerful influence upon the syphilitic organism, generally pass through the healthy body without leaving any apparent traces. The only effect of the continued use of small quantities of mercury, apart from a rather variable diuresis, is an increase in the number of red blood-corpuscles and in the body-weight, which was first noted by Ligeois in healthy men, and afterwards by Schlesinger in animals. No satisfactory explanation of this remarkable discovery has been given. It may be due to inhibited oxidation, which explains the fat-deposit observed in animals, or to stimulation, resulting in increased formation of blood and fat similar to that caused by phosphorus and arsenic. Perhaps analogous to these actions is the fact that corrosive sublimate, which is exceedingly poisonous to yeast-cells, pro-

motes fermentation in minimal quantities, and infinitesimal amounts of mercury (1 in 500,000 and less) improve the working of the excised heart of a frog. The interpretation of this may be that mercury first stimulates protoplasm to increased activity, just as very dilute solutions of quinine first stimulate the movements of amœbæ (see p. 214).

Large single doses of mercury, or the continued use of moderate quantities, produce **poisoning.** Such cases may be grouped for clearness under three heads: (1) acute, (2) sub-acute, and (3) chronic mercurial poisoning.

1. *Acute poisoning* often ends fatally; it is due to the absorption of large quantities of mercury in a short time. Sometimes the sudden absorption of insoluble preparations injected intramuscularly or the incautious employment of corrosive sublimate in operations and in washing out the uterus may be the cause. The specific action affects the *large intestine* and the *kidneys.* Two or three days after administration, and occasionally only a few hours after, the abdomen becomes distended, tender and very painful; incessant straining and diarrhœa then appear, the evacuations being first fæculent, then mingled with blood and fragments of mucous membrane. At the same time, or a little later, the urine becomes scanty, and contains albumin, blood-corpuscles and renal epithelium, or its secretion may cease. These symptoms are accompanied by a small, thread-like pulse, weak, irregular respiration, fall of temperature, and all other signs of collapse; and after a few days the patient dies from exhaustion and heart-paralysis, or, after two or three weeks, from renal disease. *Post-mortem* examination shows inflammation of the cæcum and colon, with ulcerations, parenchymatous nephritis, and very often the so-called lime-infarcts, *i.e.* white deposits of phosphate and carbonate of lime in epithelial cells and renal tubules, which may be completely blocked.

2. The *sub-acute*, " therapeutic " *poisoning* is due to the accumulation of mercury in the organism, the reason of this being that the excretion of the metal does not keep pace with its absorption. It is caused more easily by metallic mercury and calomel than by soluble compounds. The principal symptom is *mercurial stomatitis.* The first indications are a disagreeable metallic taste, often appearing immediately, and not necessarily indicative of poisoning, fœtor of the breath, swelling and injection of the points of the gums; the teeth become loose and tender, the mouth is moister than usual, and the saliva is viscid. In the present day it is very unusual to see more than this initial stage, for the drug is then discontinued, and in a few days the symptoms subside. If the poisoning proceeds further *mercurial ptyalism* sets in. The

gums, the tongue—on the sides of which are deep impressions from the teeth—the tonsils, and the entire oral mucous membrane, become swollen, and a profuse secretion flows from all the salivary and mucous glands, sometimes amounting to from 2 to 5 litres in 24 hours. In still more pronounced cases, gangrene and deep sores appear in the mucous membrane, with periostitis, necrosis of the alveolar border, and loss of teeth. In olden days, when the belief prevailed that in order to cure syphilis mercury must be employed to the point of "thorough salivation," these terrible effects, which now no longer occur, might result in death from starvation, weakness and septicæmia. *Affection of the intestine* is less frequent in sub-acute poisoning, and accompanies as a rule only the more serious cases. The kidneys may also be affected in the same way as in acute poisoning, but in a slighter degree.

Very rarely skin-affections of various kinds are seen—urticaria, eczema, widespread erythema, roseola, loss of hair. These generally disappear in 2 or 3 weeks, but may remain for months.

3. *Chronic poisoning* occurs through prolonged absorption of very small amounts of mercury, and is especially seen in those who work with the metal year after year in mines, smelting-works, looking-glass factories, etc. Effects on the *central nervous system* are the most prominent in this form of poisoning. The most characteristic symptoms are *erethismus mercurialis*—a peculiar psychic irritability expressing itself in restlessness and anxiety, sleeplessness, embarrassment and helplessness, unreasoning outbreaks of anger, and other symptoms of disturbed mental balance —and *mercurial tremor*, which, at first, is only seen on movement, but may pass into a chorea-like condition or violent convulsions. There are also many other symptoms, such as paresis, all kinds of anomalies of sensibility, psychic depression (mercurial hypochondria), attacks of giddiness in which the patient falls to the ground (mercurial epilepsy), digestive disorders, prolonged diarrhœa, and now and then affections of the mouth. All this at last produces a state of weakness which seems to offer favourable conditions for the tubercle bacillus, for tuberculosis of the lungs is often the ultimate cause of death.

Regarding the *effect* of mercury *upon various organs and functions*, it may be added that the changes in the **alimentary tract** are found almost exclusively in the mouth and the large intestine, while the stomach and the small intestine escape almost entirely. This definite localisation may be attributable to several circumstances. The most important reason is to be found in the fact that the mercury is excreted in both the large intestine and the oral cavity, acting as a protoplasm poison to the cells, and making the mucous membrane very vulnerable. Septic processes also

play an important part, being most pronounced in the large intestine and in the teeth, where particles of food easily lodge. The mouth affection can be prevented merely by cleanliness, and is rarely seen in toothless subjects. The ultimate cause of lesions of the mucous membrane is probably the mechanical injury to which the mouth, during mastication, and the large intestine, during the passage of solid fæces, are subjected.

The salivation is to some extent reflex, produced by the inflammation of the mucous membrane. It may also be profuse even though there is no great stomatitis, in which case it must be that the excreted metal in the glands stimulates the secreting cells or the secretory nerves. In some cases the abundant secretion is diminished by atropine, a fact which points to nerve stimulation.

Large doses of finely-divided metallic mercury or its insoluble compounds have a **purgative** action. This property, of which much use is made in medicine, and which is quite distinct from the specific toxic diarrhœa, is due to the formation of soluble, locally irritant compounds in the intestine.

On account of the green colour that the fæces often acquire after calomel, this drug has been supposed to be a cholagogue. Recent experiments, however, on man and dogs with biliary fistulæ have not shown any increase in the amount of bile. The colour may perhaps be due to the antiseptic action of mercury, which preserves the green bile-pigment, or possibly to the mercuric sulphide formed in the intestine. The decrease in the intestinal putrefaction is apparent from the diminished excretion of inorganic sulphate in the urine.

In fairly large doses calomel causes **diuresis,** but in an exceedingly capricious and irregular way, of which more will be said later. The nature of the action has not been definitely explained. It has been already said that in acute mercurial poisoning the kidneys are the seat of parenchymatous inflammation. In slight cases of poisoning with mercury and many other heavy metals, albuminuria appears.

The **circulation** is not generally affected by mercury. Only in the most acute cases of poisoning does the character of the pulse indicate cardiac failure; fatty degeneration has been demonstrated in such cases. In animals, injection of soluble salts of mercury into the blood causes a sudden, great fall of blood-pressure, which is mainly due to cardiac depression, but also in part to vascular paralysis.

Little is known of the effect on **metabolism.** In one case of syphilis the nitrogenous elimination was neither increased nor diminished during a course of inunction that was continued to

the point of salivation. In poisoning with corrosive sublimate, sugar is often found in the urine, and the glycogen of the liver disappears.

Absorption, Distribution and Excretion. In gaseous form, or in finely-divided particles, *metallic mercury* is very readily absorbed from all sites of application (skin, lungs, intestinal canal, subcutaneous tissue). In its ordinary fluid form, on the contrary, as shown by the old treatment of ileus with large internal doses of mercury, it is absorbed so slowly from the intestine that poisoning seldom occurs. The *insoluble salts* are absorbed from the intestinal canal, but not very quickly. Calomel has therefore a specific action in repeated small doses, but not in a single large dose, which has a purgative action, in which the calomel is evacuated in the course of a few hours. In the subcutaneous tissue and the muscles, the absorption of the metal and the insoluble compounds takes place without any regularity, now quickly, now slowly. The *soluble compounds* pass more or less rapidly into the circulation, but do not penetrate the healthy skin. All mercurial compounds, as they are absorbed, undergo the same chemical change ; they form compounds with albumin, which are soluble in excess of albumin and sodium chloride, or double salts of mercuric albuminate and common salt. In the form of these compounds the mercury circulates and distributes itself in the body, regardless of the form and site of its application, always in the same way. The greatest amount is deposited in the kidneys, the next greatest in the liver, and, finally, minute quantities in all the other organs. The greater part is excreted with the fæces, less in the urine, and a little in all secretions and excretions. A period of from a few hours to two or three days elapses between the application or absorption of the mercury and its appearance in the urine.

After the ordinary syphilis treatments, the urine contains mercury for several months. It is difficult to determine when the elimination ceases, because towards the end of the time there are interruptions in the process, and for several days or weeks the urine may contain no mercury, and then once more for a time show a slight excretion. In cases in which the urine has been for some time free from mercury, the metal may once more be made to appear by a treatment that promotes excretion, *e.g.* hot baths. An accumulation thus takes place, by which the last remnants of the drug are retained for some time.

Therapeutic Uses. Mercury was formerly the sovereign remedy for **syphilis.** In the East it has been used as far back as history goes, and in Europe it became known as an antisyphilitic in the great syphilis epidemic about the year 1500. Its excessive

use and the frequent cases of poisoning soon called forth a reaction ; and even long after its employment had been re-established on more moderate lines, the drug still had many opponents, who declared that mercury aggravated the disease, or even asserted that constitutional syphilis was only mercurial poisoning. The dissension has long since ended in the recognition of mercury as a valuable drug in the treatment of syphilis.

The question which of late has attracted greatest interest is whether mercury is only a palliative drug or a specific in the sense of acting on the spirochætes themselves or their poison. It can hardly be doubted that the latter is the correct view, for it would be difficult to understand how a drug could cure, as mercury does in syphilis, the most heterogeneous symptoms of a disease except by acting on the common cause of all those symptoms. Another weighty argument in favour of the specific action is afforded by the results of various observations of the influence of the mercurial treatment on children of parents with latent syphilis. Such a child remains healthy if the mother has been treated with mercury, but falls a victim to congenital syphilis when the treatment has been neglected ; it is therefore obvious that the drug has acted upon the causal agent.

This view has led in the present day to a change in the employment of mercury. Formerly treatment was begun when the symptoms appeared, but nothing was done in the frequently long intervals during which there were no symptoms ; whereas now the *chronic-intermittent treatment* introduced by Fournier has become general. This treatment aims at the disease, not merely at the symptoms, its object being to keep the body under the influence of mercury for several years by regularly-repeated courses of medication. The infected person is syphilitic for several years, whether the symptoms show themselves or not, and must therefore also be treated with the specific remedy in the latent periods.

In practice the chronic-intermittent treatment is carried out by first prescribing frequent and thorough courses of medication, then less frequent and shorter courses on a definite plan, regardless of the presence or absence of symptoms. These are continued with diminishing intensity for 4 or 5 years. There is some difference of opinion as to the strictness to be maintained, and various rules have been laid down, for which the student is referred to special text-books. All that need be said here is that the Wassermann reaction is a valuable guide, especially in the later stages of the disease ; when positive, treatment is indicated and repeated until the reaction becomes negative. It must be remembered, however, that in patients who have been under

treatment for a long time there is not infrequently a slight positive reaction which obstinately withstands mercury, bismuth and arsenobenzol derivatives.

Regarding the much-disputed question as to when the treatment should be begun, it has now been definitely decided that it should not be put off until secondary symptoms appear, but be begun as soon as the hard chancre is diagnosed. This question is of less interest, however, now that the treatment of the primary state consists in intravenous injections of neoarsphenamine. With regard to the results of an immediate mercurial treatment, all that is at present known is that it delays the outbreak of secondary syphilis. It may possibly, in exceptional cases, entirely prevent constitutional symptoms. Since syphilis has become accessible to experimental therapeutics through the discovery of spirochætes and of the possibility of giving the disease to animals, efforts have been made in many quarters to produce with mercury, as has already been done with arsenic, less poisonous and more parasiticidal compounds with which an abortive treatment might be obtained ; but these attempts have not up to the present been successful.

There are many modes of employing mercury in syphilis :—

1. The *inunction treatment* consists in the daily rubbing of a certain amount of mercurial ointment into the skin of various parts of the body in regular order. The ordinary amount is 3—5 grammes a day for 20—40 days. Only in very serious cases, *e.g.* diseases of the eye, with threatened blindness, are larger amounts of 7—10 grammes a day tried.

The region of skin used may be varied as follows : 1st day, left leg ; 2nd day, right leg ; 3rd day, left arm ; 4th day, right arm ; 5th day, left side of chest and abdomen ; 6th day, right side of chest and abdomen ; 7th day, rest and hot bath. The ointment is irritant, and if the same part of the body is taken constantly, it quickly produces pustules and itching exanthema on the skin. The advantages of the inunction treatment consist in the thorough and lasting, but not dangerous, action and in the sparing of the stomach ; its drawbacks are that daily rubbing is troublesome and unpleasant, and that the quantity used is uncertain, as most of the mercury volatilises in the air. Mercury can be demonstrated in the urine after 24 hours, and is still present some months after the termination of the treatment. Absorption takes place partly by inspiration of the vapour of the mercury rubbed in, partly by the slow solution of the mercury that is pressed into the follicles of the skin. Some writers have attached most importance to the absorption through the lungs, and have looked upon the inunction mainly as an *inhalation*

treatment. This has resulted in a number of preparations intended only for the lungs, and worn in bags on the chest or back, whence the mercury vapour incessantly rises. According to an experiment made by Farup on himself, the absorption takes place rapidly, and the urine contains mercury even as long as 5 months after the termination of the treatment. The clinical results seem to show, however, that this treatment is less efficacious than inunction, and is only adapted for alternate use with other and more active methods.

2. *Internal Employment.* For internal use the protoxide compounds of mercury are preferably prescribed, because, being insoluble, they give less trouble to the digestion than the caustic oxide salts.

The internal treatment with mercury is convenient, but is considered to be less efficacious than inunction, and more often causes digestive disorders and diarrhœa.

3. For *injection* sometimes the soluble, sometimes the insoluble, mercurial compounds are employed. *Hypodermic injections of corrosive sublimate*, in particular, offer many advantages. Their employment is easy, the quantity can be accurately measured, the action begins soon, and salivation rarely occurs. Originally 1 centigramme of corrosive sublimate was administered daily for 20, 30 or 40 days, but now the dose is generally from 2 to 5 centigrammes at intervals of a few days. The great drawback to the injections is that they often cause great pain and infiltrations that are slow in disappearing (precipitation of albumin). The occurrence of the latter may be restricted, but not prevented, by the addition of common salt, which dissolves the metallic albuminate. A great many soluble compounds besides corrosive sublimate have been suggested, including mercuric oxycyanide, which is administered intramuscularly or intravenously (*cf.* p. 478).

The desire to ensure the prolonged retention of the metal in the organism has led to endeavours to replace the soluble compounds with *insoluble mercurial preparations* to be injected intramuscularly. For this purpose finely-divided mercury, calomel, mercuric salicylate, etc., are especially employed, in doses of 5—10 centigrammes once a week. Technically, this method represents a great advance, as the action is both rapid and powerful, and the cure is completed in about 6 weeks. Unfortunately there are several disadvantages to be set off against these advantages. The pain is often great, and abscesses may form ; but irregularity of absorption is the greatest drawback. In the early days of the method, cases of poisoning were of frequent occurrence. The explanation given was that the deposited stores of insoluble compounds were encapsuled and subsequently, for reasons unknown,

suddenly absorbed. This is now avoided by more careful dosage and interruption of the treatment if hard infiltrations are formed after the first few injections.

Corrosive sublimate is now less used as an **antiseptic** than formerly. On wound-surfaces its efficacy is weakened by the partial precipitation of the metal as an albuminate; and its affinity for albumin has also a prejudicial effect on the healing of the sore. Its toxicity especially limits its employment. *Washing out large wounds, serous cavities, and the uterus with mercurial solutions is especially dangerous*, owing to the rapid absorption of the metal. The solution flows out apparently unchanged; but it has lost mercury, this having been kept back in the form of albuminate.

The precipitation of mercuric albuminate is obviated to some extent by combining the corrosive sublimate with common salt (corrosive sublimate tablets). Salt also has the effect of preserving the solutions, as the stable double salt $HgCl_2.NaCl$ is formed, while corrosive sublimate in pure aqueous solution is decomposed, with the formation of an oxychloride.

Preparations of mercury are employed for various *skin-diseases*, the more active for the extermination of *vegetable and animal parasites* (*e.g.* corrosive sublimate for pityriasis versicolor and sycosis of the beard, blue ointment for pediculi), the milder, such as the white precipitate, for *eczema*, and calomel as an excellent dusting-powder for intertrigo in children. The oxides are employed as ointments for *blepharitis*, *conjunctivitis* and *keratitis*. Calomel is dusted into the eye as a gentle irritant for the clearing of *corneal opacities;* but iodide of potassium must not be prescribed at the same time, as it is excreted in the tears and may form caustic iodide of mercury. Calomel and various other mercurial compounds are also employed in the *local treatment of syphilis* (tubercula mucosa, etc.).

Of the compounds used as **purgatives,** calomel is the chief. Small quantities are gradually dissolved in the intestinal contents, and elicit so gentle a peristalsis that calomel, like castor oil, can be employed even in inflammatory conditions of the intestine and causes little griping. The fæces, which are evacuated after the lapse of a few hours, are semi-solid. Laxative or smaller doses are *antiseptic* and used in *summer diarrhœa in infants*. The abortive action of large doses in *typhoid fever* is doubtful; by the time the disease is diagnosed, the typhoid bacilli are far beyond the reach of the drug. In epidemic *dysentery*, calomel is recommended in frequent small doses (5 centigrammes). It is not suitable for prolonged use as an aperient, as some of it is absorbed and in time would cause general effects. If, after a large dose,

there is no evacuation, it should be procured by some other drug, as absorption is liable to occur. The green colour of the evacuations, denoting an abundance of bile, formerly gave to calomel the reputation of being a drug that acted upon the liver. This is now considered to be very doubtful; but even in the present day a trial of calomel is recommended for *biliary colic*—5 centigrammes every 1 or 2 hours until diarrhœa sets in. Doses of 100 to 500 grammes of mercury have been employed for *ileus*, in order that the fluid metal should force its way through by its own weight; but the method has now been superseded by surgical treatment.

As early as the eighteenth century physicians knew that various mercurial compounds, especially calomel, had a **diuretic** action; but this property was lost sight of until 1885, when Jendrassik discovered it afresh. Recent clinical experience has shown that in *cardiac diseases* calomel may cause great diuresis, even in cases in which digitalis fails. As considerable doses are required, the action is sometimes accompanied by diarrhœa and salivation. As a diuretic, therefore, calomel is a remedy which requires that the general condition of the patient shall be good. In renal and hepatic diseases, and with exudation from serous cavities, it is generally unsuccessful. The action on the whole is so uncertain that exact indications cannot at present be laid down, and its action must be determined in each case. Even if the first trial gives no result, a new attempt a week later may be crowned with success. The uncertainty of the diuretic action of calomel and the dangers of mercurialism are now avoided by employing an organic preparation of mercury, Mersalyl (B.P.) or Merbaphen (U.S.P.), by parenteral injection. In the presence of dropsy due to cardiac failure the output of urine may be increased to about 5 litres per diem. The diuretic effect of these compounds is enhanced by the previous administration of calcium or ammonium chloride (1 grm. four-hourly) for 2 or 3 days. When intravenous injection is impossible, the solution should preferably be introduced into the pleural sac if there is a pleural effusion or into the peritoneal cavity if ascites be present. The drug should not be injected subcutaneously nor into œdematous muscle, owing to the risk of sloughing. Mersalyl is contra-indicated in the presence of renal damage.

On account of its supposed *absorbent* and *antiphlogistic* properties, great reliance was formerly placed in mercury as a *remedy* in inflammation of all kinds; but now, in the form of blue ointment or mercury plaster, it is only occasionally prescribed for *cellulitis*, *glandular swellings*, etc., and it is considered doubtful whether they accomplish anything more than other skin-

irritants. Also the internal employment of mercury in similar diseases is practically abandoned.

Contra-indications. Mercury is contra-indicated by great weakness and anæmia, if these conditions are not due to syphilis. With albuminuria caution is necessary, as defective excretion through the kidneys disposes to poisoning. Slight albuminuria, however, is not a contra-indication, especially as it occurs so frequently in syphilis that it must be regarded as a symptom of that disease. Pregnancy is no hindrance to taking the drug; on the contrary, experience has proved that mercury in syphilis diminishes the danger of miscarriage. In advanced tuberculosis of the lungs it is not advisable to give mercury, and the treatment of syphilis in such patients is, of course, not so important. Other contra-indications are dysentery, scurvy, serious heart-disease, and disease of the gums.

Treatment of Poisoning with Mercury. Acute poisoning with corrosive sublimate is treated by washing out the stomach and the administration of tannic acid, white of egg and milk. Salivation in any treatment with mercury may almost always be prevented by keeping the mouth and teeth clean (brushing the teeth after every meal with a soft tooth-brush), and using chlorate of potash as a mouth-wash.

Slight swelling of the gums does not necessitate the breaking off of the treatment. As the excretion takes place principally through the intestine, the bowels must be opened regularly. In chronic poisoning the excretion of the metal is procured by iodide of potassium and hot baths.

Preparations and Doses

Hydrargyrum (B.P., U.S.P.), mercury, quicksilver, a fluid, silvery white metal. *Dose*, 3—20 centigrms., ½—3 grs., by intramuscular injection, 3—6 centigrms., ½—1 gr. (B.P.). Used in finely-divided form in the following preparations:

Injectio Hydrargyri (B.P.), mercurial cream. Ten per cent. of mercury, wool fat, camphor, creosote, and olive oil. *Dose*, by intramuscular injection, 0·3—0·6 mil, 5—10 mins.

Hydrargyrum cum Creta (B.P.) 33 per cent., (U.S.P.) 38 per cent., mercury with chalk, grey powder. *Dose*, 6—30 centigrms., 1—5 grs. (B.P.); 0·25 grm., 4 grs. (U.S.P.). Used especially for syphilis in children.

Pilula Hydrargyri (B.P.), mercury pill, blue pill. Mercury (40 per cent.) rubbed up with a mixture of syrup, liquid glucose, glycerin and liquorice. *Dose*, 25—50 centigrms., 4—8 grs. Used, like calomel, as a laxative.

Massa Hydrargyri, the corresponding U.S.P. preparation, blue mass, blue pill, contains 33 per cent. of mercury. *Dose*, 0·2 grm., 3 grs.

Unguentum Hydrargyri Forte (U.S.P.), 50 per cent.

Unguentum Hydrargyri (B.P.), **Unguentum Hydrargyri Mite** (U.S.P.), *U. cinereum*, *U. Neapolitanum*, mercurial ointment, blue ointment, 30 per

cent. of mercury. *Dose*, externally in syphilis, 3—6 grms. daily for 20—40 days, not less than 150—200 grms. being used for the first courses of treatment. For phlegmon, a piece in size from a pea to a filbert. Must not be applied to the scrotum (*pediculi pubis*), as it may cause gangrene.

Unguentum Hydrargyri Compositum (B.P.), contains about 13 per cent. of mercury, together with camphor. Used for synovitis, etc.

