THE NEW PHYSIOLOGY IN SURGICAL AND GENERAL PRACTICE

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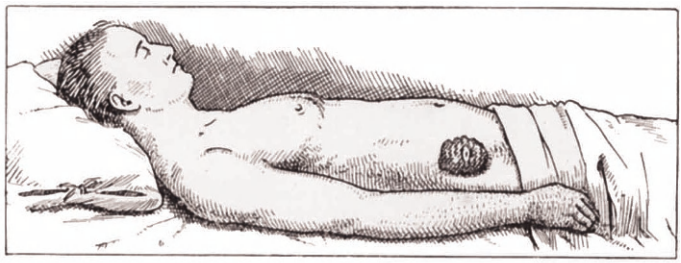

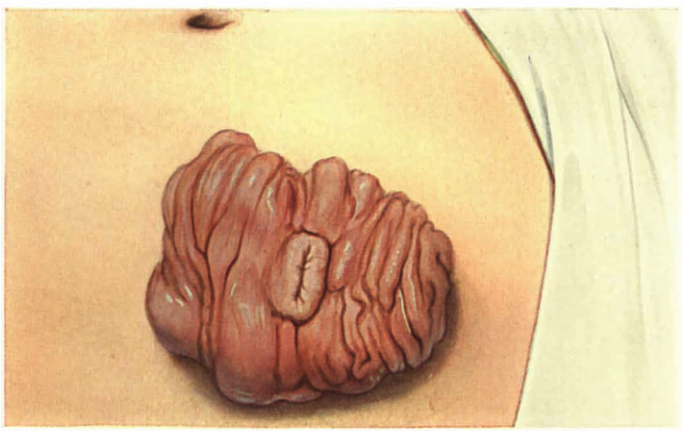