Oleum Cinereum (not official), grey oil, 40 per cent. *Dose*, for intramuscular injection, 0·2 mil (answering to 8 milligrms. of mercury) once a week for 5 weeks, then an interval of 5 weeks, after which the injections are renewed for 5 weeks. Before injection it must be ascertained that the cannula has not come upon a vein (shown by the flowing of blood through the cannula); and the treatment must be discontinued if hard infiltrations containing mercury are formed. A small, accurately calibrated syringe is necessary.

Hydrargyri Oxidum Rubrum (B.P.C.), red mercuric oxide, HgO, a red, crystalline powder, obtained by heating mercuric nitrate. Insoluble in water. Occasionally used internally as an antisyphilitic in doses of $\frac{1}{2}$ to 2 centigrms., $\frac{1}{12}$—$\frac{1}{3}$ gr., in the form of a powder or pills.

Unguentum Hydrargyri Oxidi Rubri (B.P.C.), 10 per cent. Applied externally in skin-diseases and as an antiparasitic. Must not be used in the eye, on account of the crystalline nature of the oxide.

Hydrargyri Oxidum Flavum (B.P., U.S.P.), yellow mercuric oxide, HgO, a yellow, amorphous, impalpable powder, obtained by precipitation from corrosive sublimate.

Unguentum Hydrargyri Oxidi Flavi (B.P.C.) 2 per cent., (U.S.P.) 10 per cent. Pagenstecher's ointment, a 3—4 per cent. ointment, is much used in diseases of the eye.

Oculentum Hydrargyri Oxido (B.P.), an eye ointment containing 1 per cent. of yellow mercuric oxide.

Oculentum Atropinæ cum Hydrargyri Oxido (B.P.), contains 0·125 per cent. of atropine sulphate and 1 per cent. of yellow mercuric oxide.

Hydrargyrum Oleatum (B.P.), *Oleatum Hydrargyri* (U.S.P.), prepared by dissolving 20 per cent. (B.P.), 25 per cent. (U.S.P.), of the yellow oxide in oleic acid. Used like the blue ointment, but is less practical.

Lotio Hydrargyri Flava (B.P.C.), yellow wash, and

Lotio Hydrargyri Nigra (B.P.), black wash, are preparations which were specially famous in former days, and were used for syphilitic lesions and foul ulcers. The first contains the yellow mercuric oxide, HgO, the second the black mercurous oxide, Hg_2O.

Hydrargyri Perchloridum (B.P.), **Hydrargyri Bichloridum** (U.S.P.), mercuric chloride, corrosive sublimate, $HgCl_2$. Colourless crystals or a white powder which dissolves slowly in about 17 parts of water, readily in alcohol. *Dose*, 2—4 milligrms., $\frac{1}{32}$—$\frac{1}{16}$ gr. (B.P.); 0·004 grm., $\frac{1}{15}$ gr. (U.S.P.); formerly administered by hypodermic injection in syphilis, 1 mil daily for 20—40 days, or 2—5 mils every 2nd or 5th day, of a 1 per cent. solution to which 3 per cent. of sodium chloride is added. The perchloride is now rarely used for this purpose, its place having been taken by intramuscular injections of metallic mercury and calomel, and intravenous or intramuscular injections of the oxycyanide of mercury. Externally, as an antiseptic, 1 in 5,000 to 1 in 1,000; in *gonorrhœal vaginitis*, 1 in 2,000; for the removal of *pigmentation spots, freckles, teleangiectases*, dissolved in collodion, 1 in 10, or as a poultice, 1 in 100, the blisters formed being snipped after a few hours. This form of treatment is much inferior to radium therapy.

Liquor Hydrargyri Perchloridi (B.P.), $\frac{1}{10}$ per cent.

Toxitabellæ Hydrargyri Bichloridi Magnæ (U.S.P.), each containing 0·5 grm. of mercuric chloride and 0·5 grm. of sodium chloride, for the preparation of solutions. To prevent mistakes, the tablets are to be angular in shape and tinted blue.

Toxitabellæ Hydrargyri Bichloridi Parvæ (U.S.P.), the small poison tablets contain only 0·125 grm. (2 grs.) of mercury bichloride.

Several soluble mercurial compounds are recommended for parenteral injection in syphilis. They are said to be less irritant, but have not been much employed. The following may be mentioned: *Hydrargyri Cyanidum*, $Hg(CN)_2$, *Hydrargyri Oxycyanidum*, $Hg(CN)_2HgO$, (B.P.), *dose*, by intramuscular injection, 5—10 milligrms., $\frac{1}{12}$—$\frac{1}{6}$ gr.; by intravenous injection, 10 milligrms., $\frac{1}{6}$ gr., and *Hydrargyri Succinimidum*, $Hg(C_2H_4CO)_2N_2$, (U.S.P.), *dose*, 0·015 grm., $\frac{1}{4}$ gr. Usually by subcutaneous injection. These all form colourless crystals, which are soluble in water, and are used in the same concentration and the same doses as corrosive sublimate.

Hydrargyri Iodidum Rubrum (B.P.), red iodide of mercury, HgI_2, a red powder, insoluble in water, soluble in a solution of potasium iodide. *Dose*, 2—4 milligrms., $\frac{1}{32}$—$\frac{1}{16}$ gr. (B.P.). Given internally in syphilis, in doses of up to 2 centigrms., $\frac{1}{3}$ gr.; for hypodermic injection: Hydr. Iod. Rubr., 1; Potass. Iod. 0·8; Aqua ad 50, $\frac{1}{2}$—1 mil daily.

Hydrargyrum Ammoniatum (B.P., U.S.P.), ammonio-chloride of mercury, white precipitate, $HgNH_2Cl$, a white powder, insoluble in water. Used only externally as

Unguentum Hydrargyri Ammoniati (B.P.), 5 per cent., (U.S.P.) 10 per cent. Of mild action, used in parasitic skin-diseases and eczema.

Hydrargyri Subchloridum (B.P.), **Hydrargyri Chloridum Mite** (U.S.P.), mercurous chloride, calomel, Hg_2Cl_2, a white or yellowish insoluble powder. *Dose*, 3—20 centigrms., $\frac{1}{2}$—3 grs., by intramuscular injection, 3—6 centigrms., $\frac{1}{2}$—1 gr. (B.P.); as a laxative, 0·15 grm., $2\frac{1}{2}$ grs., by intramuscular injection, 0·1 grm., $1\frac{1}{2}$ grs. (U.S.P.). The doses vary greatly, according to their purpose. In *syphilis*, for adults, 3—5 centigrms. 2 or 3 times a day with opium to prevent diarrhœa; for children, 1—2 centigrms. As a *laxative*, 30—100 centigrms. As a preliminary treatment in typhoid fever, 50 centigrms. twice a day for a few days. As a laxative for children, 1—2 centigrms. for each year of their age. In *diarrhœa in children*, 1 centigrm. twice a day, often with bismuth. As a *diuretic*, 20 centigrms. calomel + 2 centigrms. opium 3 times a day for 3 days; if without effect, the doses may be repeated in a week. *Externally*, as a dusting-powder for eczema, small running surfaces, and for insufflation in the eye. For *intramuscular injection* in syphilis:

Injectio Hydrargyri Subchloridi (B.P.), 5 per cent. of calomel in wool fat, camphor, creosote, and olive oil. *Dose*, by intramuscular injection, 0·6—1·2 mils, 10—20 mins.

Pilula Hydrargyri Subchloridi Composita (B.P.), 22 per cent., Plummer's pill. *Dose*, 25—50 centigrms., 4—8 grs.

Unguentum Hydrargyri Subchloridi (B.P.), calomel ointment, 20 per cent. Used in skin-diseases and for pruritus.

Unguentum Hydrargyri Nitratis Forte (B.P.), citrine ointment. Mercury dissolved in nitric acid and mixed with lard and olive oil. Contains not less than 6·7 per cent. of mercury.

Unguentum Hydrargyri Nitratis Dilutum (B.P.), 20 per cent. of the strong ointment in soft paraffin.

Hydrargyri Iodidum Flavum (U.S.P.), mercurous iodide, Hg_2I_2, a

yellow, insoluble powder. *Dose*, 0·01 grm., ⅙ gr. Used in syphilis in the same doses as calomel.

Hydrargyri Salicylas (U.S.P.), mercuric salicylate, a compound of mercury and salicylic acid, containing about 57 per cent. of mercury. A white powder, almost insoluble in water. *Dose*, 0·06 grm., 1 gr., by intramuscular injection twice a week.

Mersalylum (B.P.), the sodium salt of salicyl-(γ-hydroxymercuri-β-methoxypropyl)-amide-O-acetic acid. Contains 40 per cent. of mercury. A white powder, odourless, bitter taste. Soluble in 1 part of water, in 3 parts of alcohol. Introduced under the trade-name of *Salyrgan*.

Injectio Mersalyli (B.P.), 10 per cent. of mersalyl and 5 per cent. of *theophylline* in water. The theophylline is present merely to prevent decomposition of the mercurial complex. *Dose*, 0·5—2 mils, 8—30 mins. Introduced originally for the treatment of syphilis but is rarely used for this purpose now. A very effective diuretic in cardiac dropsy. Contra-indicated in the presence of renal damage. Injected intravenously or by deep intramuscular injection; œdematous tissue must be avoided to prevent sloughing. May also be administered into dropsical collections of fluid, *e.g.* pleural effusion or ascites. Its diuretic action is much enhanced by giving calcium chloride for the previous 2 or 3 days.

Merbaphenum (U.S.P.), the double salt of sodium mercurichlorphenyloxyacetate with diethyl-barbituric acid. Contains 33·5 per cent. of mercury. A white crystalline powder, odourless, soluble in water. *Dose*, by injection, 0·15 grm., 2½ grs. The indications for use and the methods of administration are the same as those mentioned under Mersalylum. Merbaphen was formerly known as Novarsurol.

5. ANTIMONY

Antimony, from the pharmacological point of view, is a link between the heavy metals and arsenic, to which it is closely allied, and which it generally accompanies in nature.

Action. The most important antimonial compound, *tartar emetic*, or the *double tartrate of antimony and potassium*, resembles the corresponding alkaline double salts of other metals in not itself having any local action, but in being decomposed by acids into simple salts which are caustic. It has in consequence a peculiar action on the **skin.** The immediate result of inunction with an ointment containing finely-divided tartar emetic is at most slight erythema; and it is only after a few days have passed, and some of the ointment has penetrated deeper and the inactive double compound has been split up by the secretion of the cutaneous glands into caustic salts, that red papules appear at the openings of the follicles, these being soon broken down into little abscesses that have a striking resemblance to small-pox pustules, and leave white, depressed scars that are indistinguishable from those of that disease. If the inunction is repeated several times on the same spot, the pustules run together into irregular, painful indolent ulcers, which eat deeply into the subcutaneous tissue,

and where there is little tissue the inflammation may attack the periosteum of adjacent bone and lead to widespread necrosis of the bone-tissue, a result which was likely to occur in former days when a vigorous treatment of the *pars capillata* with " small-pox ointment " was considered beneficial in mental diseases.

Internally, tartar emetic acts, as its name implies, as an **emetic.** Quite small doses elicit only the premonitory symptoms described elsewhere (see under " Apomorphine ") as nausea (salivation, increased bronchial secretion, and a feeling of sickness); doses of 3—5 or more centigrammes produce, in the course of 10 minutes or more, vomiting followed by rather pronounced symptoms of collapse—pallor, small pulse, cold sweat, general muscular relaxation. Emetic doses may vary, however, within wide limits. Sometimes even 1 centigramme may be sufficient, and on the other hand it is stated that in certain diseases (pneumonia, delirium tremens) very large doses do not have the usual effect. Rapid tolerance is often seen, only the first doses causing nausea and vomiting, but not the subsequent ones. Occasionally vomiting fails to take place, and when the salt reaches the intestine, diarrhœa occurs. In animals that cannot vomit (rodents), this is the regular action. The addition of opium suppresses the vomiting, and causes the secondary effects, especially the secretion of sweat, to acquire greater prominence. The evacuation of the stomach is due to reflexes from the vagus-ends of the **stomach,** which are stimulated by the antimonial salt.

Tartar emetic, in the doses usually given, is evacuated so quickly and completely that all absorption worth mentioning is prevented. If the action fails to take place, *e.g.* when the emetic is given by mistake in narcotic poisoning, and if the doses have been very large, the **specific action** may appear which resembles acute arsenic poisoning. The same choleraic symptoms occur, and are described as still more severe than in gastro-intestinal arsenic poisoning ; and they are quickly followed by convulsions, anurial collapse and death from cardiac paralysis. The smallest fatal doses are given as 0·65—1·35 grammes.

These symptoms are due to a **vaso-motor paralysis** of a nature similar to that produced by arsenic. On intravenous injection of the double tartrate of antimony and sodium into various mammals, it was found that the most marked symptom was the continuous lowering of the blood-pressure, caused mainly by peripheral paralysis of the abdominal vessels.

It is not definitely known how antimony acts upon the **central nervous system** of mammals ; they die in convulsions from cardiac and respiratory paralysis, but it is impossible to decide whether these symptoms are due to direct action on the central nervous system or are consequences of vacular paralysis and gastro-intestinal affection. In frogs a subcutaneous injection of the double tartrate of antimony and sodium produces slight

irritation of the medulla oblongata and then paralysis of the spinal cord reflexes and the motor ganglia of the heart, while the irritability of the motor nerves and the voluntary muscles is not diminished.

Chronic antimonial poisoning is very rare. The symptoms consist in constant nausea, anorexia, cardialgia and headache, watery diarrhœa alternating with constipation, albuminuria, weakening of the heart, and, finally, marasmus. Clothing-materials containing antimony (tartar emetic is used for fixing dyes in fabrics) may cause troublesome eczema.

Absorption and Excretion. Even readily soluble antimonial compounds are absorbed slowly and, unlike arsenic, remain for a long time in the body, especially in the liver, where the greater part is deposited. The excretion takes place gradually through the stomach and intestine, in the urine, the bile and the milk.

Therapeutic Uses. Upon the recommendation of Paracelsus, numerous preparations of antimony found extensive employment in the sixteenth century for almost all acute febrile diseases and many chronic ailments, but soon fell into disrepute, and in some quarters, as by the medical faculty in Paris, were even prohibited. They subsequently regained their popularity, and tartar emetic became one of the chief weapons of the antiphlogistic treatment. It has now once more, and rightly, been abandoned. It is, to say the least of it, doubtful whether large doses are successful in curtailing inflammatory processes ; and its other effects in febrile diseases (fall of temperature, smaller pulse, soothing of delirium, etc.) are only to be regarded as symptoms of collapse. Doses that were not emetic, but only sufficient to produce nausea and relaxation of the muscles, were employed before the introduction of chloroform to facilitate the reduction of dislocations and strangulated herniæ.

Tartar emetic is now employed in divided doses as an *expectorant in bronchitis* with little, tough secretion, and in full doses as an *emetic*. The effect is quick and sure, but is accompanied, as already stated, by considerable collapse, and sometimes by several days' diarrhœa. It should, therefore, be used with caution in the case of children. The indications and contra-indications for emetics will be found in the Chapter on Apomorphine, where it is also stated that emetics in general are now seldom used. The employment of tartar emetic as a skin-irritant is almost abandoned.

Tartar emetic has been found to be curative in certain parasitic diseases—schistosomiasis, leishmaniasis (kalar-azar, oriental sore and espundia), and filariasis. Intravenous injections of 3—10 centigrammes are given every day or every other day for a month, 1·3 grammes in all. A similar treatment (2—5 cubic centimetres

of a 2 per cent. solution twice a week) seems also to be useful for leprosy. Antimony is a specific remedy for granuloma inguinale. Relapsing fever, yaws, and trypanosomiasis (early cases) also respond favourably to treatment with antimonial compounds, but the organic arsenicals are more effective in these diseases. A large number of organic preparations of antimony similar to those of arsenic are now available for use in these parasitic infections, but they do not appear to have any material advantage over intravenous injections of tartar emetic.

Of the other **antimonial compounds** the *sulphur compounds* and *antimonious oxide* still enjoy a very limited employment as *expectorants*. They are dissolved by the hydrochloric acid of the gastric juice in small quantities that do not cause vomiting, but probably increased bronchial secretion. Its close resemblance to arsenic has led to attempts to treat *skin-diseases* with preparations of antimony, but it is not known whether they offer any advantages. Various organic antimonial compounds that are analogous to atoxyl have shown themselves, in animal experiments, to be efficient in syphilis and other protozoal diseases, but at present they are of no great practical importance.

Treatment of Antimony Poisoning. The stomach should be washed out, even if there is vomiting. As antidotes, black coffee or strong tea are given to precipitate sparingly soluble tannate, which is removed by the stomach-tube. Magnesia may also be employed, as in arsenic poisoning. In case of collapse the ordinary stimulants are administered, and, for continued vomiting and diarrhœa, opium, atropine, mucilaginous remedies, and small pieces of ice to suck.

Preparations and Doses

Antimonii et Potassii Tartras (B.P., U.S.P.), tartarated antimony, tartar emetic, $KSbOC_4H_4O_6 + \frac{1}{2}H_2O$, a white powder or crystals, soluble in 17 parts of water. *Dose*, 2·5—8 milligrms., $\frac{1}{32}$—$\frac{1}{8}$ gr., as an emetic, 3—6 centigrms., $\frac{1}{2}$—1 gr. intravenously, 0·03—0·12 grm., $\frac{1}{2}$—2grs. (B.P.); as an expectorant, 0·003 grm., $\frac{1}{200}$ gr. intravenously, 0·04 grm., $\frac{2}{3}$ gr. in 100 mils of normal saline (U.S.P.). For adults, about 5 centigrms. every 10 minutes until action is obtained; maximum dose for children between 2 and 4 years, 2 centigrms., $\frac{1}{3}$ gr.; under 2, 8 milligrms., $\frac{1}{8}$ gr.

Antimonii et Sodii Tartras (B.P.), sodium antimonyl tartrate. Transparent or white scales or powder, hygroscopic. Soluble in 1·5 parts water. *Doses*, oral and intravenous, the same as those of tartar emetic.

Fouadin, *Neostibosan*, and many others are organic preparations of antimony for use in certain protozoal infections (see text).

Germanin (Bayer 205). This is a proprietary remedy for trypanosomiasis. It is a white powder, soluble in water, and administered by intravenous or subcutaneous injection. A single dose suffices to eliminate trypanosomes from the peripheral blood within 24 hours. Organisms in

the central nervous system are unaffected by the treatment; it is therefore of little value in late cases. Complications arising out of its use include nephritis and impairment of vision. Its exact chemical structure is not published but it is thought to be related to naphthylamine sulphonic acid.

Moranyl (Fourneau 309) resembles Germanin in its chemical structure, action and uses.

6. IRON

Iron is found everywhere—in animals and plants, in all water, and in the dust of the atmosphere. We have a proof of its presence all over the earth's crust, for if a single square foot of earth were to lose its iron, the plants on that spot would not grow green. Physiologically, iron occupies a peculiar position among the heavy metals. While the remainder of these elements are all—according to Bertrand, with the exception of manganese—strangers to the higher animal organism, iron is a necessary constituent, which enters into the regular metabolism, is continually being excreted and must continually be supplied. In the vegetable kingdom it plays the same important part. Although chlorophyll contains no iron, the higher plants are unable to form this colouring matter if their food is devoid of iron, and evidences are not lacking of its necessity also for the lower plants that are without chlorophyll.

In man and the higher animals, by far the greater amount of the iron is found in the red blood-corpuscles; but it is also present in the white cells, and occurs in considerable quantities in invertebrate animals which possess no fluid that answers to our blood. Iron is probably a constituent of all protoplasm.

Action. The **local action** of the ordinary iron salts is either astringent or caustic, according to the degree of ease with which the compound is dissociated, and the acid with which the metal is combined, as the iron unites with albumin, and the liberated acid acts independently.

In the mouth the iron salts have in a marked degree the astringent, inky taste that is common to all substances that precipitate the albumin of the epithelial cells, an action which in the stomach causes cardialgia and dyspeptic symptoms. After long use the teeth may be stained black by the precipitation of the iron by the tannic acid of the food, or by the formation of sulphide of iron. These compounds attach themselves most easily where the surface is rough, or where there are cracks, and thus make visible previously unobserved defects. Iron may also, perhaps, promote dental caries by acting as a carrier of oxygen (*cf.* the oxidation of wood round iron nails). The strongly acid salts are, of course, injurious. The strongest local action is that of

ferric chloride, which in concentrated solution is a true caustic. When applied to bleeding surfaces, it acts as a hæmostatic by forming a clot of blood which closes the open vessels ; but it is only of value for slight oozing hæmorrhage. Large quantities of ferrous sulphate or ferric chloride taken internally cause widespread corrosion of the gastric mucous membrane, and after very large doses (abortive remedy), death has occurred with symptoms of acute gastro-enteritis and consequent collapse. A frequent result of the ordinary employment of iron is constipation, induced by the union of the iron with the irritant alkaline sulphides of the intestinal contents.

The **general action of the iron ion** is only apparent when soluble double salts, which do not precipitate albumin, are injected directly into the blood. According to the investigations of Meyer and Williams, the action in mammals presents a striking similarity to that of arsenic and antimony, as the principal symptoms consist in fall of blood-pressure and diarrhœa, with injection and inflammation of stomach and intestine. Both are probably dependent on a peripheral vascular paralysis of the same kind as that mentioned in the Chapter on Arsenic.

None of these symptoms are seen in man from the internal use of iron, partly because very little is absorbed and partly because all the iron, before it reaches the blood or lymph, is converted into fixed compounds, which are not dissociated into iron ions.

Absorption and Excretion. The absorption of iron was originally considered to be a very simple process. The marked effect in chlorosis, and the rapid increase in the amount of hæmoglobin that was attained by the use of ferric chloride, Blaud's pills, etc., seemed to show so clearly that the iron in these and many similar preparations was absorbed through the mucous membrane of the intestinal canal that it was almost unnecessary to make any chemical investigations to prove its absorbability. When such investigations were made, however, great interest was aroused by the discovery that during the employment of iron there was no increase in the elimination of iron in the urine, nor could it be shown by quantitative analysis that any of the iron administered disappeared from the intestine.

According to these results, there appeared to be an irreconcilable disagreement between the chemical investigations and clinical experience ; the former taught that the iron was not absorbed, the latter showed unmistakably that iron, in chlorosis, increases the amount of hæmoglobin, which indicates absorption. Prolonged research has now solved the problem, and shown that the iron compounds are absorbed, but in varying degrees.

In the ordinary salts formed with inorganic and organic acids,

the iron is loosely combined, that is to say, these salts are dissociated and furnish iron ions, and consequently give all the reactions known to analytical chemistry, such as the black precipitate of ferric sulphide with ammonium sulphide. In articles of food (meat, eggs, milk, vegetables, etc.) there is no loosely-combined iron, but only firm compounds that are not dissociated, and therefore give no iron reaction. It is in the form of such compounds, which are represented by *hæmatogen*, produced by Bunge from hen's eggs, and *ferratin*, found by Schmiedeberg in the liver and other organs, that the food-iron is taken up. The absorption is very easily demonstrated by giving animals a definite amount by weight of ferratin, and then analysing the contents of their intestine. After 12—14 hours, only half, or even less, of the iron is found.

The ordinary salts form with the alkaline sulphides of the intestine insoluble ferric sulphide, which is eliminated with the fæces, to which it gives the well-known black colour. As already mentioned, disappearance from the intestine cannot be demonstrated by quantitative analysis. Many animal experiments have shown, however, that young, growing animals of various species which receive food containing no iron, or only very little, do not thrive, but become anæmic, while animals of the same age that receive the same food, but with the addition of small quantities of inorganic iron salts, develop normally and contain far more iron. These and similar investigations have given physiological proof that the inorganic iron is really absorbed.

Where the absorption takes place seems at last (1896) to have been determined by Hochhaus, Quincke and others, who have worked with greater success than their numerous predecessors in this field of research by turning their attention to the intestine-walls instead of examining the contents of the intestine, and by substituting for the ordinary analytical methods the finer micro-chemical mode of demonstration. They gave animals various preparations of iron, inorganic among them, and after a short time killed them and examined the whole of the intestinal canal, section by section, beginning at the stomach, and also various organs, such as the spleen, liver and kidneys. As a staining reagent they employed ammonium sulphide, which precipitates iron in the form of tiny black granules, or, where the amount of iron is minimal, merely gives a diffuse green colour to the tissues. The result was that after feeding for a short time with preparations, they found strong iron reaction in only two places, namely, the duodenum and the upper part of the large intestine.

The microscopical results could only be interpreted as showing

that the iron in the duodenum was in the process of absorption, but in the large intestine was on its way to the surface of the mucous membrane. These discoveries, which have since been confirmed in all essentials, clearly indicate that *the iron is absorbed in the upper section of the intestine and excreted in the large intestine.*

Circulation of the Iron in the Organism. Probably more or less complete conversion of the compounds into chlorides occurs in the stomach, and lower down these are further changed into carbonate, hydroxide and soluble albuminates. The albuminates penetrate the epithelial cells, and are there precipitated in the form of fine grains which are seen in the thoracic duct and the mesenteric glands. The iron is thus carried through the blood to the spleen and the liver, where it is stored up, utilised as required, and finally excreted into the large intestine. The iron injected directly into the blood is first deposited for some time in the liver, and is subsequently excreted in the same way as that absorbed from the intestine, only a small part being eliminated through the kidneys (Jacobj). There is no absorption through the skin.

The daily elimination of iron amounts to a few milligrammes, the greater proportion of which is found in the fæces, and only ½ to 1½ milligrammes in the urine. Small quantities are also lost in other secretions and in the hair and epidermis. The amount of iron in the daily food is estimated at from 8 to 11 milligrammes.

The old iron medicines have thus, by the researches referred to above, been reinstated, but the difference between the compounds with loosely-combined iron and those with the iron firmly combined is by no means effaced. Of the former, at any rate, only very small quantities are absorbed, but for therapeutic purposes these are generally sufficient.

Therapeutic Uses. Iron is the specific remedy for the typical *chlorosis* appearing in women at about the age of puberty. In the majority of cases the effect is so certain that a negative result calls for a careful search for other diseases, *e.g.* incipient tuberculosis. In chlorosis the improvement begins after 1 or 2 weeks ; strength returns, the appetite improves, palpitation and headache cease, the menses return, etc., and the blood regains its normal character. The nature of the action is not exactly known, nor is it clear why any extra supply of iron should be needed at all, as the daily food, as far as we know, always contains an abundance of iron. This is apparent from the experience gained from other forms of anæmia. Very considerable loss of blood in surgical operations is made good without treatment with iron ; and women in child-birth, who are often liable to serious hæmorrhage, and in addition have a new daily expenditure of iron in the secretion of

milk, recover rapidly without any medicine. Chlorosis, on the contrary, is generally but little affected by dietetic treatment, and improvement only begins when iron is given in doses that seem as if they must far overshoot the mark. These circumstances have led to various assumptions that the importance of the medicinal iron in chlorosis lies not only in its direct employment in the building up of hæmoglobin, but also in some other, as yet unknown, action that it possesses, which may perhaps stimulate the formation of blood as phosphorus does the formation of bone-tissue. More interesting still is the fact that the number of cases of chlorosis has steadily diminished during the past twenty years. On the other hand, anæmia seems to occur with increased frequency in middle-aged women at the menopause. This condition also responds rapidly to the administration of adequate doses of iron. It is of great practical importance that the iron shall not, as so often happens, be left off as soon as an improvement is shown, but be continued for some time after the cure seems to be complete ; for otherwise there is risk of an early relapse.

With *other forms of anæmia* the effect is far less certain than in chlorosis, though often satisfactory in poorness of blood and weakness after *protracted febrile diseases*, *chronic diarrhœa* and *bronchitis*, *malarial cachexia*, *tuberculosis*, and *rickets* with pronounced anæmia, etc. For *syphilitic anæmia*, mercury and arsenic are first used, then iron. No effect is to be expected in *leucæmia*. Ordinarily, pernicious anæmia does not, of course, improve with iron therapy. However, under the influence of liver treatment the number of red blood-corpuscles may increase so rapidly that a relative deficiency of hæmoglobin becomes apparent, as indicated by the falling colour index. In these circumstances iron is beneficial in pernicious anæmia. In *nervous ailments* iron is only indicated when their cause is anæmia, and the same is true in *anomalies of menstruation*.

Children reared by hand are often anæmic, as their pale flabbiness shows. This is easily explained, as cows' milk contains less iron than human milk. Hence, although man, like various mammals, comes into the world with a reserve store of iron, it will often be well to make up the difference between the natural and the artificial food with one of the preparations that do not affect the digestion.

Freshly precipitated ferric hydrate is used as an *antidote* in arsenic poisoning.

Externally, ferric chloride is employed as a *hæmostatic*, and is very efficient when the bleeding is from small vessels and the wound-surface is easily accessible. *Internally*, in bleeding from the stomach, some effect may perhaps be looked for, but little or

none in intestinal hæmorrhage, as there is no likelihood that the drug will reach the site of the hæmorrhage unchanged. In bleeding from the lungs or kidneys, or in nephritis, no remote hæmostatic or astringent action is possible, as the small quantities that are absorbed can only exist in the blood as protein compounds, which, of course, no longer possess the property of coagulating albumin. Crude ferrous sulphate is employed as a cheap *disinfectant* for sewage, etc. It acts chiefly as a deodorant by fixing the hydrogen and ammonium sulphides, but it also has a slight antiseptic action due to its acid reaction and precipitation of proteins, which carry away the bacteria mechanically.

Before iron is prescribed, dyspeptic symptoms should be treated, unless they arise from chlorosis, in which case they are often best combated with iron. Attempts have also been made to avoid irritation of the stomach by hypodermic injections of iron, but these are of doubtful value. The amount of iron that can be given by intramuscular injection is limited by the toxic effect of the metal. Absorption is slow and irregular owing to the precipitation of the iron in the muscle as the albuminate. All foods containing tannic acid, which forms insoluble tannates with iron (coffee, tea, fruits containing abundance of tannin), are contra-indicated during treatment with iron. *Constipation* is treated with laxatives, *e.g.* aloes.

On the Choice of a Preparation. There is a very large number of iron preparations to select from, where a few would be sufficient. They may be divided into three groups.

1. *Ferrous Salts.* These are the least irritating of the inorganic iron compounds. The preparations in common use are ferrous carbonate (*Blaud's pills*), ferrous sulphate, and the syrup of ferrous iodide. Ferrous chloride fulfils most requirements for therapeutic purposes, but is unstable and therefore administered as the citrated salt.

2. *Ferric Salts.* The disadvantage of the ferric salts lies in their astringency, which may result in nausea and vomiting after moderate doses. Dyspeptic symptoms arising from the use of these and other preparations may be prevented by prescribing the iron at meals, so that it is offered the protein of the food instead of that of the gastric mucous membrane. Ferric chloride is given as a 15 per cent. liquor in doses up to 1 mil. The scale preparations are made from ferric hydroxide, but the iron is present in a complex form which is non-astringent (see below).

3. *Scale Preparations.* (*Iron and Ammonium Citrate*, and *Iron and Quinine Citrate.*) These are freely soluble, but on dissociation the iron containing ion is complex and has no astringent effect in the alimentary canal. Thus the same principle is used as in the

case of citrated ferrous chloride. The scale preparations do not cause constipation, and this is an advantage over the inorganic ferrous and ferric compounds. Not infrequently, indeed, large doses of iron and ammonium citrate result in looseness of the bowels. The official *Injectio Ferri* (B.P.) contains an ammonium ferric citrate.

The mucous membrane is spared still more completely if the iron is prescribed in compounds in which its affinity for albumin and allied substances is already satisfied, *e.g.* the non-official trade-preparations known as iron albuminates, caseinates, peptonates, etc. In most of them, however, the iron is only loosely combined, and they differ from the ordinary salts, not as regards their absorption, but only in not being local irritants. This is also the case with the various *preparations of blood*, generally bullocks' blood, which consist of more or less impure hæmoglobin with derivatives and products of decomposition. Their frequent recommendation as " directly blood-forming " is based upon a twofold error. In the first place they are not absorbed more easily than the inorganic salts, and in the second place their absorption would be of doubtful value, as the hæmoglobin of animals is different from, and cannot replace, that of man. Iron also forms more or less stable and non-irritant compounds with sugar, *iron saccharates*, which form palatable solutions.

Preparations and Doses

Ferrum Redactum (B.P.), *Ferrum Reductum* (U.S.P.), reduced iron, a fine, greyish black powder, obtained by the action of hydrogen upon ferric hydroxide. *Dose*, 6—60 centigrms., 1—10 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.). May be prescribed in pilular form.

Tinctura Ferri Perchloridi (B.P.C.), *Tinctura Ferri Chloridi* (U.S.P.), contains 4·5—5 per cent. of iron, corresponding to about three times the amount of ferric chloride. *Dose*, 3—10 decimils, 5—15 mins. (B.P.C.); 0·6 mil, 10 mins. (U.S.P.). Is a favourite preparation with many medical practitioners for the hypochromic anæmias. On account of its highly acid reaction is must be taken in a very dilute form, *e.g.* in half a tumbler of water, and through a glass tube to avoid injury to the teeth.

Liquor Ferri Perchloridi (B.P.), 5 per cent. of iron. *Dose*, as of the tincture.

Liquor Ferri Chloridi (U.S.P.), 10—11 per cent. of iron. *Dose*, 0·2 mil, 1½ mins.

Syrupus Ferri Iodidi (B.P., U.S.P.), a pale green liquid with a strong iron taste. Both preparations contain about 5 per cent. of ferrous iodide. Dilute hypophosphorous acid is added to retard oxidation of the ferrous iodide. *Dose*, 2—8 mils, ½—2 fl. drs. (B.P.); 1 mil, 15 mins. (U.S.P.).

Though less used now, these preparations were formerly much employed for goitre with the object of combining the effects of the iron and the iodine.

Ferri Sulphas (B.P., U.S.P.), ferrous sulphate, $FeSO_4 + 7H_2O$, bluish

green crystals, easily soluble in water, and *Ferri Sulphas Exsiccatus*, a white powder, slowly soluble in water, are employed in the three following very important preparations, together with potassium or sodium carbonate, thus forming the green *ferrous carbonate*, which has only a slight taste of iron, and does not as a rule disturb the digestion. *Dose* of ferrous sulphate: 0·06—0·3 grm., 1—5 grs. (B.P.); 0·2 grm., 3 grs. (U.S.P.).

Pilula (Pilulæ) Ferri Carbonatis (B.P., U.S.P.), iron pills, chalybeate pills, Blaud's pills, the most used of all iron preparations. *Dose*, 3—20 decigrms., 5—30 grs. (B.P.); 3 pills (U.S.P.). In cases of constipation, a few milligrammes of aloes is added to each pill.

Ferri Carbonas Saccharatus (B.P.), saccharated ferrous carbonate, a green powder, soluble in acids. The purpose of the sugar is to prevent oxidation, but the delay attained is brief, and only the freshly-prepared powder therefore should be prescribed. *Dose*, 6—20 decigrms., 10—30 grs.

Mistura Ferri Composita (B.P.C.), Griffith's mixture, an emulsion containing ferrous carbonate, myrrh, sugar and flavouring agents. It is at first green in colour, but in a few days turns a rusty brown (ferric hydroxide, oxidation). *Dose*, 15—30 mils, ½—1 fl. oz. Is employed especially for chronic bronchitis in anæmic patients. Ought to be freshly prepared.

Pilula Aloes et Ferri (B.P.), contains 10 per cent. of ferrous sulphate, and 20 per cent. of aloes. *Dose*, 25—50 centigrms., 4—8 grs.

Syrupus Ferri Phosphatis Compositus (B.P.), Parrish's Food, 0·9 per cent. of ferrous phosphate. *Dose*, 2—8 mils, ½—2 fl. drs.

Syrupus Ferri Phosphatis cum Quininâ et Strychninâ (B.P.), 1 dr. contains about ½ gr. of iron and about $\frac{1}{60}$ gr. of strychnine hydrochloride (see p. 74).

Ferri et Ammonii Citras (B.P.), **Ferri et Ammonii Citrates** (U.S.P.), dark red scales, readily soluble in water, and with a slightly sweet, astringent taste. *Dose*, 1·3—2·6 grms., 20—40 grs. (B.P.); 2 grms., 30 grs. (U.S.P.); 2·6 grms. contain 0·5 grm. of iron.

Injectio Ferri (B.P.), an ammonium ferric citrate. Neutralised and sterilised. *Dose*, by intramuscular injection, 1—2 mils, 15—30 mins. 30 mins. contain about $\frac{1}{10}$ gr. iron (see text).

Ferri et Ammonii Citrates Virides (U.S.P.), *dose*, by parenteral injection, 6 centigrms., 1 gr.

Ferri et Quininæ Citras (B.P.) (see p. 221).

Ferri Subchloridum Citratum (B.P.), citrated ferrous chloride. A preparation of ferrous chloride and citric acid. Contains 68 per cent. of ferrous iron. A buff-coloured powder, acid, metallic and astringent taste. Soluble in 1 part of water. *Dose*, 0·2—0·3 grm., 3—5 grs.

Magma Ferri Hydroxidi (U.S.P.), a preparation of ferric hydroxide obtained by mixing a solution of ferric sulphate with a mixture of magnesium oxide in distilled water. Must be freshly prepared. Used as an antidote for arsenic poisoning. It is of doubtful value.

Among the non-official preparations, the following may be noted :—

Ferri Lactas, ferrous lactate, $FeC_3H_5O_3 + 3H_2O$, a powder or crusts of a pale greenish white colour, and a sweetish, slightly ferruginous taste, slowly soluble in water. Is one of the least irritating of the iron salts. *Dose*, 20—30 centigrms., 3—5 grs., in pills, often with a bitter, *e.g.* equal parts of *Extractum gentianæ*.

Liquor Ferri Albuminati. Under this or similar names are sold various solutions of iron albuminates or caseinates to which sugar, aromatic tinctures, and often a little alcohol have been added. They contain as a rule about ½ per cent. of iron, are agreeable to the taste and do not disturb

the digestion, and are thus suitable for children. *Dose*, 1 dessertspoonful to 1 tablespoonful after meals.

7. SILVER

The most important of the compounds of this metal is the nitrate of silver, to which have been added in the course of the last few years several organic preparations of silver.

Action. The investigations of recent years have shown that silver is very strongly **antiseptic.** When a sheet of silver is placed upon agar-agar or gelatine on which a bacteria culture has been sown, all growth is prevented in the part covered by the sheet and a few millimetres beyond it all round, while outside this the bacteria grow normally. The reason of this is that various acids are formed, especially lactic, during bacterial growth, which dissolve minute amounts of silver, and these are diffused through the nutrient substratum and are bacteria poisons. Silver lactate in a solution of 1 in 1,000, kills in 5 minutes staphylococci, streptococci, and anthrax bacilli, and in blood-serum prevents their development in a solution of 1 in 80,000. This and other silver salts have a stronger anti-bacterial action in the tissues than corrosive sublimate, as the mercuric albuminate formed is comparative inactive, while the silver albuminous compounds are still highly antiseptic, probably because, while slowly dissociating, they give up silver ions.

Silver has a very strong affinity for proteins. If a few drops of a nitrate of silver solution be added to dissolved albumin, a heavy, white precipitate at once appears, which soon becomes grey on exposure to light, as reduction takes place. The same reaction occurs when nitrate of silver comes in contact with **skin, mucous membranes,** or **wound-surfaces.** A firm crust of metallic albuminate is formed, which for a few seconds is white, but rapidly turns grey and at last black from the formation of silver and silver oxide. The tissues that in this way are acted upon are completely destroyed, the liberated nitric acid also contributing to this ; but the crust that is formed prevents the further penetration of the salt and the acid. The peculiarity in the action of silver nitrate, upon which its employment in practice depends, is that it is a powerful, but superficial, caustic. When very dilute solutions are employed, the layer of silver albuminate is thin, and the effect only astringent. When stronger solutions are used and are left on for some time, or when silver nitrate is applied as an ointment that penetrates the skin, they produce inflammation and vesicles accompanied by burning pain.

Taken internally, nitrate of silver has a very disagreeable,

bitter, astringent, metallic taste, but in doses of a few centigrammes produces no gastric symptoms as the metal is taken up by the albumin and sodium chloride of the gastric contents. When the dose amounts to 0·05—0·10 gramme, there is a feeling of warmth and burning in the epigastrium, nausea and sometimes vomiting. Even enormous quantities (32 grammes), although they cause severe acute gastritis, have only very rarely endangered life, partly because their action is superficial, and partly because a large proportion of the salt is immediately fixed as albuminate and chloride of silver by the gastric contents. The accidental swallowing of a piece of the stick of lunar caustic with which the throat is being touched is never followed by serious results.

The **general action** of silver is only known from animal experiments. Subcutaneous and intravenous injections of silver compounds, which must of course be of a kind that is not precipitated by albumin or common salt, produce a paralysis of the central nervous system which, when the dose is sufficiently large, quickly results in death. In cats and dogs there is profuse bronchial secretion, the cause of which is not known. Death occurs as a consequence of paralysis of the respiratory centre, the heart being less affected and continuing to beat after respiration has ceased. In frogs the paralysis is preceded by violent convulsions.

In man the general action is unknown. The only specific symptom observed is *argyria*, the name given to a dark bluish-slate discoloration of internal organs and the skin after long-continued use of silver preparations. Argyria distinctly shows that silver salts are slowly absorbed from the intestinal canal, the metal circulating in the blood as some soluble compound, which is finally deposited in the form of black granules. This takes place especially in the skin, and affects particularly those parts that are exposed to the light; the mucous membrane of the mouth, the intestine and mesentery, the liver, the kidneys, and the vessels are also coloured. Local argyria may ensue from prolonged treatment of the eye, throat, etc., with nitrate of silver, and is seen in photographers and others who work much with silver salts.

Wherever the dark granules have once been deposited, there they remain through life. Argyria is therefore incurable, but is not attended with toxic symptoms, and has no other disadvantage than the conspicuous appearance it gives, which suggests southern extraction. A record exists of an army-chaplain who was treated by his doctor with silver nitrate until he became so black that the Swedish queen of that time expressed her astonishment that a negro should have been made a priest (Lewin). Formerly, when silver was much used for nervous diseases, numerous attempts

were made to remove the colour of such patients, but without success. Vesicants are useless, as the pigment lies too deep. The doses which produce argyria are estimated at from 15 to 30 grammes of nitrate of silver, in rare instances far fewer.

Therapeutic Uses. Its powerful but superficial action makes **silver nitrate** useful in cases in which a deep corrosion is not intended, but only a destruction of the surface, with sloughing of dead or infected tissue. Nitrate of silver is employed in solid form as a caustic for *small epithelial growths* (warts), *foul ulcers, e.g. hard and soft chancre, tubercula mucosa, syphilitic affections of the mucous membranes*, wounds with *loose, proliferating granulations*, etc.

Nitrate of silver is most widely employed in acute and chronic *inflammation and catarrh of the mucous membranes*, in solutions of concentrations varying according to the site of application and to the action, caustic or astringent, desired. The *disinfection of the eyes of new-born infants* with a 2 per cent. silver nitrate solution, introduced by Credé senior, is of special importance. By this treatment, which is of the greatest value in public lying-in hospitals, where patients frequently suffer from gonorrhœa, ophthalmia neonatorum, which was formerly one of the most frequent causes of blindness, is prevented. Also, various preparations of silver are of great importance in the cure of *gonorrhœal urethritis*. In the rare cases in which the disease is presented for treatment in its earliest stage, before the gonococci have penetrated far or have spread far back in the urethra, a thorough washing-out of the fossa navicularis and injection 3—4 cm. into the urethra may be successful in arresting the disease ; and if not, it can do no harm. In developed gonorrhœa, nitrate of silver is still one of the most frequently employed remedies. Its drawback, however, is that in the urethra silver is precipitated by sodium chloride and albumin, and its action is thereby limited to the surface of the mucous membrane. For *cystitis*, injections of nitrate of silver solution may be very efficacious.

Internally, silver nitrate is used in the form of pills or solution for *chronic catarrh of the stomach* and *gastric ulcer*, often with good results. In order that the action shall benefit the mucous membrane, the drug must be taken some time before a meal, for in a full stomach it will only react with the albumin and salt of the gastric contents. It is of far less value in *chronic diseases of the intestine* and *diarrhœa ;* it is probable that none of the silver nitrate reaches the intestine unchanged. Silver nitrate was formerly much used for its specific action in nervous diseases, *e.g.* tabes and other diseases of the spinal cord, and epilepsy, but has now been abandoned.

A great number of new organic silver compounds have been produced, the aim of which is to impart to the silver the depth of action so desirable in gonorrhœa, and which is lacking in the nitrate. These all possess the property of not being precipitated by common salt and albumin. The most important of the newer preparations is **protargol,** which, on Neisser's recommendation, has acquired extensive use in gonorrhœa and as a substitute for silver nitrate in general.

Silver Proteinate, which dissolves with the greatest ease in water, is poisonous to bacteria, and is now proposed as an antiseptic to act both locally and over the whole body. For the latter purpose it is best employed in the form of intravenous injections, or as an ointment that is carefully rubbed into the skin. It has been tried for lymphangitis, septicæmia, and for septic infection in diseases of all kinds, *e.g.* puerperal fever, scarlatina, erysipelas, typhoid fever, furunculosis, etc. The reported results vary greatly, but in many cases seem to be good when the treatment is begun early.

Treatment of Poisoning with Silver Nitrate. White of egg and common salt are given as chemical antidotes ; if large quantities of silver nitrate solution have been taken internally, the stomach must be washed out. Argyria is incurable. External silver marks may be removed with cyanide of potassium.

Preparations and Doses

Argenti Nitras (B.P., U.S.P.), silver nitrate, lunar caustic, $AgNO_3$, colourless, tabular crystals, very soluble in water. *Dose,* 8—16 milligrms., $\frac{1}{8}$—$\frac{1}{4}$ gr. (B.P.) ; 0·01 grm., $\frac{1}{6}$ gr. (U.S.P.). Internally, in the form of pills, but for gastric ulcer better in solution, 3 times a day, 1 hour before meals. Externally, in solutions of varied concentration ; for disinfection of the eye, 2 per cent. (followed by washing with a salt solution) ; for ordinary conjunctivitis, 0·25 per cent. ; to abort gonorrhœa, 2—4 per cent. ; for ordinary syringing, 0·05—0·5 per cent. ; for injection into the bladder, up to 10 per cent. ; for lavage, 1 in 3,000—1 in 1,000 ; for painting the mouth, throat and nose, 2—10 per cent. ; for inhalation, 1—2 per cent.

Argenti Nitras Induratus (B.P., U.S.P.), toughened caustic, moulded silver nitrate, is the nitrate fused with a small quantity of potassium nitrate or silver chloride to toughen the mass, and poured into proper moulds. Externally, as a caustic.

Argenti Citras (not official), silver citrate, $AgC_4H_5O_3$, a white powder, sparingly soluble in water. Externally, as a dusting-powder on wounds, or as a solution of 1 in 4,000 ; for washing out large cavities, 1 in 10,000—1 in 4,000 ; for gonorrhœa, the same concentrations, beginning with the weakest, as also for diseases of the eye. The solutions must be freshly prepared.

Argenti Lactas (not official), silver lactate, $AgC_3H_5O_3 + H_2O$, a white powder, soluble in 15 parts of water. Externally, as an antiseptic on wounds, for lavage, as a gargle in a solution of 1 in 2,000. Both this and the citrate are powerful antiseptics.

Argentoproteinum (B.P.), **Argentum Proteinicum Forte** (U.S.P.), strong silver protein. A brown powder, odourless, hygroscopic, soluble in water, insoluble in alcohol. Solutions should be freshly prepared and should be dispensed in amber-coloured bottles. Contains about 8 per cent. of silver. It should be noted that silver proteinates are described as "strong" or "weak" according to the quantity of *ionisable* silver in the preparation; *cf. Argentum Proteinicum Mite* (U.S.P.) below. The solution is not precipitated by albumin nor by sodium chloride. Externally, in gonorrhœa, $\frac{1}{8}$—$\frac{1}{4}$ per cent. solution, later $\frac{1}{2}$—1. According to Neisser, 10 c.c. is injected 3 times a day, the first two injections being kept in the urethra 5 minutes, and the last, if possible, 30 minutes. According to experiments made by Welander (infection of the healthy urethra with gonococci), it is probable that micturition and subsequent injection of 5—6 c.c. of a 4 per cent. protargol solution will prevent gonorrhœa, when the disinfection takes place within 1 or 2 hours after coition. Protargol is employed in the eye as a prophylactic for blennorrhœa, in solutions up to 20 per cent. Even a 50 per cent. solution, or pure protargol, is said not to cause corrosion. *Protargentum* is a nearly-allied American preparation containing 8 per cent. of silver, and is employed in the same way as protargol. Of the numerous similar compounds may be mentioned **Argentum Proteinicum Mite** (U.S.P.), mild protein silver, a preparation derived from protein and silver oxide, containing 25 per cent. of silver, and forming black, glistening scales, which are very soluble in water. Employed as the preceding. *Argyrol* and *Albargin* are proprietary protein-silver compounds similar in action and uses to the official preparations.

Argentum colloidale, collargol, black pieces containing 70—80 per cent. of colloid silver, and forming with water a brown pseudo-solution. Externally, as an ordinary antiseptic for wounds in a 1 per cent. solution; for intravenous injection against sepsis, 5—15 c.c. of a 2 per cent., or 3—9 c.c. of a 5 per cent., filtered solution. The injection may be repeated after 12—24 hours. The solutions must be freshly prepared; if allowed to stand, floccules are precipitated, which may cause emboli. For epidermic use as a 15 per cent. ointment (Credé's ointment), of which 2—3 grms. for adults, 1 grm. for children, is rubbed in from 1 to 4 times a day after the skin has been washed with benzine or chloroform. Internally, as a 1 per cent. solution for infectious gastric and intestinal diseases, typhoid fever, dysentery, etc., 1 teaspoonful to 1 tablespoonful 3 or 4 times a day.

8. COPPER

Copper is widely distributed in organic nature. It is a normal constituent of the blood of several invertebrate animals, and passes in considerable quantities from the soil into many plants. Various kinds of grain contain 5—14 milligrammes, beans 18—20 milligrammes, cucumbers 30 milligrammes, of copper per kilogramme of dry substance, and in 1 kilogramme of new bread Galippe found 3—5 milligrammes of copper.

There is thus frequent opportunity of absorbing copper, and it is, therefore, always to be found in man. Formerly it was thought that copper had no part to play in human metabolism, but in recent years evidence has accumulated which tends to show

that a minute quantity of this element is necessary as a catalyst in the synthesis of hæmoglobin. The daily requirement is said to be as little as one-tenth of a milligramme, and more than enough is therefore contained in an ordinary diet. It is rarely necessary to prescribe copper in the treatment of anæmia. Whereas copper is not injurious to the higher plants, and in many cases even seems to promote their growth, it is exceedingly poisonous to many fungi and algæ, and has been much employed as a disinfectant in parasitic diseases in important cultivated plants (vine, grain, potato).

Action. As regards **local action,** copper stands between the caustic and the astringent metals, but nearer to the former. Copper salts have an exceedingly disagreeable, nauseous, rusty taste, and when highly concentrated, are powerful caustics to the gastric mucous membrane. Large single doses, however, can be taken without harm, as they are rapidly removed by reflex vomiting. The action of copper salts differs from that of other emetics in the almost entire absence of the unpleasant preliminary stage of nausea and increased secretion from various glands, which is an advantage when the emptying of the stomach is all that is required, but entails the absence, with small doses, of the expectorant action usual with other emetics.

Specific Action. *Acute copper poisoning* is occasionally seen in man, generally caused by the consumption of foods containing acids—*e.g.* fruit—that have been cooked in copper utensils. In general the action is confined to irritation of the mucous membranes, with metallic taste, great thirst, repeated acts of vomiting, the vomit being sometimes of a bluish green colour (of diagnostic importance), abdominal pain, tenesmus and violent diarrhœa. Early vomiting may prevent absorption, but, if not, this takes place through the corroded mucous membranes, and exhaustion, drowsiness, convulsions and jaundice follow, while the urine becomes scanty and albuminous, and death may occur with the usual symptoms of cardiac and respiratory failure. It is difficult, however, in this, as in other kinds of poisoning with caustic substances, to draw the dividing-line between gastro-enteric and specific symptoms. Acute poisoning with copper was formerly supposed to be rather common, but in many of the cases placed under this head there seems to have been a wrong diagnosis (tainted food).

The question of *chronic poisoning with copper* is of great hygienic interest, as in many articles of food copper constantly occurs in small quantities, partly naturally, partly taken up from copper cooking-utensils, and partly added intentionally. In preserved vegetables, for instance, it occurs almost regularly, for

vegetables lose their green colour in the process of preserving, and regain it by the aid of copper, which gives a beautiful green compound with a product of the decomposition of chlorophyll, formed during the boiling. Very careful investigations have been made by French and German toxicologists, who believe that *there is no such thing as chronic copper poisoning*. The skin, hair and sweat of workers in copper may become green from the conversion, by the acids of the skin-secretion, of particles of copper into coloured salts, which under the microscope have the appearance of a crystalline coating, and there is a bluish green line along the teeth ; but no injury to the health ascribable to the copper has ever been definitely observed. What were formerly taken to be symptoms of " ærugism " or " chronic cuprism," *e.g.* the so-called copper colic, have proved to be due to lead poisoning.

Copper is very poisonous when injected into the blood or subcutaneously in the form of soluble double compounds that do not precipitate albumin, *e.g.* sodium cupric oxide tartrate. It produces a motor paralysis interpreted as paralysis of the striated muscle and ascending paralysis of the spinal cord, which begins with weakening of all voluntary movements, uncertain gait, etc., and ends with cardiac paralysis and respiratory standstill. When the course is slower, inflammation of the intestine and diarrhœa ensue (an action which is common to many heavy metals) destruction of the red blood-corpuscles, jaundice, fatty degeneration and extravasation of blood in various organs.

In man, copper is easily *absorbed* from wound-surfaces, and, though far less easily, in demonstrable amounts from the alimentary canal, and is deposited in the liver. Its *excretion* appears to take place quickly, principally in the bile, to a less extent in the urine, saliva and milk.

Therapeutic Uses. Copper sulphate, like other *emetics*, is now seldom employed as such. In *phosphorus poisoning* it acts (as mentioned under Phosphorus) as a chemical antidote.

Externally, copper sulphate in solid form is used as a superficial but powerful caustic for the destruction of the granulations in *trachomatous conjunctivitis*. Both the components of the salt take part in this, the copper uniting with the albumin to form a firm albuminate, and the liberated sulphuric acid contributing its share towards the corrosion and pain, but being soon diluted by an abundant secretion of tears. In *ordinary conjunctivitis* and (less frequently) in gonorrhœa, dilute solutions are used.

Treatment of Acute Copper Poisoning. Although evacuation is performed by the organism (by vomiting), washing out of the stomach is indicated. A dilute solution of a few grammes of ferrocyanide of potassium, which precipitates a brown, insoluble ferrocyanide of copper, and powdered iron, which takes up the

acids and precipitates metallic copper, are two good chemical antidotes. Gastro-enteritis is treated with mucilage, and opium is useful for the persistent vomiting, pain and diarrhœa.

Preparation

Çupri Sulphas (B.P., U.S.P.), copper sulphate, $CuSO_4 + 5H_2O$, blue crystals, readily soluble in water. *Dose*, 16—120 milligrms., ¼—2 grs.; as an emetic, 3—6 decigrms., 5—10 grs. (B.P.); 0·3 grm., 5 grs. (U.S.P.); for children, 3—10 centigrms., ½—1½ grs. For corrosion in trachoma, a pointed crystal is taken, and its sharp edges smoothed down in a wet towel; for conjunctivitis, ¼ per cent., and for injection into the urethra, a ¼—1 per cent. solution.

9. ZINC

Zinc is also one of the most widely-distributed elements. It is found almost everywhere in the soil, and, consequently, in plants and herbivorous animals. In man it is present even in the fœtal stage, but is not considered to possess any physiological importance. As regards both local and general action, it resembles copper.

Action. Locally the zinc salts have an astringent or a corrosive action, according to the acid with which the metal is combined. Chloride of zinc is highly corrosive, its powerful action being due less to the metal than to the acid and the strong affinity of the salt for water. It spreads over moist tissue, dissolves and sinks deep, and therefore corrodes thoroughly, causing great pain. When the deep, pale grey eschar sloughs after 1 or 2 weeks, it leaves a clean, well-granulating wound-surface. Internally, chloride of zinc produces violent gastro-enteritis similar to that produced by concentrated mineral acids, while the other salts induce mild corrosion, a metallic taste, vomiting, etc., like the copper salts; very occasionally death occurs, following dyspnœa, convulsions and collapse.

Little is known of the **specific action** of the zinc salts. After a large single dose the symptoms seem to come only from corrosion of the mucous membranes. Chronic zinc poisoning in man is not definitely known, although considerable quantities of the metal may be taken up by the organism through the medium of plants that grow on soil containing zinc, from drinking-water supplied by pipes containing zinc, and from domestic utensils made of zinc and brass. In metal-foundries, intermittent attacks of fever occur ("zinc chill," "brassfounder's ague"), which are ascribed to the inhalation of zinc fumes. A disease resembling tabes, and various paralytic conditions, occur in zinc workers,

but appear to be due to contamination of the metal with lead and arsenic.

Soluble double salts *injected into the blood* cause paralysis of striated muscle and ascending paralysis of the spinal cord—the same symptoms in all essentials as those mentioned in the preceding chapter.

Therapeutic Uses. **Zinc oxide** is credited with a sedative action, and, until it was superseded by the bromides, was a highly-esteemed remedy for neuroses accompanied by convulsions. It is now prescribed very occasionally for *epilepsy*, especially in children. Externally, zinc oxide is frequently used as a drying and slightly antiseptic remedy for *weeping eczema*, *excoriations in damp folds of skin*, *ulcers*, etc., but not when there is any great inflammation, as it is then too irritant.

Zinc sulphate has been almost discarded as an emetic, but is one of the most frequently-used astringents, especially in *conjunctivitis* and in *gonorrhœa*, in the latter disease being quite equal in efficiency to the many new anti-gonococcic preparations. Dilute solutions have a very mild action, and may be injected for gonorrhœa from the very beginning, unless the inflammation is unusually great. In conjunctivitis it must not be given until the symptoms of acute irritation have begun to subside. Crude zinc sulphate is employed for disinfection (concerning action, see Ferrous Sulphate, p. 488), and for baths in cases of widespread moist eczema.

Zinc chloride is used in solid form, as a paste or a caustic pencil, for *septic sores*, *syphilitic condylomata*, *lupus*, *glandular swellings* and *malignant growths* such as *cancer of the breast.* Concentrated solutions are good deodorants of *gangrenous and fœtid sores.*

Treatment of Acute Zinc Poisoning. After washing out the stomach, alkaline carbonates should be given, *e.g.* bicarbonate of soda, which precipitates insoluble zinc carbonate, or tannic acid (strong coffee or tea) to convert the metal into the slowly-soluble tannate. Subsequently symptomatic treatment should be adopted as in acute poisoning with copper.

Preparations and Doses

Zinci Oxidum (B.P., U.S.P.), zinc oxide, a light, white powder, insoluble in water. *Dose*, 2—6 decigrms., 3—10 grs. (B.P.). Daily doses, not exceeding 1 grm. for adults and 3 decigrms. for children, can be employed for a very long time, *e.g.* 1 year, without deleterious consequences. Externally, as a dusting-powder with starch, lycopodium or talc in the proportion of 1 to 10 or 1 to 5, for intertrigo, etc. Zinc jelly : zinc oxide and gelatine, 10 grms. of each ; glycerin and water, 40 grms. of each, forming a firm, white mass which melts with gentle heat, to be applied with a brush and

left to stiffen into a membrane, which comes off in a few days. For a stiffer jelly, more gelatine ; for more liquid, less.

Unguentum Zinci Oxidi (B.P., U.S.P.), 15 per cent. and 20 per cent. respectively.

Gelatinum Zinci (B.P.), Unna's paste. 15 per cent. of zinc oxide, gelatin, glycerin, and water.

Pasta Zinci Oxidi Composita (B.P.), 25 per cent. of zinc oxide and 25 per cent. of starch, in soft paraffin.

Zinci Stearas (B.P., U.S.P.), a compound of zinc with fatty acids, principally stearic acid. A white, amorphous powder, employed as a soothing protective to inflamed surfaces, eczema, etc.

Unguentum Zinci Oleatis (B.P.), employed as the above.

Calamina (B.P.C.), calamine, native zinc carbonate. A pink, insoluble powder. Externally, as a sedative and protective in lotions (10 per cent.).

Zinci Sulphas (B.P., U.S.P.), zinc sulphate, $ZnSO_4 + 7H_2O$, colourless crystals which effloresce in dry air and are readily soluble in water. *Dose*, 6—20 centigrms., 1—3 grs. ; as an emetic, 6—20 decigrms., 10—30 grs. (B.P.) ; 1 grm., 15 grs. (U.S.P.). Externally for conjunctivitis, ¼ per cent. ; for gonorrhœa, a ¼—1 per cent. solution.

Zinci Chloridum (B.P., U.S.P.), zinc chloride, $ZnCl_2$, white rods or powder, very deliquescent. Externally, as a corrosive mixed with flour (Canquoin's paste) in the proportion of 1 to 1 or 1 to 2, or as caustic pencils, fused together with 1—5 parts of saltpetre, to burn sores and growths in the cervix uteri, and for intra-uterine corrosion, 50 per cent. ; for antiseptic washes, 8—10 per cent. ; for wound-dressings, 0·5 per cent. ; for gonorrhœal vaginitis and endometritis, warm irrigation with a 1 per cent. solution twice a day.

Zinci Acetas (U.S.P.), an easily soluble salt which may be employed externally in the same concentrations as the sulphate.

10. LEAD

Lead occupies an important toxicological position among metals, partly on account of its frequent employment, and partly owing to the peculiar circumstances of its absorption and elimination.

Lead is **absorbed** slowly from the intestinal canal, though more readily than most of the other heavy metals. It is also absorbed from wound-surfaces, and through the lungs when its compounds are inhaled in the form of fine dust. When once absorbed it *remains for a very long time in the body*, being deposited in almost all the organs, in greatest abundance in the bones, liver, spleen, kidneys and brain. Its slow **excretion** takes place through the kidneys, the intestinal epithelium, the bile, the saliva and the milk. The metal excreted in the intestine is converted by the alkaline sulphides of the intestinal contents into insoluble lead sulphide, which is evacuated with the fæces.

Action. The characteristic feature in the **local action** of lead is derived from its giving, with albumin, an insoluble, dense

deposit, which forms a close covering and confines the action to the surface. Lead is, therefore, as mentioned in the introductory chapter of this section, the type of an astringent metal. On *unbroken skin* its compounds are almost inert; but when, by prolonged use of solutions, or lead plasters and ointments, the skin is softened and has become like a mucous membrane, they exert an astringent action. It may be that in these conditions absorption also takes place. On *wound-surfaces* an aseptic crust is formed, its firmness being increased by the precipitation of lead carbonate by the carbonic acid of the air and the alkalies of the tissues.

Lead salts in solution have at first a sweet flavour (whence the name, sugar of lead, for the acetate), this being followed by a disagreeable, astringent taste. Dilute solutions on *mucous membrane* produce a very superficial coagulation of the albumin, which diminishes the secretion, expels the blood from the tissues, and arrests small hæmorrhages by contracting the vessels and closing them by coagulation. The thin, dead crust sloughs off without much reaction and without visible loss of substance. Concentrated solutions produce the ordinary symptoms of acute gastro-intestinal irritation, nausea, vomiting—the vomit sometimes containing blood—abdominal pain, violent diarrhœa with bloody stools, and serious collapse.

General Action. When organic lead compounds which are not precipitated by albumin or by the carbonic acid of the blood are injected into the veins of mammals, the action is seen to affect principally the intestinal canal and the central nervous system. In the intestine there are both increased peristalsis resulting in diarrhœa, and also constriction of large sections of the intestine, accompanied by severe colic and tenderness of the whole abdomen. The symptoms from the central nervous system appear, especially in dogs and cats, in the form of ataxic movements, irregular twitchings and convulsions resembling those of chorea, and arising from an irritation of the cerebellum and the posterior section of the cerebrum. Both these series of symptoms are interesting, because similar symptoms are seen in chronic lead poisoning in man.

On account of the slow absorption, *acute specific lead poisoning* is very seldom seen in man. As a rule, even after very large doses taken internally, *e.g.* 15—30 grammes of lead acetate, there are only symptoms of gastro-enteritis (which may end fatally), and the poisonous salt is removed by vomiting and diarrhœa before absorption can take place.

The effect produced by constant employment with lead is more important. As elimination takes place even more slowly than

absorption, the metal accumulates in ever-increasing quantities in the body, and after a time produces a dangerous intoxication, **chronic lead poisoning,** which is the most frequent of all chronic metal poisoning. It occurs especially among lead-smelters, workers in white-lead factories, painters, japanners, printers and type-casters, workers in earthenware and china factories (glaze containing lead), in glass factories, etc. Another not uncommon cause is the keeping of food in leaden receptacles, especially when the food contains organic acids which dissolve lead. It is especially the minute particles of the metal that are dangerous, larger particles being less so, although cases have been known of soldiers, who for years have carried a leaden bullet in their body without any symptoms, at last succumbing to lead poisoning. In workshops, etc., the lead compounds are taken into the body partly through the lungs as dust, partly by contamination of food by unwashed hands. Some persons show greater predisposition than others, for out of a number apparently living under similar conditions, some may show signs of poisoning after a few weeks, others no symptoms for years, and others again escape altogether. Traces of lead have often been found in dead bodies, though the patients showed no symptoms during life.

One peculiar feature of chronic lead poisoning is its irregular and intermittent character. It occurs in attacks that are often separated by long periods of apparent health, and relapses may suddenly occur years after all employment with lead has ceased.

The symptoms are as a rule at first vague—indefinite changes in the general condition, disinclination for food, generally constipation, lack of energy, wasting, anæmia and amenorrhœa. Abortion is said to be frequent among women workers in white-lead factories. A change in the blood is of constant occurrence at this stage; the red blood-corpuscles contain granules that stain with basophile dyes ("dotted erythrocytes"). Another early sign is the *lead line*, a slaty grey discoloration of the gums, due to the excretion of the metal through the oral cavity. A microscopical examination of the mucous membrane shows the presence of tiny black granules consisting of lead sulphide; the lead is precipitated by the hydrogen sulphide formed by the putrefaction of fragments of food between the teeth. The lead line may be the very first sign of the disease, it is seldom absent in pronounced cases of poisoning, and remains long after all supply of lead has ceased. It is not a certain sign taken alone, for both bismuth and silver may produce a similar line. When the diagnosis is made early, and the patient's occupation with lead ceases, the poisoning may be confined to these premonitory

symptoms. Otherwise an insidious form of lead poisoning occurs, of which the chief symptoms are *lead colic*, *lead arthralgia*, *lead palsy* and various *disorders of the brain* comprised under the name of encephalopathia saturnina.

Lead colic is generally the symptom that brings the patient to the doctor. After a period of indisposition and constipation, sudden, violent griping pain in the abdomen commences, most severe at the navel, and radiating thence in all directions. The pain occurs in paroxysms, each in itself brief, but with remissions and long intervals of freedom, often extending over several days or weeks. During the paroxysms, the muscles of the abdomen are contracted and the surface drawn in and hard ; there is sometimes obstinate constipation, and vomiting occasionally occurs. The patient often lies on his face, as pressure on the abdomen relieves the pain. Lead colic is a prolonged tonic spasm of the intestine, and is probably due to the fact that lead, like barium, acts directly on the muscles, for a similar action is seen in experiments with isolated loops of intestine from which the Auerbach's plexus has been removed. During the spasms, the pulse, as frequently happens during severe pain, is slow (40—50) and very hard ; but also in the intervals of freedom from pain there is contraction of the arteries (action on the muscle) and high arterial tension.

If the patient changes his employment after the first attack of lead colic, he may make a complete recovery, but, on the other hand, fresh attacks of colic may occur without fresh importation of lead.

Lead arthralgia, arthralgia saturnina, expresses itself in attacks of sharp or burning pain, most frequently in the muscles in the neighbourhood of the joints of the lower extremities, more rarely in those of the upper extremities. During the attack, which lasts for some days, the limbs affected are stiff and helpless. Every movement causes pain in the joints, but no inflammatory symptoms are to be seen, and pressure relieves the pain. The arthralgia is of nervous origin, and must be distinguished from real gout, which, as will be shown, often occurs in lead poisoning.

Lead palsy, paralysis saturnina, is one of the later symptoms, and at once makes the prognosis doubtful. It is not observed in the region of the cerebral nerves, the larynx excepted (aphonia saturnina), but with this exception it may appear almost anywhere, but is most frequently seen in the radial nerve. The paralysis often affects both arms, but is at first monoplegic, beginning in the arm that is most used (thus in the left in left-handed persons). First the extensors of the fingers are affected, then the rest of the muscles supplied by the radial nerve, the

supinators, however, long remaining normal. The paralysis ascends from the forearm to the upper arm and shoulder, with special partiality for the deltoid muscle, and may thence extend to the thorax. In the lower extremities the peroneal muscles and extensors of the toes are first affected, while the tibialis anticus, like the supinator longus, escapes. In lead palsy there is very early degeneration and atrophy of the nerves attacked and the muscles they supply. There are various theories as to the pathogenesis, some writers considering the paralysis to be of central origin, while others hold that it is peripheral neuritis.

The **cerebral affections** occurring in chronic lead poisoning are of various kinds. The most ordinary symptom is persistent headache, which may be the forerunner of mental disease. The end is not infrequently convulsions having the character of epileptic fits, which may follow one another so rapidly that death occurs in the course of a few days (saturnine epilepsy).

In addition to these principal symptoms of lead poisoning, there are many other nerve complaints, for the description of which text-books on toxicology must be consulted. Among the more important is *saturnine anæsthesia*, a brief anæsthesia of various localities. Some cases of temporary *lead amblyopia* must be regarded as anæsthesia of the retina ; in other cases there are anatomical changes, inflammation and degeneration of the optic nerve ; also amblyopia and amaurosis may result from disease of the kidneys (albuminuric retinitis). Lead, like alcohol, may also produce a typical *red granular nephritis* with all its consequences—albuminuria, cardiac hypertrophy, dropsy, and finally uræmia. A late symptom is *gout*, which, especially in France and England, is so frequently observed with lead poisoning that there can be no doubt about the connection. Both clinically and in its pathological-anatomical character, the disease presents the appearance of ordinary gout, with the one difference that it spreads over many joints more quickly than real gout, and that the prognosis is less favourable, as permanent deformities are soon formed.

Therapeutic Uses. The *internal* employment of lead preparations is scarcely ever indicated. Not long ago lead acetate was frequently prescribed as a hæmostatic in lung hæmorrhage, in hæmorrhagic nephritis, pneumonia, œdema of the lungs, and bronchitis with profuse secretion. This treatment has now generally been given up, and rightly so. The lead circulating in the blood as albuminate cannot have any astringent action from precipitation of albumin, and a general contraction of the vessels will scarcely be obtainable with therapeutic doses. The only field still left for the internal employment of lead is diseases of the alimentary tract (gastric and intestinal hæmorrhage, diarrhœa)

which are directly accessible to the drug, but these are better treated with less poisonous remedies.

Externally, lotions (Goulard water), ointments and plasters are much used for *excoriations, bed-sores, discharging ulcers, burns*, etc.; they dry the surface and promote granulation, and the healing is often rapid. In *bruises with unbroken skin, acute inflammation of joints*, etc., a Goulard water poultice is pleasantly cooling (evaporation), although no very deep action is to be expected. A solution of lead acetate is also much used as an astringent in *chronic inflammation of mucous membrane, e.g. gonorrhœa, vaginitis* and *conjunctivitis*, the last, however, not when ulceration is present, as infiltration of the cornea with insoluble lead salts occurs. Lead oxide ointment (diachylon ointment) is a very valuable preparation for the treatment of *chronic eczema*.

Treatment of Lead Poisoning. In acute poisoning the stomach is emptied, and mucilaginous drinks are given, milk, white of egg, and sulphates (Glauber's salt, Epsom salts), which form insoluble lead sulphate. In chronic poisoning the prognosis must always be made with great reservation, as the lead stored in the body may, after lying latent for a long time, again produce very serious symptoms. The treatment is designed to promote the excretion of the metal (iodide of potassium, hot baths, regular use of aperient mineral waters or salts), and to relieve the symptoms. In lead colic, hot baths or fomentations are useful; very severe pain indicates large doses of opium or morphine, which relax the spasms; inhalation of amyl nitrite has also been tried. Evacuation of the bowels is induced by enemata of water, oil, or glycerine, whereas internal aperients generally seem to make the condition worse when the attack is violent. Arthralgia often requires morphine injections. Paralysis is treated in the usual way; the cerebral symptoms defy all treatment.

Preparations and Doses

Plumbi Monoxidum (B.P., U.S.P.), lead oxide, litharge, PbO, a heavy powder or scales of a yellowish red colour, insoluble in water.

Emplastrum Plumbi (B.P.), lead plaster, diachylon plaster, serves as a basis for other plasters.

Unguentum Diachylon, diachylon ointment, Hebra's ointment. Externally, for ulcers, weeping eczema, acne and various other skin-diseases. Combines the astringent, drying properties of the lead with the protective, softening attributes of the fat.

Plumbi Acetas (B.P., U.S.P.), lead acetate, sugar of lead, $Pb(C_2H_3O_2)_2 + 3H_2O$, forms colourless crystals of a sweet, astringent taste, efflorescent and readily soluble. *Dose*, 3—12 centigrms., ½—2 grs. (B.P.); 0·06 grm., 1 gr. (U.S.P.). To avoid the risk of poisoning, must at any rate be used only for a short time. Externally, for injection in the urethra, ¼—½ per

cent.; in the vagina, 1—4 per cent.; and as an eye lotion, a ¼—1 per cent. solution.

Suppositorium Plumbi cum Opio (B.P.). See Opium.

Liquor Plumbi Subacetatis Fortis (B.P.), Goulard's extract, generally used in the official dilution given below.

Liquor Plumbi Subacetatis Dilutus (B.P.), lead water, Goulard's lotion or water. As a poultice for all kinds of bruises and injuries with or without lesion of the skin; it acts as a surface astringent. For application to delicate mucous membranes it should be diluted 1 in 40 with water. Must be freshly prepared.

Unguentum Plumbi Subacetatis (B.P.C.), 12·5 per cent., externally for burns, shallow ulceration, etc.

11. ALUMINIUM

From a pharmacological point of view, aluminium belongs to the heavy metals. Most of the soluble aluminium salts, like the zinc salts, precipitate albumin and have an astringent action, but are more antiseptic than zinc salts. Large doses of alum may cause a fatal gastro-enteritis; but specific action is unknown, and the present employment of aluminium for cooking-utensils is productive of no danger to health.

After subcutaneous injection of sodium-aluminium lactate into mammals (rabbits, cats, dogs), a very slow process of poisoning ensues, ending in death; the symptoms are dysorexia, obstinate constipation and sometimes vomiting, emaciation and loss of strength, lessened sensation, motor weakness that may be combined with convulsions and peculiar forced movements, paralysis of the muscles of the tongue, lower jaw and palate, and, finally, respiratory paralysis. The *post-mortem* examination shows congestion and swelling of the intestinal mucous membrane and fatty degeneration of the liver and kidneys.

Therapeutic Uses. Aluminium forms with various metals and sulphuric acid some crystalline compounds, the so-called alums. Of these **potassium alum** is official. Its taste is both sweet and very astringent. Taken internally it is highly irritant, and in solution astringent; it is employed for catarrh of various mucous membranes (for *diarrhœa*, as a gargle for *sore throat*, and for lavage in *leucorrhœa*). When potassium alum is carefully heated, the water of crystallisation escapes (with too great heat the sulphuric acid also volatilises) and *burnt alum* remains. The loss of its water of crystallisation renders the substance hygroscopic, and strengthens its local action.

Aluminium acetate does not precipitate albumin and is not astringent; but it is a strong antiseptic, and before the time of carbolic acid was recommended for the treatment of wounds by Burow, after whom a solution of this salt has been named. It is still used occasionally in addition to the newer antiseptics.

Preparations and Doses

Alumen (B.P., U.S.P.), alum, potassium alum, $KAl(SO_4)_2 + 12H_2O$, or ammonium alum, $NH_4Al(SO_4)_2 + 12H_2O$, colourless, crystalline masses with a sweetish, astringent taste, slowly soluble in 10 parts of cold water. *Dose*, 3—6 decigrms., 6—10 grs. (B.P.); 0·5 grm., 8 grs. (U.S.P.). As a gargle for sore throat, a 2 per cent. solution; finely pulverised for insufflation in the larynx; mixed with 10 parts of talc for snuffing up into the nose.

Glycerinum Aluminis (B.P.), 20 per cent. *Dose*, 2—4 mils, ½—1 fl. dr.

Alumen Exsiccatum (B.P.), *Alumen Ustum* (U.S.P.), burnt alum, very astringent. On tampons for gonorrhœal vaginitis.

Aluminis Hydroxidum (not official), aluminium hydroxide, $Al(OH)_3$, a white, bulky, amorphous powder, insoluble in water. Externally, as a mild astringent and desiccant.

Liquor Aluminis Acetatis, Burow's solution, contains nearly 5 per cent. of neutral aluminium acetate, $Al(C_2H_3O_2)_3$; *Liquor Aluminis Subacetatis* contains about 8 per cent. of the basic salt, $AlH(C_2H_3O_2)_2$. Both these non-official solutions are powerful antiseptics, and are used to poultice wounds, diluted with 5—10 parts of water.

A great number of antiseptic and astringent aluminium preparations have recently been introduced, *e.g. Alsol*, a combination of the acetate and the tartrate of aluminium, forming colourless, soluble crystals, which are used in ½—1 per cent. solutions; *Alumnol* (naphthol sulphonate), used as a dusting-powder, as a 5—10 per cent. ointment, and as a 1—5 per cent. solution. *Alocol* is a colloidal preparation of aluminium hydroxide.

12. CHROMIUM

Chromium is a heavy metal which, in chemical affinities, resembles iron on the one side and aluminium on the other. Of its compounds only *chromic trioxide*, generally called chromic acid, is employed in medicine.

Chromic acid is exceedingly hygroscopic, and takes up water with great avidity from moist tissues. It is also a powerful oxidising agent, and even at ordinary temperatures oxidises organic compounds and sets free green chromic oxide ($2CrO_3 = Cr_2O_3 + O_3$). In solid form or concentrated solution it is a powerful, but slow, corrosive, forming a dry crust, which sloughs off in the course of 6—8 days. Dilute solutions of chromic acid or chromates precipitate albumin and harden the tissues (used in microscopy). These compounds are readily absorbed from sores, and may give rise to a characteristic poisoning, the symptoms of which are vomiting and diarrhœa, during which yellowish-green and, later, bloody, gastric and intestinal contents are evacuated. When taken internally (potassium bichromate has been tried for syphilis), gastric symptoms begin to appear with doses of 0·03 gramme. Animal experiments with larger quantities show that chromium, like other heavy metals, acts

upon the central nervous system, inducing convulsions and paralysis. In factories for the production of chromic acid preparations the workers suffer from obstinate rhinitis and sometimes perforation of the cartilaginous septum of the nose, caused by the inhalation of tiny particles, which attach themselves to the moist mucous membrane of the septum.

In solid form or concentrated solution chromic acid is employed for *condylomata* and *phagedœnic chancre ;* in dilute solutions, for *syphilitic ulcers* and for *hypertrophy of the mucous membrane* of the nose and throat. Careful painting is efficacious for *sweating feet.*

Preparations and Doses

Chromii Trioxidum (B.P., U.S.P.), chromic anhydride or acid, chromium trioxide, CrO_3, dark red, deliquescent prisms, with a metallic lustre. Externally, as a corrosive, a few crystals or a concentrated solution, applied by means of a glass rod ; for painting ulcers and mucous membrane, a 5—10 per cent. solution ; for sweating feet, after washing and drying the feet, painting once a week for 3 weeks with a 5 per cent. solution, avoiding raw spots.

Potassii Bichromas (B.P.C.), potassium bichromate, $K_2Cr_2O_7$, orange red crystals, soluble in 10 parts of water. *Dose*, 6—12 milligrms., $\frac{1}{10}$—$\frac{1}{5}$ gr.

13. PHOSPHORUS

Phosphorus occurs in two forms, the *ordinary yellow* or *white phosphorus*, which is volatile and luminous in the dark, and the *red*, so-called *amorphous, phosphorus*, which is inert. The cause of this striking difference between two modifications of the same element is that the red phosphorus is neither volatile nor soluble, and consequently lacks the necessary conditions for activity. Formerly phosphorus attracted much attention because it was shown to have a stimulating action on the osteoblasts (see below). This led to its employment in rickets, but with a better understanding of the pathogenesis of this disease, administration of phosphorus therapeutically has been abandoned.

The Action of Small Quantities of Phosphorus. The decided and most important action of long-continued minute doses of phosphorus is a peculiar effect upon the **growth of bone-tissue,** which was very carefully studied by Wegner, and defined as "*a formative stimulation of the osteogenic tissue.*" The action is best followed in young, still immature animals. If young rabbits are given daily for several weeks from $\frac{1}{10}$ to $\frac{1}{5}$ milligrm. of phosphorus, dense bone-tissue is formed, especially in the long bones, at the expense of the cancellous tissue. Instead of the ordinary porous bone-tissue filled with red marrow, there is developed from the epiphysis-lines, a dense, hard substance of the same nature as that which forms the outer shell of the diaphysis. The bone newly formed from the periosteum is

also denser than the normal, and the Haversian canals are not well developed. Simultaneously with this growth, the physiological absorption of cancellous tissue previously deposited at the epiphysis-lines continues, so that the medullary cavity is lengthened, and at last the whole of the long bone consists almost entirely of dense tissue. According to Kochmann's investigations, the percentage of lime is reduced. When, in still growing animals, the administration of phosphorus is discontinued from time to time, alternate layers of porous and dense tissue are deposited at the epiphyses, the dense tissue representing the phosphorus periods. In fully-developed animals the effect is less marked, but in their case, too, the dense tissue increases disproportionately. In birds the medullary cavity may even disappear altogether, so that some of the long bones are transformed into solid columns of bone. In addition to these changes, *proliferation of the interstitial connective tissue* of the gastric mucous membrane, liver and kidneys, has been mentioned as a consequence of the employment of small doses of phosphorus.

The bone-tissue of man reacts to phosphorus like that of animals. The same process goes on in the so-called *phosphonecrosis*. When gaps in the alveolar border are continually exposed during a long time to phosphorus fumes (in match-factories), an ossifying periostitis is produced. First a porous and then a hard, compact deposit appears upon the alveolar border. By infection from the abundant supply of bacteria in the mouth, suppuration and loosening of the periosteum follow as secondary effects. The result is necrosis of the old bone-tissue, which sooner or later either crumbles away in fragments or forms a continuous sequestrum, while the newly-formed osteophytes act as caps to the sequestrum. Spontaneous recovery is rare at this stage. In most cases new secondary necrosis develops, the sequestrum capsule is destroyed, and if operative treatment is not begun in time, large portions of the upper or lower jaw, more frequently the latter, are lost. It appears, generally, to be carious teeth which give access to the phosphorus fumes; but also in persons with sound teeth, by neglect of due attention, the deposit of tartar may push back the gum and expose the alveolar border. The necrosis is therefore not the actual effect of the phosphorus, but makes its appearance with the advent of pus, or more frequently tubercle bacilli. The phosphorus only produces ossifying periostitis.

The Action of Large Doses of Phosphorus. The characteristic features of **acute phosphorus poisoning** usually fall into two distinct sections, first the local effect of the poison on the stomach, and then, after an interval almost without symptoms, the consequences of its absorption.

The earliest symptoms are not very violent. An hour or two after doses of a few centigrammes a gradually increasing feeling of warmth and discomfort begins, followed later by moderate *pain* in the epigastrium, frequent eructation, and finally *vomiting*, the vomited matter being phosphorescent in the dark and having an odour of garlic. There may also

be diarrhœa with bloody stools, but often there are no signs of any great intestinal irritation.

If the vomiting has been sufficiently free, or if the stomach-tube has been employed in time, the matter ends with these initial symptoms ; but as a rule it is not so. After a brief apparent recovery—in rare cases the gastro-intestinal symptoms continue without interruption—about the 2nd or 3rd day of the poisoning, *jaundice* is observed ; the skin and scleræ become intensely yellow, and the urine dark with bile-pigment. The liver is tender and enlarges rapidly, so that the area of hepatic dulness increases from day to day ; and abdominal pain and continual vomiting which makes eating impossible return once more. At the same time the *general condition* becomes worse, and there is restlessness, anxiety, prostration and muscular depression, impaired heart-action with small soft pulse, irregular, often high *fever*, disposition to *hæmorrhage* from the nose, intestine and uterus, petechiæ on the skin, and in cases of pregnancy often abortion. *Derangement of metabolism* occurs as shown by the presence of bile-pigment, albumin, fat and other abnormal products in the scanty urine. In the course of a few days the heart-weakness increases rapidly, the pulse becomes almost imperceptible, secondary systolic murmurs are audible, the area of cardiac dulness increases in width (dilatation), the respiration is frequent and laboured, and a subnormal temperature (32° C., 89·6° F.) takes the place of the previous pyrexia. The patient is generally conscious until a short time before death, when drowsiness and coma supervene, the end being occasionally preceded by convulsions.

Anatomical and chemical changes are the basis of all the above symptoms, and show that phosphorus has a **toxic influence on the metabolism.**

A *post-mortem* examination shows an *abnormal appearance of fat in numerous organs.* In all striated muscle, especially the heart, in the glands of the alimentary canal, in the kidneys and liver, and in the walls of the smaller arteries, the cells are found full of granules and large globules of fat. These are responsible for the clinical symptoms—cardiac depression, enlargement of the liver, oliguria, the appearance of fat-globules in the urine, and the numerous hæmorrhages caused by the weakness of the vascular walls, and occurring the more readily as the coagulability of the blood diminishes. The greatest amount of fat is found in the liver, which in the course of a few days may become so enlarged that it fills a great part of the abdomen. Whether the fat is formed in the liver (fatty degeneration) or brought to it from some other source is a question that has frequently been investigated, the result arrived at being that the greater part is conveyed from the subcutaneous fat to the liver, for the proportion of fat in the entire body is not increased. If another species of fat, *e.g.* cod-liver oil, be injected into an animal poisoned with phosphorus, the oil is found again in the liver. Another process, which is less marked after poisoning with a single large dose than after several small doses, each not in itself fatal, is the *interstitial proliferation of the connective tissue*, which, after the absorption of the fat, leads to a typical cirrhosis and diminution of the enlarged organ. The same shrinking also takes place in the kidneys, and the gastric glands that have undergone fatty degeneration ; these may be replaced so entirely by connective tissue that the surface of the gastric mucous membrane becomes almost smooth. These *cirrhotic degenerations*, which take some time, are seldom observed, however, in man, who as a rule succumbs at an earlier stage. The fatty degeneration of the muscles, in cases of recovery, leaves prolonged weakness, more rarely pronounced atrophy.

It is supposed that the extensive fatty degeneration is due to the greatly *increased destruction of protein*, which is shown by an enormous *increase in the nitrogenous elimination*.

The determination of the several nitrogenous constituents in the urine shows that, besides causing increased protein destruction, phosphorus also *inhibits the normal oxidation of the products of protein metabolism*, for the amount of urea does not increase in proportion to the nitrogenous elimination, often it is even diminished, while intermediary products appear, such as *amino-acids* and *peptone-like bodies*. The *excretion of ammonia* is also greatly increased. This indicates an abnormal formation of acid in the blood, and it is found that both in man and in animals considerable quantities of *lactic acid* are present in the urine. In normal conditions this is oxidised to carbonic acid and water, and therefore does not appear in the urine. Like the sugar which is also sometimes seen, it comes from glycogen, which almost disappears from the liver in phosphorus poisoning. The increased excretion of *phosphates* indicates a destruction of nuclein substances (destroyed cell-nuclei) or lecithin. According to Heffter, the amount of lecithin in the liver is reduced by about 50 per cent. in phosphorus poisoning. The *excretion of uric acid* shows no constant change. The *jaundice* occurring in all serious cases seems, according to Stadelmann's investigations, to be a secondary symptom ; the cells of the liver, which are filled with fat, compress the smaller bile-ducts, and prevent egress by the intestine, and the bile passes into the blood.

Cases of acute poisoning with phosphorus were formerly frequent, and in many countries formed a large percentage of the total of fatal cases of poisoning. From statistics collected by Mörner for Sweden for the period 1872—1892, about 95 per cent. of the cases were women of between 20 and 30, a circumstance which clearly enough indicates attempts to procure abortion as their motive. The smallest fatal dose may be put at 5 or 6 centigrms., but even 1½ centigrms. may give rise to serious symptoms. In 99 out of 100 cases the objectionable lucifer matches furnish the poison. As each match-head contains about 3 milligrammes of phosphorus, 20 are sufficient to cause death.

After enormous doses of phosphorus, the poisoning takes quite a different form. When sufficient quantities of a fine phosphorus emulsion are injected into the blood of mammals, the *heart* is paralysed in a short time without any fatty degeneration being apparent. In man, too, when the dose has been very large or the phosphorus very finely divided, so that absorption takes place rapidly, death occurs in the course of a few hours, with symptoms of cardiac paralysis.

For the rest phosphorus does not appear to have any special action on the organs. **Nerves** and **muscles** are not affected by a saline solution containing phosphorus. Taussig has found, in acute poisoning, a brief but considerable increase in the number of red blood-corpuscles. In chronic poisoning the bone-marrow first becomes hyperæmic, afterwards the seat of a gelatinous degeneration in which many marrow-cells are destroyed. Drawn blood is scarcely changed by phosphorus. The reason why the blood coagulates so slowly in acute poisoning is not known. The suprarenal glands of animals poisoned with phosphorus are stained less with chromic acid than those of normal animals, and thus produce less adrenaline.

Phosphorus possesses no marked **local action.** On the gastro-intestinal mucous membranes it produces only irritation, not actual corrosion. According to some writers, inunction of oil of phosphorus causes redness and burning, while in the experience of others there was no reaction.

The **fate** of phosphorus **in the organism** is only partially known. Probably the greater part is oxidised, but with extreme slowness. Although outside the body it takes up oxygen with such avidity, it seems to circulate for a long time unchanged in the warm arterial blood. According to Selmi, during the first few days of acute poisoning, phosphoric, volatile bases (" phosphato-ptomaines ") are found in the urine.

Numerous therapeutic experiments have been made of late years with organic phosphorus compounds, especially with the so-called *lecithins*, esters of cholin with glycerophosphoric acid and higher fatty acids. Such compounds occur all over the body, especially in the brain, and it is supposed that they play an important part in the cell-metabolism, as, unlike the fats, they can take up water. Lecithin, *e.g.* in the form of hens' eggs—from which it is, as a rule, produced—may be regarded as a food containing phosphorus; but whether it has any other special action is not known. According to Bain, large doses of lecithin cause, in rabbits, an increase in the amount of hæmoglobin and in the number of red blood-corpuscles and lymphocytes. Some writers ascribe to lecithin stimulating action on the heart and nervous system. It has been tried clinically in functional and organic nervous diseases, in neurasthenia and in various conditions of weakness, anæmia and tuberculosis, but without convincing results. Numerous animal-experiments show that the healthy organism, at any rate, does not require organic phosphorus compounds, but builds them up from inorganic phosphates.

Glycerophosphoric acid, a product of the disintegration of lecithin, has also been credited with a beneficial influence on the nutrition, especially that of the nervous system, and is used for neurasthenia, in convalescence, etc. The value of the treatment is very doubtful, and the synthetic glycerophosphoric acid employed in medicine is not identical with that occurring in lecithin.

The *treatment of phosphorus poisoning* consists in quickly and thoroughly washing out the stomach. As the absorption is slow, this is indicated even if 12 hours have elapsed. Next in efficacy are emetics, either apomorphine or sulphate of copper (1—2 decigrammes every 10 minutes until vomiting is induced); the latter also acts as a chemical antidote, as it deposits a layer of copper on the particles of phosphorus, and thus hinders absorption. For the purpose of oxidising the phosphorus to non-poisonous phosphoric acids, permanganate of potash is employed (1 in 1,000 for washing out the stomach), old turpentine or a solution of Sanitas (*cf.* p. 312). The poison that has reached the intestine is removed by a quickly-acting purgative, but not castor oil, which, like all other substances containing fat (milk), is contra-indicated because it dissolved phosphorus. Fully-developed cases of poisoning must be considered as practically beyond treatment; transfusion and saline infusion have been recommended.

Preparations and Doses

Phosphorus (not official), yellow or white wax-like rods or pieces, insoluble in water, sparingly soluble in alcohol and in ether, more readily in fixed oils.

Lecithinum (not official), a yellowish white, waxy mass, soluble in alcohol and in fixed oils. *Dose*, internally, 20—50 centigrms., 3—8 grs., a day ; hypodermically, 1—3 mils of a 5 per cent. solution in olive oil. Eggs are better and cheaper.

Calcii Glycerophosphas (not official), calcium glycerophosphate, $C_3H_5(OH)_2PO_4Ca$, a fine, white powder, soluble in about 50 parts of water. *Dose*, 0·25 grm., 4 grs.

Sodii Glycerophosphas (not official), sodium glycerophosphate, $C_3H_5(OH)_2PO_4Na_2$, white crystals or powder, very soluble in water. *Dose*, like the preceding. *Liquor Sodii Glycerophosphatis*, 50 per cent. *Dose*, 0·35 mil, 6 mins.

None of these preparations is of proved therapeutic value.

14. METALS LESS FREQUENTLY EMPLOYED

Manganese is allied to iron and has often been recommended, but on insufficient grounds, for chlorosis and other forms of anæmia. It is found in numerous plants, many of them cultivated species, *e.g.* cereals, potatoes, lentils, peas, cocoa and coffee ; but as almost none is absorbed through the intestine, it is found only in minute quantities in the human body, where it must be regarded as a chance foreign substance. Manganese salts have a caustic action upon mucous membranes ; when injected into the blood they produce inflammation of the kidneys and intestine during excretion, epileptiform convulsions, fall of blood-pressure and death from respiratory failure. (Potassium permanganate is an oxidiser, and is mentioned in the Chapter on Oxidisers.) *Manganese Butyrate* and colloidal preparations of the metal are injected intramuscularly in the treatment of boils. The results of this form of therapy have not yet been satisfactorily assessed.

Nickel and **Cobalt** also belong to the iron group, and are both very poisonous when injected into the blood. When injected into animals the usual inflammation of the intestinal canal, convulsions of various kinds and central paralysis occur, followed by death. Some interest has of late been attached to nickel on account of its frequent employment for domestic and cooking utensils. It is probably not absorbed, or only in infinitesimal amounts, for no cases of poisoning have been recorded.

Tin is one of the many discarded remedies for epilepsy. It is found in harmless amounts in many preserved foods. Large quantities may produce gastro-intestinal symptoms. No undoubted cases of specific poisoning have been noted, and the cases of reported tinned-food poisoning must be ascribed to tainted food.

Gold, like silver, has had a very varied existence. It was once believed to be a protection from the evil influence of the stars, and a drug that ensured long life. It was subsequently employed for dyscrasic ailments of all kinds (syphilis, cancer, tuberculosis), and until comparatively recently was considered efficacious in diseases of the spinal cord and neuroses. Not long ago it was a vaunted " cure " for chronic alcoholism. Intravenous injections in animals show that gold is far less poisonous than many other heavy metals, *e.g.* iron, but otherwise it has the same general action—gastro-intestinal disorder, and later, convulsions, paralysis and death. The effects of intravenous injection of sodium aurithio-sulphate (Sanocrysin) in pulmonary tuberculosis has aroused much interest. Although not toxic to the tubercle bacillus, gold appears to enhance the defensive mechanism of the tissues in this disease. The treatment is usually fol-

lowed by discomfort in the chest, a febrile reaction and increased cough. Most striking is the rapid disappearance of the tubercle bacillus from the sputum, and this is accompanied by improvement in the lungs on physical and radiographic examination of the chest. Simultaneously, there is subjective and objective evidence of improvement in the patient's general condition. The mode of action of gold in phthisis is not understood, but it is thought that the metal increases the vascularity of the tissues around the lesions and that it may favourably influence the reticulo-endothelial system. Pyrexia is not a contra-indication for gold therapy. The list of possible toxic effects arising from the administration of gold is a formidable one; exfoliative dermatitis is a rare but almost invariably fatal complication.

Favourable reports have recently appeared regarding the value of gold in rheumatoid arthritis. A course of 10 intramuscular or intravenous injections of 0·1 grm. of such preparations as Solganol or Lopion is said to result in relief of pain and much of the disability no matter how severe the disease, and in a few early cases complete cure has been claimed.

Platinum has been tried for syphilis. Its action is like that of gold, but it is more poisonous.

Osmium belongs to the same group of precious metals as platinum. *Osmium tetroxide*, OsO_4, is in the form of yellow prisms, and gives off an exceedingly acrid vapour, which affects the eyes and respiratory mucous membrane. It is much used in microscopy, under the name of *osmic acid*, for hardening and staining, as it is reduced by organic substances with elimination of finely-divided black metal. *Doses* of 0·3—1 c.c. of a 1 per cent. solution have been tried for hypodermic injections in obstinate sciatica and trigeminal neuralgia, and for parenchymatous injections into malignant tumours. Nothing has been reported concerning its general action.

Vanadium is classed in the so-called nitrogen group of the periodic system, together with antimony and arsenic. It resembles the latter element as regards its toxic action, and, according to Berthol, also therapeutically. Several salts (*potassium*, *lithium* and *iron vanadates*; dose, 4—5 milligrms. 3 times a day, 3 days in the week) are said to sharpen the appetite and improve the nutrition in conditions of weakness, especially tuberculosis.

Tellurium, which is in close chemical relationship to sulphur, possesses the peculiar property of arresting the secretion of sweat, probably by paralysing, like atropine, the glandular nerves. In consumptive patients 3—5 centigrms. of *potassium* or *sodium tellurate*, Na_2TeO_4, completely checks night sweats, but is impossible to use, as the breath and all secretions acquire a penetrating odour of garlic, which may remain in the fæces for 2 months and in the breath for even 6 months after the drug has been discontinued. This remarkable phenomenon has been explained by investigations by Hofmeister, who has shown that the tellurium salt is deposited in the body, perhaps as metallic tellurium, and finally converted very slowly into the volatile, strong-smelling methyl-tellurium, $Te(CH_3)_2$. Even excised organs, *e.g.* lungs, liver and testicles, have the power of performing this unusual synthesis.

Cerium. Compounds of the metal cerium, when injected into the blood, produce paralysis of the ganglia and muscles of the heart, and inflammation of the gastro-intestinal tract and kidneys. The oxalate, *Cerii Oxalas*, is a white powder, insoluble in water, and is used in cases of obstinate vomiting that is not due to gastric disease, *e.g.* the vomiting of pregnancy and sea-sickness. In what way it acts is not known. *Dose*, 0·2 grm., 3 grs.

V.—FERMENTS AND FOOD-STUFFS

1. FERMENTS

Pepsin

PEPSIN, the ferment of the gastric juice, occurs in nearly all vertebrate animals (only some species of fish being without it). As is well known, it digests albumin only in acid solution. For medicinal uses it is prepared from the gastric mucous membrane of the pig, sheep or calf, and is prescribed as a digestive remedy for dyspepsia in all kinds of acute and chronic diseases, but, as a rule, with no great benefit, as the condition for its employment is seldom present. Experiments in artificial digestion with gastric juice taken from dyspeptic patients nearly always show that the digestion becomes normal as soon as the necessary amount of hydrochloric acid is added, and that it is not the ferment that is wanting. In practice, however, this diagnostic method cannot, as a rule, be employed. Pepsin, like other ferments, is not procurable in a pure condition.

Pancreatin

Pancreatic juice contains a ferment which converts starch into sugar, another which digests albumin in alkaline solution, and a third which saponifies fat. All three are to be found in the pancreatin of the pharmacopœias. The benefit of this preparation is even more doubtful than that of pepsin, as the ferments are probably destroyed during their passage through the acid-reacting contents of the stomach.

Papain (papayotin)

In many plants, among them being species of the insectivorous *Drosera*, ferments have been found which are allied to pepsin. One of these, papain, which occurs in the milky juice of the leaves, and in the unripe fruit, of the South American melon tree, *Carica Papaya*, has attracted attention owing to its power of digesting albumin, both in feebly acid, feebly alkaline, and neutral solutions. No encouraging results have been obtained, however, from therapeutic experiments. The preparations have exhibited a very irregular action, generally weaker than that of pepsin. Attempts have also been made to arrest the growth of cancer by injecting

papain, but without success. It was hoped that the ferment would digest the tumour.

Diastase

Both in the animal and in the vegetable kingdom there is a widespread occurrence of ferments called diastasic ferments which convert starch into sugar. In plants they are especially abundant when the seed germinates and the reserve nutriment, which is deposited as starch, is to be converted into soluble carbohydrates. The active diastase in germinating barley is of great technical importance, as it converts the starch into dextrin and maltase, and thus makes malt out of the barley. During the malting process, the ferment is formed in great abundance. If the malt is macerated with water and the extract evaporated at a low temperature, the finished product, extract of malt, contains not only soluble food-stuffs, but also some diastase, and digests starch.

Yeast

Beer-yeast—*Saccharomyces cerevisiæ*—and other species of *Saccharomyces* produce several ferments, among them being *zymase*, which forms alcohol from sugar, and the albumin-solvent yeast-endotrypsin. Yeast also contains the anti-neuritic vitamin (see next chapter). In France, yeast is an old popular remedy said to be efficacious in diseases of most varied character, *e.g.* tuberculosis, diabetes, gastro-enteritis and skin-diseases. The systematic experiments made during recent years have shown that certain obstinate cases of acne and furunculus can really be cured by internal treatment with yeast (beer-yeast or baker's yeast). In explanation it has been said that the disease in these cases is caused by an intestinal auto-intoxication, which the yeast cures by destroying the noxious micro-organisms. In leucorrhœa yeast has also been employed ; it is introduced into the vagina, together with a little sugar, and is believed to destroy the local bacteria.

Preparations and Doses

Pepsinum (B.P., U.S.P.), a fine, white or yellowish white powder or thin scales, giving an opalescent solution with 50 parts of water. *Dose*, 3—6 decigrms., 5—10 grs. (B.P.) ; 0·5 grm., 8 grs. (U.S.P.). To be taken after food.

Pancreatinum (B.P., U.S.P.), pancreatin. Contains the enzymes

trypsin, amylase and lipase. Assayed. A colourless or buff-coloured amorphous powder with a meaty odour. Soluble in water, forming a slightly turbid solution. *Dose*, 0·2—0·6 grm., 3—10 grs. (B.P.); 0·5 grm., 8 grs. (U.S.P.).

Diastasum, a yellowish powder or translucent scales. *Dose*, 0·5 grm., 8 grs.

Fœx, yeast (not official). The ordinary trade preparation forms a damp, yellowish grey mass. *Dose*, 1 teaspoonful or more, 3 times a day. *Fœx Medicinalis Sicca*, dried yeast.

2. FOOD-STUFFS

In morbid conditions, in which the activity of the digestive organs is impaired, prepared foods are now often used, manufactured substances that are considered to be very easily digested and absorbed, or which contain already-digested food-stuffs. When wisely used, such preparations may be of benefit in many cases; but at present there are signs of overdoing their employment. Many of the newer foods represent trade enterprises which have nothing to do with the science of medicine; and, in order that they shall not be lost sight of in the competition, they are advertised and extolled out of all proportion to their importance. It is therefore wise to keep in mind that the nutrition of the diseased, as of the healthy, organism must be based upon the ordinary articles of food—milk, eggs, bread, meat, etc., which contain the nutritive substances in the form to which the intestinal canal is accustomed. To make nutrition independent of the intestinal canal, by the aid of food-stuffs that are already digested, is good in theory; but in practice it meets with the obstacle that such preparations frequently produce digestive disturbances when they are used in large amounts. They can therefore, as a rule, only be given in such small quantities that the part they play in nutrition is insignificant. Regarding the almost miraculous action ascribed especially to various albuminous preparations, it should be remembered that such preparations cannot contribute more to the maintenance of the body than the same weight of ordinary albumin, that 10 grammes of an albuminous preparation can never make up for more than 10 grammes of the body's need of albumin, and—expressed in the form of calories—cannot yield more than 40, which is about as much as half an egg or 4 tablespoonfuls of milk.

It should also be noted that foods in the preparation of which a high temperature or strong chemicals are employed may easily be lacking in important properties of which the corresponding raw products are in possession. Recent research shows that our apparently well-grounded theory of nutrition has been incom-

plete in certain points. Until a short time ago it was assumed that the organic food-stuffs, protein, carbohydrates and fat, in combination with salts and water, were sufficient for the normal growth and development of man and animals. During the last few years it has become apparent that this is not the case. When young animals are fed with these substances in a perfectly pure form, various morbid conditions appear, which, as a rule, sooner or later end in death. The above-mentioned nutritive substances obtained from the animal and vegetable kingdoms contain, in addition to protein, carbohydrates and fat, a number of formerly unknown bodies, which are called accessory food-factors (Hopkins) or vitamins (Funk), and are necessary to the growth and maintenance of the body. Their chemical nature has in some instances been elucidated (*e.g.* the anti-scorbutic vitamin and the anti-rachitic vitamin), but for the most part they can at present only be recognised by the disturbances in development or the diseases which appear when they are lacking in the food. As far as we know they are formed mainly in plants, and are taken up from them into herbivorous and omnivorous animals. The anti-rachitic vitamin, however, can be synthesised by the superficial tissues of mammals, including man, on exposure to ultra-violet light or sunlight in a clear atmosphere.

By animal-experiments, in combination with experience of man, the following vitamins, or groups of vitamins, have come to our knowledge :—

(1) The fat-soluble vitamins : vitamin A ; vitamin D (calciferol) ; vitamin E.

(2) The vitamin B complex, including vitamin B_1 (the anti-neuritic vitamin) and vitamin B_2 (the anti-pellagra vitamin) and several others.

(3) The anti-scorbic vitamin, vitamin C or ascorbic acid.

Of these groups the vitamin B complex is perhaps the most widely-distributed in nature. It occurs in great quantities in the bran and germ of grain (but not in the inner, starchy parenchyma), in many other seeds and fruits (*e.g.* peas, lentils, beans, prunes, nuts, bananas), in green leaves, in yeast, in eggs and milk, and a little in flesh, and also in various organs, such as the liver, kidneys, brain and thymus. Rats stop growing and die in paralysis if there is a deficiency of these vitamins in their diet. In birds polyneuritis occurs when they are deprived of vitamin B_1, and in man the allied disease, beri-beri. This first became generally known when the Japanese abandoned their primitive method of milling their principal article of food, rice, and imported machines from the West, which removed the bran and germ (polished rice). The anti-neuritic vitamin has been used with

some success in the treatment of peripheral neuritis—especially that associated with subacute combined sclerosis of the cord and with chronic alcoholism. Recent work tends to show that the vitamin B complex plays some part in the maturation of the red blood cells. Tropical macrocytic anæmia responds favourably to the administration of vitamin B concentrates such as Marmite and Beemax. Good results have also been reported in sprue and cœliac disease. Lack of vitamin B_2 appears to be one factor in the ætiology of pellagra ; the results of treatment of this disease on these lines are, however, still *sub judice.*

The anti-scorbutic vitamin, which is chemically ascorbic acid (a hexuronic acid), is found in the juice of oranges and lemons (these fruits have long been known as an efficient remedy in scurvy), in fresh vegetables (especially those belonging to the *Cruciferæ*, such as cabbage and various species of beet), in prunes, spinach and tomatoes, in flesh and in liver. This vitamin is rather unstable, and is destroyed by boiling, and even deteriorates considerably by drying at ordinary temperatures.

Vitamin E is concerned in reproduction. Its chemical composition is as yet undetermined, but this vitamin is apparently a stable compound unaffected by acids, alkalis and ordinary thermal changes. Vitamin E is of no importance to man. Lack of this factor in experimental animals has been shown to produce sterility after three or four generations.

The other fat-soluble vitamins will be mentioned in the chapter on cod-liver oil.

Albuminous Preparations

Attempts have been made to make nutrition with albumin easier by *pulverising* the albumin, or by administering it in a more or less *digested* form.

Pulverised Albumin. The earliest preparation of this was *meat-powder*, which was beef freed from fat, dried and powdered. It was supposed that in this form the albumin would be more easily acted upon by the gastric juice than in ordinary meat. It has not proved practical, however, as it has a peculiar odour, which arouses distaste, especially in patients who may have little desire for meat.

In cereals the whole of the inner parenchyma contains starch, while the outside layer of cells contains the albuminous aleurone granules. From these "*aleurone-flour*" is obtained as a by-product in the manufacture of starch. This flour, while containing 81—86 per cent. of albumin, has only 6 or 7 per cent. of starch, and is recommended as an article of food for diabetic patients. A light, palatable bread can only be produced, however, when

this preparation is mixed with an equal amount of wheat-flour. Aleurone bread, made in this proportion, contains about half as much carbohydrates as ordinary bread, and a correspondingly larger amount may thus be allowed to diabetic patients. If the bread contain only a small amount of aleurone-flour, as is sometimes the case, it is about as deleterious as ordinary bread. In prescribing this bread, therefore, it is necessary to make sure that its composition is correct.

Digested Albumin. *Peptones* were introduced into therapeutics on the assumption that when gastric digestion is impaired, pepsin and hydrochloric acid could be dispensed with by giving albumin in a pre-digested form. It was soon apparent, however, that peptones can only be tolerated in small doses. They have a bitter taste resembling that of bile, and when taken in large quantities have a directly harmful effect, as they irritate the gastric mucous membrane and often cause diarrhœa.

To obviate the disadvantages of peptones, artificial semi-digestion products of protein-digestion were used, the so-called *albumoses.* These preparations have the advantage of being tasteless and odourless, are readily soluble, and can be absorbed without further preparation. Albumoses, however, are able to satisfy only a small proportion of the albumin requirement ; in large doses they cause diarrhœa, and are also said to prevent the assimilation of other proteins.

Meat-juice and **meat-extract** belong more properly to beverages than to food-preparations. The *juice* expressed from fresh beef contains 92—93 per cent. of water, 3—4 per cent. of extractive substances (creatin, etc.), and only 2—3·5 per cent. of albumin. Its nutritive value, therefore, contrary to the popular belief, is very trifling. As fresh meat-juice does not keep long, and acquires an unpleasant taste after only a few hours, it has been superseded by evaporated extracts, the co-called *extracts of meat.* The best known of these is *Liebig's Extract of Meat,* which is manufactured in enormous quantities in South America by the maceration of chopped beef in hot water, with the subsequent evaporation of the liquid and removal of separated albumin and fat. The finished product contains about 20 per cent. of soluble albumins and 38 per cent. of " meat-bases " (creatin, creatinine, hypoxanthine, etc.). Extract of meat is employed only in small doses, and, as Liebig has pointed out, is of no importance as an article of food, but by its caffeine-allied meat-bases acts as a stimulant. With its taste and odour it also stimulates the appetite, and may therefore in sick-nursing be employed with advantage in beef-tea and as a flavouring agent in insipid gruels, etc. There is a large number of widely-advertised preparations occupying an inter-

mediate position between meat-juice and extract of meat; but they are quite superfluous and often expensive.

Carbohydrates

It has been already stated that in disease the attempt has been made to replace some of the ordinary albumin, which requires considerable manipulation, by pre-digested albumin. Long before the plan was tried on albumin, **digested starch** had been employed to supplement sick-diet, in the form of **malt-extract,** *i.e.* an evaporated watery extract of germinated barley, the starch of which is converted by ferments into maltose and soluble dextrin. In addition to these carbohydrates, the extract contains a small percentage of albumin, a little fat, inorganic salts and, if the evaporation has been conducted at a low temperature, still active diastase. It may thus also contribute to the digestion of starch. Extract of malt has a peculiar, mawkishly sweet taste, which is especially liked by children, and is used in their case principally as an addition to their other food in convalescence, anæmia, scrofula and chronic bronchitis. It is a convenient preparation, but is of no great nutritive value, as the largest doses that can be given, namely, 3 to 4 tablespoonfuls daily, contain only about 30—40 grammes of carbohydrate, which equals 120—160 calories. The disadvantage of feeding with sugars on a large scale is that disturbances of digestion occur which are absent during normal starch-digestion, as the sugar is removed from the intestine by absorption quite as quickly as it is formed.

Preparations of flour, in which the starch has been converted in various ways into dextrin and sugar, are sometimes used as substitutes for milk, or to supplement it in the first few months of a child's life, before the secretion of starch-digesting ferments begins. These preparations will not be described here, as they are intended for regular feeding, and are not reckoned as drugs.

Preparation

Extractum Malti (B.P., U.S.P.), a thick, brown liquid. *Dose,* 4—16 mils, 1—4 drs. (B.P.), 15 grms., 4 drs. (U.S.P.).

Fats (Cod-Liver Oil)

Cod-liver oil is the liquid fat from the liver of the large sea-cod, *Gadus morrhua,* and other species of cod, which at certain seasons make their way in from the sea to the west coast of Norway and to Newfoundland, to spawn upon the banks lying off these coasts.

Cod-liver oil was used medicinally by the Norwegian fisher

population long before it found its way, in the beginning of last century, into other countries. The method of extracting the oil was primitive. The liver was cut out of the fish and placed, without any special cleansing, in barrels, where it was left to itself. With the bursting of the liver cells under the pressure, or their decomposition, the oil flowed out spontaneously, and was drawn off as required. This home-made cod-liver oil was yellow or brown, had a rancid, rather bitter taste and a strong fishy odour, and contained numerous products of the decomposition of both protein and fat.

After cod-liver oil had shown itself also in the physician's hands to be a valuable drug, the reason of its efficacy became a much discussed and variously answered question. The first explanation given was that it contained small quantities of iodine or phosphorus, and some importance was attached to the bile salts; later, when bodies resembling alkaloids were discovered by French investigators (originating in the autolysis or decomposition of the liver), attention was turned to them. All these hypotheses had to be given up, however, when on going over to the use of the newer kinds of cod-liver oil, which are free from the above impurities, the therapeutic results proved to be the same.

It was subsequently found that cod-liver oil occupies a peculiar position chemically, for it contains, besides the ordinary species of fat, glycerides of very non-saturated fatty acids not found in other oils and at present little known, which are remarkable for the great ease with which they are oxidised and also form fine emulsions. This gave rise to the view that cod-liver oil must not be considered as a drug in the ordinary sense of the word, but only as a food which is absorbed more quickly in the intestine, and is more readily oxidised in the body than more resistant fats. This explanation, however, especially in view of the striking effects in rickets, is not altogether satisfactory.

Through the investigations of a number of English and American scientists, attention has now been directed to vitamins A and D, which are soluble in fat. Vitamin A occurs in green leaves and in roots, in the chaff and germ of cereals, in eggs, in the fat of milk and consequently in considerable quantities in butter, a little in beef and in ordinary fat, but not usually in lard. It is also practically absent from vegetable oils, but is found in fish-oils, above all in halibut liver-oil and cod-liver oil, in which the percentage of vitamin A far exceeds that of any other hitherto examined products of the animal or vegetable kingdom. Chemically, vitamin A is related to carotene, $C_{40}H_{56}$, which is present not only in carrots but also in many green vegetables.

Vitamin A seems to be indispensable in the earliest period of

life. When first young rats are put upon a diet which, though complete in other respects, is lacking in this vitamin, their normally rapid growth stops, and for a short time the growth-curve runs horizontally. After this, notwithstanding continued good appetite, their body-weight begins to diminish, and a disease of the eye appears, which strongly resembles xerosis of the conjunctiva and the cornea in man ; the animals acquire an atrophic appearance and exhibit increased susceptibility to infectious diseases, especially pneumonia, and before long die. If a sufficient amount of vitamin A is administered in time, their condition rapidly improves, growth recommences and continues normally.

In 1918, Mellanby discovered the anti-rachitic vitamin (vitamin D) of cod-liver oil. Other fish-liver oils contain this vitamin in abundance, and it is also present in milk, egg-yolk and green vegetables. Its chemical composition is now established and in the crystalline form it is known as *calciferol*. Vitamin D presides over the absorption of calcium and phosphorus in the correct proportions for the requirements of the tissues, and it plays an important part in the mobilisation of these elements in the formation of bone and teeth. Lack of this vitamin results in the various manifestations of rickets, including softening of the bones, which are then easily deformed by the weight of the body, and overgrowth of the epiphyses, which are nevertheless imperfectly calcified. The teeth erupt late and are often poorly formed. The rachitic child is also very liable to develop catarrhal conditions of the mucous membranes, particularly in the alimentary and respiratory tracts.

Therapeutic Uses. Cod-liver oil is the principal remedy for rickets. As already stated, the vitamin D which is contained in the cod-liver oil is concerned in the retention of lime and its deposition in the bone-tissue. This action can also be shown experimentally. McCollum and his co-workers were able with a suitable diet to induce rachitis, or a very similar condition, in rats. Cod-liver oil was then added to the insufficient diet, and in a few days the incipient deposition of lime in the growing-zone of the diaphyses could be demonstrated microscopically. These observations have been amply confirmed in recent years by numerous workers. From its nature it will be understood that the action is also prophylactic. Systematic experiments were made by Hess and Unger in New York, where 90 per cent. of the negro children have rickets. Of 32 children who from their 4th month were given 8 or 9 grammes of cod-liver oil daily for 6 months, 30, *i.e.* 93 per cent., remained healthy ; with continually reduced doses and shorter treatment, the results were correspondingly less good ; and out of 16 children who received no cod-liver oil, only 1, *i.e.* 6 per cent.,

escaped the disease. Graduated doses of ultra-violet light have the same beneficial action owing to the synthesis of vitamin D in the body-tissues. As an anti-rachitic measure, however, such treatment is somewhat inconvenient and expensive.

The disease of the eye, *keratomalacia*, appearing in rats from the want of vitamin A, is also known, as has been said, in man. It is seen frequently in India, in districts where the population lives principally on polished rice and vegetable oils, and it occurred during the War in many places in Europe, owing to the scarcity of fat. It has also been reported from children's hospitals, where separated milk, almost devoid of fat, has been used. In all such cases cod-liver oil has shown itself to be an almost specific remedy.

Cod-liver oil is often employed with excellent effect on those children—especially numerous in large towns—who, without suffering from any definite disease, have an *atrophic appearance*, *grow slowly*, *constantly suffer from catarrh*, and *fall an easy prey to infectious diseases*. It will be seen that these symptoms resemble those produced in the rat by lack of the fat-soluble vitamins.

In chronic wasting diseases of later life, *e.g. chronic bronchitis* and *tuberculosis*, cod-liver oil is also a good and much used remedy. Its value in such conditions lies perhaps less in its containing vitamins than in supplying the body with much combustible material in a small compass ; as a fat it furnishes a large amount of heat and is free from water, while most other foods contain from 60 to 70 per cent. of water. A tablespoonful of cod-liver oil furnishes about 120 calories, and 3 tablespoonfuls, therefore, 360, a no small portion of the daily requirement. The old, brown kinds of cod-liver oil often caused nausea and dyspeptic symptoms, but the newer kinds are generally taken without much difficulty, and as a rule tolerated well when the precaution of beginning with small doses and increasing them slowly is observed. Like all kinds of fat, cod-liver oil is better tolerated in cold weather than in hot. It should be taken between meals, if possible. When there is an unconquerable aversion to the oil, one of the numerous emulsions on the market may be tried, or calciferol may be prescribed. Inunction has also been recommended, since cod-liver oil is readily absorbed through the skin ; but it is a troublesome treatment to continue for any length of time, and alternative preparations which are now available for oral administration make it quite unnecessary.

As far as *prophylactic measures* are concerned, it is rarely necessary to resort to pharmacopœial preparations of the vitamins. Judicious selection of natural food-stuffs suffices to avoid the deficiency diseases such as scurvy, rickets, keratomalacia, etc. In treating these conditions once they have developed, dietetic

adjustments must not be overlooked, though it must be admitted that the use of vitamin concentrates in these circumstances often accelerates the rate of recovery of the patient.

Preparations and Doses

Oleum Morrhuæ Non-Destearinatum (U.S.P.), this is the crude preparation from which medicinal cod-liver oil is prepared.

Oleum Morrhuæ (B.P., U.S.P.), cod-liver oil, Oleum Jecoris Aselli, a pale yellow oil with a fishy, but not rancid, odour, and a fishy taste. When the number of units of vitamin D in cod-liver oil is stated, the units should be those described under the Biological Assay of Anti-rachitic Vitamin in the B.P. With regard to the U.S.P. preparation, it is stipulated that each gramme must contain at least 600 U.S.P. units of vitamin A and 85 U.S.P. units of vitamin D, with not more than 1 per cent. of any official flavouring substance. *Dose*, prophylactic, 1—2 mils, 15—30 mins. thrice daily; therapeutic, 3—6 mils, 45—90 mins. thrice daily (B.P.); adults, 8 mils, 2 drs., infants, 4 mils, 1 dr. administered thrice daily (U.S.P.).

Extractum Malti cum Oleo Morrhuæ (B.P.), extract of malt with 10 per cent. of cod-liver oil. *Dose*, 4—16 mils, 1—4 drs.

Emulsum Olei Morrhuæ (U.S.P.), 50 per cent. Is often taken more easily than the oil alone.

Calciferol (B.P.), $C_{28}H_{43}OH$. Prepared by the ultra-violet irradiation of ergosterol in a suitable solvent. 1 milligrm. containing 40,000 units of anti-rachitic activity (vitamin D). Colourless crystals, odourless, insoluble in water, soluble in alcohol. *Dose*, prophylactic (daily) for an infant 0·025—0·05 milligrm., $\frac{1}{2400}$—$\frac{1}{1200}$ gr. (1,000—2,000 units); therapeutic (daily) for an infant, 0·05—0·075 milligrm., $\frac{1}{1200}$—$\frac{1}{800}$ gr. (2,000—3,000 units). *Liquor Calciferolis* (B.P.), a solution of calciferol in oil. 1 grm. contains 3,000 units of anti-rachitic activity (vitamin D). *Dose*, prophylactic (daily) for an infant, 0·3—0·6 mil, 5—10 mins. (1,000—2,000 units); therapeutic (daily) for an infant, 0·6—1 mil, 10—15 mins. (2,000—3,000 units).

Liquor Ergosterolis Irradiati (U.S.P.). Viosterol in Oil. This is an edible vegetable oil containing ergosterol which has been activated by irradiation with ultra-violet light. *Dose*, 0·3 mil, 5 mins. It contains 10,000 units of vitamin D in 1 grm.

Proprietary preparations containing both vitamin A and vitamin D in concentrated form include Adexolin, Advita, Radiomalt, Radiostoleum, and Collosol Halibut Liver Oil.

Acidum Ascorbicum (B.P.), Ascorbic Acid, Vitamin C. Chemically it is enolic form of 3-keto-l-gulofuranolactone, O.CO.C(OH) : C(OH).CH.CHOH.CH_2OH. 1 grm. contains 20,000 units of anti-scorbutic activity (vitamin C). Obtained from ripe fruits of Capsicum annuum, and other vegetables sources, or by synthesis. Minute colourless crystals, odourless, acid, lemon taste. Soluble in water. *Dose*, prophylactic (daily), 0·025—0·05 grm., $\frac{2}{5}$—$\frac{4}{5}$ gr. (500—1,000 units); therapeutic (daily), 0·1—0·25 grm., $1\frac{1}{2}$—4 grs. (2,000—5,000 units).

Pulvis Vitamini B_1. Adsorbate of vitamin B_1. This preparation consists of an adsorbate of vitamin B_1 (the anti-neuritic vitamin) upon fuller's earth. 1 grm. contains 100 units of anti-neuritic activity (vitamin B_1). Prepared from rice polishings, yeast or wheat embryo by acid extraction

and adsorption on fuller's earth. *Dose*, prophylactic (daily), 1—2 grm., 15—30 grs. (100—200 units); therapeutic (daily), 2—6 grms., 30—90 grs. (200—600 units).

There are several proprietary preparations of vitamin B_1 for subcutaneous injection.

VI.—ANTITOXINS AND BACTERIAL PRODUCTS

1. GENERAL REMARKS

In this section the terms *antitoxic* and *bactericidal serum*, *passive* and *active immunity*, are of frequent occurrence. The following remarks may serve to explain these terms.

The pathogenic micro-organisms produce injurious substances in the body called *toxins*, which differ in many respects from other poisons. Their most remarkable property is that they elicit the formation of antidotes or antitoxins, which render the toxins harmless by uniting with them to form non-poisonous compounds in the same way as an acid neutralises a base. How the formation of the antitoxin takes place is not known. Ehrlich's well-known "side-chain hypothesis" assumes that the toxins in the body combine with certain components of the cells, and that the part of the protoplasm that is thus used (the side chain) is replaced in greater abundance than before by a strong reaction on the part of the organism; these fresh side chains pass into the blood, which then possesses the power of combining with fresh quantities of toxin. The formation of antitoxin may thus be compared to a process that goes far beyond its aim. If the disease is overcome, not only is all the poison formed by the bacteria neutralised, but the serum of the healed animal or man contains an excess of unutilised antitoxin. This **antitoxic** serum, when injected into another subject, is now able to combine with a corresponding amount of toxin. The reaction between toxin and antitoxin takes place, like other chemical reactions, according to definite proportions. If 1 c.c. of serum has the power of neutralising a certain amount of toxin, 10 c.c. can combine with 10 times that amount of toxin.

The combination of toxin with antitoxin is formed both outside and inside the body. If corresponding amounts of toxin and antitoxin are mixed in a test-tube, they combine, and the compound may be injected into an animal without producing poisoning. This is also the case when they are injected separately, provided that the injections are performed simultaneously or the antitoxin is given first. If the toxin is injected first, it is soon combined with the susceptible (toxiphile) cells, and when this has happened, the calculated doses of antitoxin are no longer sufficient, a great excess of it being required to remove the toxin. If some time has passed, the toxin has become definitely fixed to the cell-

substance, and an antitoxin treatment will be fruitless. Hence the very important practical rule that a serum treatment must be begun as early as possible.

The antitoxic sera, of which the diphtheria and the tetanus sera are the typical representatives, only produce **immunity against poison** ; that is to say, they only fix the respective poisons, but have no effect upon the living bacteria—indeed, diphtheria bacilli can grow in diphtheritic serum. Besides antitoxins, the bacteria can also cause the formation of substances that are poisonous to themselves, and which either destroy or dissolve them without having any effect upon the toxins. Blood-serum containing such substances is called **bactericidal serum,** and the immunity it produces is termed **bacterial immunity.** Among these are the anti-pneumococcic, anti-streptococcic and anti-dysenteric sera.

A distinction is also made between **active** and **passive immunity.** The former is acquired by supplying the body with bacteria or bacterial products which produce a reaction in the tissues which leads to the formation of protective substances. Passive immunity, on the other hand, consists in furnishing the organism with protective substances already formed. From a practical point of view there is an important difference between these two kinds of immunity. The active form, which depends upon substances which the patient himself must produce, is not attained for some time, but, when attained, is kept, as a property acquired by the organism, for a long time : a number of bacterial diseases leave a lifelong immunity. Passive immunity, on the contrary, begins immediately, but lasts usually only for a short time, as the injected substance produced by another organism behaves like a foreign body, and is soon eliminated or disappears in some other way.

The immunising processes are of a strictly specific nature. The diphtheria antitoxin neutralises only diphtheritic toxin, the tetanus antitoxin only tetanus toxin, and so forth. Each separate serum is, therefore, only effectual for one particular disease.

For the sake of clearness, only bacteria and bacterial toxins have been mentioned here. In reality, the formation of antitoxic and bactericidal substances represents only a special form for a general reaction on the part of the organism against foreign bodies of an albuminoid nature. Not only microbes and their poison, but also foreign blood-corpuscles and other cells, foreign serum, milk, sperm, snake and insect venom, ricin and allied substances (see p. 330), the pollen of many plants, etc., etc., cause the formation of specific *antibodies*, after more or less violent reaction. Substances which produce these are known by the common designation of "*antigens.*" Man's reaction to the serum of horses, so often employed in medicine, is of special practical importance. (See next chapter.)

2. DIPHTHERIA ANTITOXIN

The aim of the serum treatment of diphtheria is to confer **passive immunity against diphtheria toxin.**

The diphtheria serum is obtained from horses that are actively immunised by subcutaneous injections of diphtheritic toxin, *i.e.* cultivations of diphtheria bacilli in which the bacilli are destroyed. The first injections are so small that the animal does not become seriously ill, but reacts with the production of a certain amount of antitoxin. When this has taken place, rather larger doses can be injected, which are responded to by the formation of more antitoxin, and so the dose is increased until the animal attains the highest degree of immunity, which protects it against enormous doses of the toxin. After 2 or 3 months a sufficient degree of immunity is reached, and the blood-serum of the animal contains a large amount of antitoxin, with which poisoning in human subjects suffering from diphtheria can be combated. For this purpose the horse is bled from the jugular vein, and the serum is separated, carbolic acid or cresol being added as a preservative. For its practical employment the strength of the antitoxin must be known. This is determined by experiments on guinea-pigs, and the immunising unit is the quantity that is just sufficient to neutralise a certain amount of the toxin (test dose). When it is necessary to inject massive doses of antitoxin, serum is available which contains 3,000 or more units per cubic centimetre. For this highly virulent cultures and suitable animals are required, for all horses are not equally susceptible.

Action and Employment. Behring's introduction of the serum treatment of diphtheria (1893) forms one of the great boundary marks in the history of medicine, both because it has decidedly reduced the mortality of one of the most dangerous of infectious diseases, and still more because it represents an extraordinarily far-reaching therapeutic principle. The serum treatment has great influence not only on the general intoxication, but also on the local process. If a sufficient amount of antitoxin has been administered, the patient's temperature has fallen and his whole condition has improved in 12—24 hours after the injection. At the same time the false membrane becomes less coherent, acquires a yellowish colour, and, after gradually loosening at the line of demarcation which forms, is generally entirely cast by the 4th or 5th day. Laryngeal and other forms of diphtheria, *e.g.* in the eye, are influenced in the same way as faucial. The prospects in tracheotomy cases are also much better than formerly, and no membrane ever makes its appearance in the tracheotomy-wound of patients who have received the serum—a dreaded complication

which was formerly very common, and contributed to the bad results of the operation.

The prognosis in uncomplicated diphtheria seems, in the main, to depend upon how early the antitoxin is given. According to reports from a hospital in Christiania, out of 857 cases, the mortality among those who had received the serum on the 1st day of the illness was 0 per cent.; of those treated on the 2nd day, 1·5 per cent.; on the 3rd day, about 6 per cent.; on the 4th day, about 8 per cent.; on the 5th day, about 14 per cent.; and on the 6th day, about 21 per cent. Even before the days of serum therapy it was recognised that, in cases that did not come for treatment until the 5th or 6th day, or even later, the prognosis was more unfavourable (because it is mainly the more serious cases that come in so late in the disease), but the difference was not nearly so great as that now seen. The reason of this striking difference between the results of an early and a late treatment is that, as mentioned in the preceding chapter, it is only the free toxin that can be easily neutralised by the antitoxin. When the toxin is fixed to the cells, a reaction which quickly takes place, it is with difficulty separated from them by the aid of a large excess of antitoxin, and at last a stage ensues in which fatal quantities of poison are firmly fixed to the cells and withdrawn from the influence of the antitoxin. The great importance of an early treatment is well illustrated by animal experiments made by Dönitz, who injected large quantities of toxin—*e.g.* 15 times the fatal dose—directly into the blood of rabbits. With such enormous doses large quantities are fixed to the cells, not in the course of days, as in diphtheria in man, but in the course of minutes; and it could be seen from minute to minute how the amounts of antitoxin must be increased in order to save the animal, until a critical moment arrived when even the largest doses were without effect.

Every fresh case of diphtheria should be treated with the serum, and the doses should be large. It will be easily seen from what has been said about the fixing of the poison to the cells that this refers especially to the more serious cases, in which treatment is not begun until the disease has run several days, and in which its first day is not known. Large doses can be given without danger when the antitoxin is not poisonous. Ill effects (called serum-sickness) occur in from 6 to 12 per cent. of the cases in which the serum has been given, consist in exanthemata, pyrexia and pains in the joints, and are not dangerous. They are not due to the antitoxin, but to the foreign serum; for similar symptoms are also seen after injections of the serum of horses that are not immunised. After repeated injections, a hypersusceptibility, or *anaphylaxis*, may

appear, which does not develop until after about a fortnight, and is thus not taken into account when the second injection follows close upon the first ; but it lasts a long time, perhaps for life. In animals this hypersusceptibility expresses itself in very dangerous forms, particularly vaso-motor paralysis and bronchial spasm (anaphylactic shock). In man this is of the rarest occurrence, and is seen principally after intravenous injection, which therefore should not be given to patients who have previously been treated with serum. The cure consists in hypodermic injections of adrenaline or atropine to relax the bronchial spasm. In persons with congenital hypersusceptibility, who exhibit indisposition or attacks of asthma when in close proximity to horses, the ordinary diphtheria serum may elicit strong symptoms of shock, and intravenous injections must therefore be avoided. The serum of oxen and sheep has been tried in these cases, but the percentage of antitoxin is much smaller than in the horse. Cases of hay-fever and other allergic manifestations must also be treated with caution. When there is reason to suspect sensitiveness to foreign protein, a few drops of a 1 in 10 dilution of the serum should be instilled into the conjunctival sac or injected intradermally. A local reaction occurring within half an hour indicates the need for " desensitisation." This is carried out by injecting intramuscularly 0·2, 0·5, 1, 3, and 5 mils of serum at intervals of 20 minutes. If no local or constitutional disturbances are produced, an appropriate therapeutic dose of antitoxic serum should be injected intramuscularly and half an hour later a supplementary dose may be administered intravenously if necessary. In all cases intravenous injections must be given *slowly* and the serum must be kept warm. A syringe containing 1 mil of adrenaline solution should be in readiness for immediate use should anaphylaxis occur.

It is important to remember that the serum treatment does not exempt from observation of the ordinary precautions against the spread of infection, for the diphtheria antitoxic serum protects only from the toxin of the diphtheria bacillus, without killing the bacilli. Persons treated with the serum very likely carry bacilli in their nose and throat, and may thus act as carriers of infection.

In *hæmophilia*, hæmorrhage is sometimes seen to cease after injection of diphtheria serum. In explanation of this it has been said that the blood is supplied with a coagulating ferment. Thus other sera may be used, but the diphtheria serum is, as a rule, the most easily obtained.

Diphtheritic serum is also efficacious as a prophylactic remedy, and may be indicated in conditions where isolation is difficult to

arrange. The immunity lasts, as far as is known, for only 3 or 4 weeks.

When " contacts " can be kept under *close observation* by the physician, it is preferable to withhold antitoxin until the susceptibility of the individual has been investigated by means of the Schick Test (see p. 540) and the examination of swabs taken from the nose and throat. The following scheme can then be utilised for the management of the " contacts."

SCHICK.	SWABS.	CONDITION.	MANAGEMENT.
Neg.	Neg.	Immune.	Discharge.
Pos.	Neg.	Susceptible.	*Active* immunisation.
Neg.	Pos.	Carrier.	Isolate. Test virulence.
Pos.	Pos.	Clinical diphtheria.	Isolate. Inject 4,000 units of antitoxin.

The appearance of clinical evidence of diphtheria during the investigation indicates the immediate injection of antitoxin, *e.g.* 8,000 units. As a rule the observations can be completed within 48 hours, but the Schick Test should be inspected daily for a week so that delayed positive reactions will not be overlooked.

3. TETANUS ANTITOXIN

This is prepared by immunising horses in the same way as for diphtheritic antitoxin.

In practice tetanus antitoxin differs from the diphtheritic in that its curative value is doubtful. A few cases have been described in which the treatment is said to have saved patients whose life was despaired of; but, as a rule, it seems to have no effect upon already diagnosed tetanus. The reason of this, according to investigations by H. Meyer and Ransom, is that the tetanus toxin does not travel to the central nervous system through the blood or lymphatics, but through the nerve-trunks, while the antitoxin takes the usual way through the circulation, and is not taken up by the nerve-elements. Thus antitoxin and toxin do not meet, and therefore cannot unite with one another. To be of any use an antitoxin should be given while the poison is still within reach; but with tetanus this is not easy, for the disease cannot be diagnosed before convulsions begin, and these indicate that the toxin has already reached the nerve-cells. The serum-treatment has no deleterious consequences, however, and a trial may therefore still be made. Somewhat better results have been attained of late by intraspinal injections; and local applications to the wound and endoneural injections have also been tried.

As a prophylactic, on the other hand, tetanus antitoxin is very efficacious. It is easy to prove by animal experiments that an injection of the antitoxin gives protection against a subsequent injection of tetanus toxin, and clinical experience points in the same direction. At a lying-in hospital in Prague, for instance, an epidemic of tetanus that it had not been possible to arrest with disinfecting precautions, ceased instantly upon the introduction of a preventive treatment with serum. In such circumstances and in suspicious injuries, *e.g.* with nails or splinters of wood that may carry earth or street-dust, prophylactic injections are the right treatment.

4. OTHER KINDS OF SERUM

Scarlet Fever Antitoxin is obtained from horses which have been immunised by injections of the toxins produced by certain strains of streptococci which are believed to be the causal organisms in scarlet fever. The immediate benefits of serum-treatment of this disease are as obvious as in the specific treatment of diphtheria. It is also established that the use of scarlatina antitoxin reduces the incidence of complications in so far as the course of the disease is frequently shortened and its severity lessened. Once developed, however, the treatment has no effect upon the complications of the disease. The antitoxin is injected as early as possible by the intramuscular route, and it may be repeated if necessary in the course of the first three days. Intravenous administration of large doses of antitoxin are indicated in severe cases where there is considerable toxæmia. On the other hand, serum-therapy is often omitted in mild cases of the disease. Susceptible " contacts " can be protected temporarily by an intramuscular injection of a small dose of antitoxin.

Antipneumococcus Serum. Patients suffering from lobar pneumonia caused by infection with the Pneumococcus Type I or the Pneumococcus Type II may be treated with appropriate sera. These sera are obtained in the usual way, *i.e.* following the immunisation of horses with the particular strains of pneumococci, but the protective substances contained in the sera are *bactericidal* on account of the agglutinins they contain. Typing of the pneumococcus is carried out by means of high-titre sera. Sometimes the direct method of agglutination, using the patient's sputum for the test, is unsatisfactory. In these circumstances an emulsion of the sputum is made and injected into the peritoneal cavity of a mouse, and a pure culture of pneumococci is usually obtainable on aspirating the abdomen in about 24 hours. Accuracy in bacteriological diagnosis is essential in order that a monovalent serum may be

used. No antisera are available for Type III infections, nor for pneumonia caused by the organisms in Group IV. Failing facilities to identify the type of pneumococcus present, a polyvalent serum containing a mixture of agglutinins for Type I and Type II pneumococci may be employed, but for obvious reasons this is less satisfactory. Carefully controlled investigations have shown that antipneumococcus sera are valuable when administered early in the course of the disease—preferably at the onset, but not later than the third day of the illness. In Type I and Type II infections the duration of the disease and the mortality have been considerably reduced. Injections of antipneumococcus serum should invariably be administered *intravenously* and in large doses.

Antimeningococcus Serum. Four distinct serological types of meningococcus have been isolated, and this has an important bearing upon specific therapy in meningococcal injections. To be effective, treatment must be carried out with the appropriate monovalent serum and large doses must be injected early in the course of the disease. About 50 mils of cerebrospinal fluid is first withdrawn and then 40 mils of warm serum is allowed to flow slowly into the subarachnoid space from a funnel held above the patient. At the same time a similar amount is administered intravenously. This treatment may be repeated several times according to the course of the disease as judged clinically and from bacteriological examinations of the cerebrospinal fluid. As a result of the introduction of serum treatment of cerebrospinal fever, the mortality has fallen from about 80 per cent. to about 40 per cent.

Antidysenteric Serum (Shiga). This serum is employed in cases of bacillary dysentery due to B. dysenteriæ (Shiga). Intravenous administration is preferable and, as with other forms of specific therapy, the serum must be given in adequate doses as soon as possible after the onset of the disease. According to Shiga, the use of this serum has reduced the mortality from bacillary dysentery in Japan from 35 per cent. to 9 per cent. Experience in the Great War, 1914—1918, confirmed these results. Dosage is in units, the standard being an arbitrary one fixed by the Medical Research Council. The method of assay is comparable to that employed for diphtheria antitoxin.

Gas Gangrene Antitoxin. Infection of wounds with B. Welchii and other gas-forming organisms is a common complication of war-wounds. Prophylactic injections of antitoxin are administered when circumstances indicate its use. For therapeutic purposes the doses are relatively large and the intravenous route is employed. Separate antitoxins are prepared from the allied gas-producing bacteria—B. œdematiens, B. aerogenes capsulatus, and

Vibrion septique—and they are used in the same manner as above.

Staphylococcus Antitoxin. This is a comparatively recent preparation used in the treatment of staphylococcal infections of the skin, *e.g.* boils, carbuncles, etc. Good results have been reported, but the method is still on trial.

Antistreptococcus Serum. Polyvalent sera are available for use in various streptococcal infections—cellulitis, erysipelas, septicæmia, etc.—but, on the whole, their action has been disappointing.

Many workers have tried to find a chemical compound which would cure streptococcal infections by a specific action on the organisms. Promising results are now being obtained with *p*-aminobenzene-sulphonamide. It would appear that the treatment is most successful in the prevention and cure of puerperal sepsis due to hæmolytic streptococci. The treatment of erysipelas on these lines has also yielded results which justify further observation. Some years must elapse before the value of this development in therapeutics has been accurately assessed and its limitations defined. The drug is given by mouth in doses of 7½ grains thrice daily. It can also be injected intravenously, but contrary to the usual experience, the parenteral route is said to produce less satisfactory results.

Among the toxic effects of the compound the most important is sulphæmoglobinæmia. This is not an infrequent occurrence, and it is apparently more common when patients have been taking sulphates in the form of Epsom salts or Glauber's salt.

p-Aminobenzene-disulphonamide is said to be much more effective than "sulphonamide" and to compare very favourably with the latter with regard to toxicity toward the host.

Sclavo's Anti-Anthrax Serum. Considerable success has attended the use of this bactericidal serum. In an ordinary case of malignant pustule 30—40 mils of serum is injected subcutaneously, not more than 10 mils being injected at one place. This is repeated 12 hours later if necessary. As a rule there is rapid improvement in the local and general condition. In severer cases the serum must be administered intravenously. There is some difference of opinion as to the advisability of resorting to free excision of the pustule and surrounding tissues in addition to serum treatment.

Antivenomous Serum. The venom of snakes bears a close resemblance to bacterial poison. Both kinds of poison are amorphous substances, quite unknown chemically; they are active in the minutest doses, and lose their toxicity when heated. Snake venom also causes the development of antibodies, which have been demonstrated by Calmette, and employed in

the serum-treatment of snake-bite. The serum is obtained from horses which are inoculated with snake-venom, of which the toxicity is at first greatly weakened by the addition of sodium hypochlorite. The dose of *Calmette's antivenene* (for adder's bite) is 20 c.c. for an adult, 10 c.c. for a child ; in very serious cases, twice the amount is given.

Normal Horse-Serum. Doses of 10—20 mils of horse-serum are sometimes injected subcutaneously to increase the rate of coagulation of the blood in cases of hæmorrhage, *e.g.* in hæmoptysis, hæmatemesis, and certain "blood-diseases." Several proprietary sera (Hæmoplastin, Hæmostyl, etc.) are available also which are obtained from horses recovering after hæmorrhage. These sera are said to contain large quantities of fibrin-ferment. It is extremely doubtful whether they are of any practical value.

Convalescent Measles Serum. Intramuscular injection of serum from measles-convalescents within four days of exposure to infection will usually prevent the onset of the disease. Prophylactic treatment between the fourth and seventh days of the incubation period is likely to result in an aborted form of measles, *e.g.* coryza and a slight morbilliform eruption. The course of the disease is usually uninfluenced by injection of serum later than the seventh day. Potent serum from recent cases of measles is effective in doses of about 5 mils. Alternatively, 25 mils of whole blood from an adult known to have had measles may be used, but this is much less satisfactory. As a rule, it is best to try to produce a *forme fruste* of the disease, thus conferring life-long immunity on the patient without causing serious constitutional upset. Attempts to prevent completely the appearance of any evidence of measles should be reserved for weakly children or those suffering from debilitating illness, especially respiratory infections. Measles-prophylaxis has been of particular value in controlling the spread of the disease in children's hospitals and, most of all, in fever hospitals.

Convalescent serum has also been used to prevent or abort anterior polio-myelitis. The main difficulty lies in diagnosing the condition during the pre-paralytic stage in cases occurring sporadically. Furthermore, it is possible that antibody injected intramuscularly or intravenously cannot reach the causative organism, which is said to spread from the naso-pharynx by nervous pathways. In view of the serious nature of the disease, however, serum should invariably be used when there are reasonable grounds for suspecting infection.

Preparations and Doses

Antitoxinum Diphthericum (B.P., U.S.P.). Diphtheria Antitoxin. A preparation containing the antitoxin globulins which have the specific power of neutralising the diphtheria toxin. Biologically assayed and its potency expressed in units. *Dose*, by parenteral injection, prophylactic 500—1,000 units, therapeutic 10,000—20,000 units (B.P.) : prophylactic 1,000 units, therapeutic 10,000 units (U.S.P.).

Antitoxinum Scarlatinæ Streptococcicum (U.S.P.). Scarlet Fever Antitoxin. The antitoxic substances obtained from the blood-serum or plasma of a horse immunised to the toxins of certain strains of streptococci believed to be the causal organisms of scarlatina. Contains also sodium chloride and some preservative. Strength not less than 400 units per mil. *Dose*, by parenteral injection, prophylactic 2,000 units, therapeutic 6,000 units.

Antitoxinum Tetanicum (B.P., U.S.P.), Tetanus Antitoxin. Biologically assayed. *Dose*, prophylactic 1,000—2,000 units, therapeutic 20,000—40,000 units (B.P.); prophylactic 1,500 units, therapeutic 20,000 units, by parenteral injection (U.S.P.).

Antitoxinum Welchicum (B.P.), Gas-gangrene Antitoxin. Neutralises the toxins formed by B. perfringens (B. Welchii). Biologically assayed. *Dose*, prophylactic 4,000 units by parenteral injection, therapeutic 10,000—20,000 units by intravenous injection.

Antitoxinum Œdematiens (B.P.), Gas-gangrene Antitoxin (Œdematiens). Neutralises the toxin formed by Clostridium œdematiens. Biologically assayed. *Doses*, by parenteral injection, prophylactic 20,000 units, therapeutic 50,000—100,000 units.

Antitoxinum Vibriosepticum (B.P.), Gas-gangrene Antitoxin (Vibrion Septique). Neutralises the toxin formed by the Clostridium commonly known as Vibrion septique. *Dose*, by parenteral injection, prophylactic 5,000 units, therapeutic 10,000—20,000 units.

Serum Antidysentericum (Shiga) (B.P.), Antidysenteric Serum (Shiga). Contains the immune substances which have a therapeutic value in persons infected with B. dysenteriæ (Shiga). Biologically assayed. *Dose*, by parenteral injection, 4,000—10,000 units.

Antitoximum Staphylococcicum (B.P.), Staphylococcus Antitoxin. Neutralises the toxin formed by certain strains of Staphylococcus. Biologically assayed. *Dose*, by parenteral injection, 5,000—20,000 units.

Serum Antipneumococcicum I (B.P., U.S.P.), Antipneumococcus Serum (Type I). A serum or a preparation from serum containing the immune substances which have a specific effect when injected into persons suffering from certain diseases due to the Diplococcus pneumoniæ (Type I). *Dose*, by intravenous injection, 50,000—150,000 units.

Serum Antipneumococcicum II (B.P.), Antipneumococcus Serum (Type II). Description and doses as in Type I.

Serum Antimeningococcicum (U.S.P.), Antimeningococcic Serum. Obtained in the usual way from the blood of horses immunised with cultures of several types of meningococci. *Dose*, by parenteral injection, 20 mils.

5. PROPHYLACTIC AND DIAGNOSTIC AGENTS

Diphtheria Prophylactic. The hypodermic injection of diphtheria toxin leads to the formation of antibodies in the tissues. Active immunisation of susceptible subjects can thus be accomplished in a few weeks. The ill-effects of such injections are greatly reduced by detoxicating the preparations by the addition of antitoxin or by otherwise modifying the condition of the toxin. It is usual to inject 1 mil of the prophylactic mixture three times at intervals of a fortnight. Six months later the Schick Test

should be repeated. Only on the rarest occasions are further doses of prophylactic found to be necessary.

Scarlatina Prophylactic. The mode of action of this preparation is the same as that of diphtheria prophylactic. A sterile filtrate from a broth culture of the hæmolytic streptococcus of scarlet fever is made up in suitable dilutions expressed in Skin Test Doses. At fortnightly intervals injections of 500, 2,500, 10,000 and 25,000 skin test doses are given hypodermically. Immunisation to diphtheria and scarlet fever may be carried out simultaneously, if necessary, by adding 1 mil of toxin-antitoxin mixture to the first three doses of scarlatina prophylactic.

Tuberculin. The preparation now called old tuberculin is produced by growing tubercle bacilli in broth containing glycerin, which is sterilised by heat for 1 hour, and then reduced by evaporation to $\frac{1}{10}$ of its original volume, the dead bacilli being finally filtered off. The filtrate is called tuberculin, and contains about 40 per cent. of glycerin, which does not volatilise in the process of evaporation, and serves as a preservative; the tuberculin contains all the bacterial products that are soluble in glycerin and water.

Tuberculin contains unknown bodies of very great toxicity, and possesses the property of acting with far greater intensity on tuberculous than on healthy animals and persons. While a healthy guinea-pig is not affected by an injection of $\frac{1}{2}$—1 c.c. of tuberculin, 0·10—0·15 c.c. is sufficient to kill tuberculous animals in the course of 24—48 hours. The tuberculous human being is still more sensitive, and even $\frac{1}{10000}$—$\frac{1}{1000}$ c.c. may produce a characteristic *reaction* of both general and local nature. How small these doses are, and how intensely poisonous the active substance in tuberculin must be, will be understood when one remembers that this substance forms only a very small proportion of the tuberculin, which consists mainly of water, glycerin and the solid constituents of the broth.

The *general reaction* consists in rise of temperature from 38° to 41° C. (100·4°—105·8° F.), generally preceded by rigor, pains in the limbs, languor, cough, often nausea and vomiting, rarely jaundice and eruptions. These symptoms begin 4 or 5 hours after the injection, and last from 12 to 15 hours.

The *focal action*, which also begins some time after the injection, can be seen directly in lupus. The diseased area becomes red, moist and prominent; after 2 or 3 days the swelling goes down and the lesion becomes covered with a crust, which in a few days sloughs off with the diseased tissue and its bacilli, and leaves a pink, smooth scar. The same process takes place wherever there are tubercle bacilli—in the lymphatics, the bone-tissue, joints and lungs. In the last-named place it reveals itself by moist râles and increased expectoration.

The healthy individual scarcely reacts to $\frac{1}{100}$ c.c. of tuberculin, and it is only after very large doses, *e.g.* $\frac{1}{4}$ c.c., that a strong general reaction sets in of a character similar to that which tuberculous patients show after small doses.

According to Koch's view, the tuberculin should kill, not the bacilli, but the tuberculous tissue by increasing the production of a "necrotising substance," which the tubercles were supposed to produce; and this

should so act upon the tuberculous tissue that it would be destroyed and slough away together with the bacilli contained in it.

The great expectations of the therapeutic effects of tuberculin on man were, unfortunately, not fulfilled. After careful trial it has been discarded by most authorities. A few still adhere to it, but employ it only in the beginning of the disease for patients with no, or with very little, pyrexia, and in such small doses that no reaction is observable. It is feared that large doses, which cause œdematous softening of the tuberculous foci, may spread the bacilli and thus set up a general infection.

In *veterinary medicine* tuberculin has acquired extraordinary importance in the *diagnosis of latent tuberculosis in cattle.*

In man, too, injections of tuberculin were used for some time as an aid in diagnosis, but this was given up as being too dangerous. Of late years the employment of tuberculin has been resumed under new forms, namely, as "*skin reaction*" and "*eye reaction.*" The first, which is due to von Pirquet (1907), is brought about by dropping on to the extensor side of the forearm, prepared by washing the skin, preferably with spirit, 2 drops of 25 per cent. tuberculin (1 drop of tuberculin is mixed with 3 drops of water on a sterilised watch-glass), and then scarifying the skin as in ordinary vaccination under the drops. In tuberculous individuals, redness will appear in the infected cuts after about 3 hours, and in 12—24 hours will develop into a small papule, vesicle, or eruption resembling herpes tonsurans, and end with desquamation. After 48 hours the reaction is over without pyrexia. Delayed reaction, beginning after some days and lasting several weeks, is seen but rarely. The reaction is also produced by rubbing in some drops of undiluted tuberculin, or an ointment consisting of equal parts of tuberculin and lanolin, upon an area of unbroken skin of about the size of a florin ; the redness, etc., is not seen for 1 or 2 days. Clinically the skin-test is too delicate, as it gives a positive result if once tubercle bacilli have appeared in the history of the patient and elicited hypersusceptibility for tuberculin. It not only indicates active tuberculosis, but also disease long since healed, and is therefore positive in almost all individuals above 15 years of age. The eye-test (Wolff-Eisner, 1907) consists in putting into the eye a drop of 1 per cent. tuberculin (*e.g.* 1 drop of the mixture used for the skin-reaction + 24 drops of water). A positive result is the appearance of injection in the conjunctiva after 6—24 hours, and with stronger reaction also swelling and muco-purulent secretion, accompanied by slight photophobia, and burning or a feeling as of dust in the eye. In the case of already existing disease of the eye, tuberculous, or otherwise, the test must not be made.

In 1897 Koch produced a new tuberculin (T.R., tuberculin-residue). It is made from virulent cultivations, which are dried, pulverised, and then submitted to centrifugal action with water. Of the two layers thus formed, the upper contains those constituents of the bacteria which are soluble in water, and in action corresponds with old tuberculin ; the lower layer, or residue (T.R.), contains the insoluble parts of the bacteria-bodies ; these are preserved by adding glycerin. With this preparation Koch succeeded in immunising animals so that they bore the injection of fully virulent cultivations of tubercle. His purpose with T.R. was to introduce the poisonous bacteria-bodies themselves, so that they should produce an active immunity in man. The new tuberculin, however, has not shown itself to be useful in practice.

Wright's vaccines are suspensions of bacteria killed by heat, the

suspensions being obtained by cultivation of the patient's own bacteria (*autogenous vaccine*). The object is to obtain races that will produce antibodies which have a specific action on the races that the patient himself harbours. Among these is the *staphylococcal vaccine*, which has been employed with success for furunculosis and other chronic staphylococcal diseases. *Colon vaccine* (bacillus coli communis) is said to act favourably in colon-infection of the urinary passages (pyelitis).

A large number of vaccines have, moreover, been produced for all kinds of diseases, some of them *polyvalent vaccines*. An account of them will be found in special works on the subject.

In India active immunisation against *plague* is largely practised. Subcutaneous injections are given of killed cultures which contain the poisons from the bodies of the bacteria. After the injections there is high fever and considerable general indisposition, which disappear in the course of 24 hours, after which time some immunity should have developed. It is not certain, however, after only one injection ; but in any case, the disease in the person vaccinated is said to be very much milder than it would otherwise be.

Gonococcal vaccine seems to have a favourable action upon chronic gonorrhœal epididymitis, prostatitis and arthritis, without having any influence upon the urethral inflammation.

Smallpox Vaccine. See Preparations and Doses.

Diagnostic Agents

Diphtheria toxin is used in the *Schick Test* to determine susceptibility to diphtheria. A small quantity of the toxin is injected intradermally into one arm, and, as a control, heated toxin is injected into the skin of the other arm. In a susceptible individual having little or no antibody to diphtheria in his tissues there is a positive reaction in the form of an area of erythema at the site of injection of the toxin. This is usually about 1 inch in diameter and takes 24—48 hours to develop, but inspections should be made daily for 5 days following the test as delayed positive reactions are not uncommon. The redness begins to fade in 2 or 3 days, and there may be a little branny desquamation and staining of the skin. Apart from the effects of trauma no reaction occurs on the control arm. An immune subject shows no reaction on either arm. A pseudo-reaction is sometimes seen ; the erythematous area develops rapidly in both arms and is surrounded by a pink, slightly œdematous areola. This also indicates immunity. Occasionally a combined pseudo- and positive-reaction occurs, and this is probably associated with some degree of susceptibility to diphtheria. The Schick Test is of value in determining whether or not active immunisation against diphtheria is necessary. When the diagnosis of diphtheria is in doubt the result of the Schick Test may be decisive, but it is essential that the observer should have a wide experience of the test (see also p. 532).

Scarlatina Toxin is employed diagnostically in the *Dick Test* for susceptibility to scarlet fever. The test is similar in principle to the Schick Test. Readings can be made in 24 hours in the majority of cases, and as pseudo-reactions are exceedingly rare, the control injection can be omitted.

Histamine Acid Phosphate. Injected subcutaneously, this substance normally causes a profuse secretion of gastric juice. It is therefore employed as a diagnostic agent in cases of suspected achylia gastrica, *e.g.* in the course of pernicious anæmia.

Preparations and Doses

Toxinum Diphthericum Detoxicatum (B.P., U.S.P.), Diphtheria Prophylactic. The toxicity of the toxin is reduced by several methods, for details of which special works on bacteriology should be consulted. *Dose*, by subcutaneous injection, the volume indicated on the label as the dose, twice or thrice at intervals of two weeks (B.P.); 1 mil (U.S.P.).

Toxinum Scarlatinæ Streptococcicum (U.S.P.), Scarlet Fever Toxin for Immunisation and the Dick Test. A solution in broth of the toxin resulting from the growth of certain strains of hæmolytic streptococci thought to be the causal organisms of scarlatina. *Dose*, Dick Test: 0·1 mil (one skin test dose) injected intradermally. Immunisation doses: graduated doses at proper intervals until the individual fails to react positively to the Dick Test. In practice it is usual to inject the following doses at intervals of a fortnight: 500, 2,500, 10,000 and 25,000 skin test doses. The doses should be reduced if any of the injections produce considerable constitutional upset. A final dose of 50,000 skin test doses is occasionally necessary to complete the immunisation.

Vaccinum Typhosum (U.S.P.), Bacterial Vaccine made from the Typhoid Bacillus. A prophylactic against typhoid fever. 1 mil contains at least 1,000 million of killed typhoid bacilli. *Dose*, prophylactic, by hypodermic injection, 0·5 mil and 1 mil, the latter dose to be repeated once.

Vaccinum Typho-paratyphosum (B.P., U.S.P.), Anti-Typhoid-Paratyphoid Vaccine. T.A.B. Vaccine. Contains in 1 mil 1,000 million of dead B. typhosus, 500 million of B. paratyphosus A. and 500 million of B. paratyphosus B. Should not be used later than 18 months after preparation. *Dose*, by subcutaneous injection, 0·5 mil (first dose), 1 mil (second dose after 7 to 10 days' interval) (B.P.); prophylactic, by hypodermic injection, 0·5 mil, and 1 mil, the latter dose to be repeated once (U.S.P.).

Vaccinum Rabies (U.S.P.), Rabies Vaccine, Pasteur Prophylactic. The vaccine consists of a bacteriologically sterile suspension of the attenuated, diluted, dried or dead, fixed virus of rabies. In favourable circumstances it is possible, by means of this vaccine, to establish immunity to rabies. The Pasteur treatment consists in inoculation with the dried spinal cord of rabbits infected with rabies virus, the cords having been stored under suitable conditions for varying periods to ensure attenuation of the organisms. The treatment may be effectual for persons already infected, because the incubation-period for rabies is very long (some weeks or months) and active immunity may be established by the series of injections during this time. As a result of the Pasteur treatment the mortality from hydrophobia was reduced to vanishing-point. Rabies is now a relatively uncommon disease owing to the success of public health measures.

Vaccinum Vaccinæ (B.P.), **Vaccinum Variolæ** (U.S.P.). Vaccine lymph. A preparation for active immunisation against small-pox. Healthy calves are vaccinated on the scarified, shaved, abdominal wall with *cow-pox* lymph. When the vesicles have fully formed they are scraped off with a spoon and the purified product, preserved in glycerin, is put up in capillary tubes. If stored below 0° C., the lymph keeps its potency for long periods, but if stored above 10° C. the potency cannot be assured for more than 7 days. Vaccination is the classic example of active immunisation and was introduced by Jenner in 1796. The unknown micro-organism is so altered by its passage through animals that it produces in man only slight indisposition and an immunity of several years' duration.

B.C.G. Vaccine. Attempts were soon made in the history of vaccine-therapy to immunise against tuberculosis by injecting graduated doses of the causal organisms. B. tuberculosis in the virulent state was found to produce dangerous effects. B.C.G. vaccine (Bacillus Calmette-Guerin) is a culture of bovine organisms attenuated by more than 200 passages in 13 years on potato-glycerin. There is some difference of opinion as to the value of prophylactic treatment with this vaccine, but some authorities are satisfied that a mild degree of immunity is conferred by its use and the risk of *severe* tuberculosis is thereby eliminated.

Tuberculinum Pristinum (B.P., U.S.P.), Old Tuberculin. A concentrated filtrate from a fluid medium on which B. tuberculosis has been grown for a period of 6 weeks or more. A transparent, viscous liquid, yellow to brown in colour. Odour like that of honey. Biologically assayed. If undiluted, is stable at ordinary temperatures. When prescribed with suffix T, is prepared by growing the human bacillus; the suffix PT indicates the bovine bacillus. *Dose*, by subcutaneous injection, diagnostic 0·001—0·005 mil, $\frac{1}{60}$—$\frac{1}{12}$ min.; therapeutic 0·000001 mil, gradually increased, $\frac{1}{60000}$ min. (B.P.); by intracutaneous injection 0·001 mil, $\frac{1}{70}$ min. (U.S.P.).

Toxinum Diphthericum Diagnosticum (B.P., U.S.P.), Schick Test Toxin. Diphtheria toxin diluted so that 0·2 mil contains the test dose (U.S.P., 0·1 mil). The test dose contains $\frac{1}{50}$ of the minimal lethal dose. The solution is injected intradermally.

Toxinum Diphthericum Calefactum (B.P.), Schick Test Control. This is Schick Test Toxin which has been heated to a temperature of not less than 70° C. for not less than 5 minutes. It is prepared from the same batch of Schick Test Toxin as that with which it is issued for use. *Dose*, by intradermal injection, 0·2 mil, 3 mins.

Histaminæ Phosphas Acidus. The di-acid phosphate of histamine, $C_5H_9N_3$, $2H_3PO_4$. Colourless crystals, odourless, soluble in 4·5 parts of water, slightly soluble in alcohol. *Doses*, by subcutaneous injection (for diagnostic purposes), 0·5—1 milligrm., $\frac{1}{120}$—$\frac{1}{60}$ gr.

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LONDON AND TONBRIDGE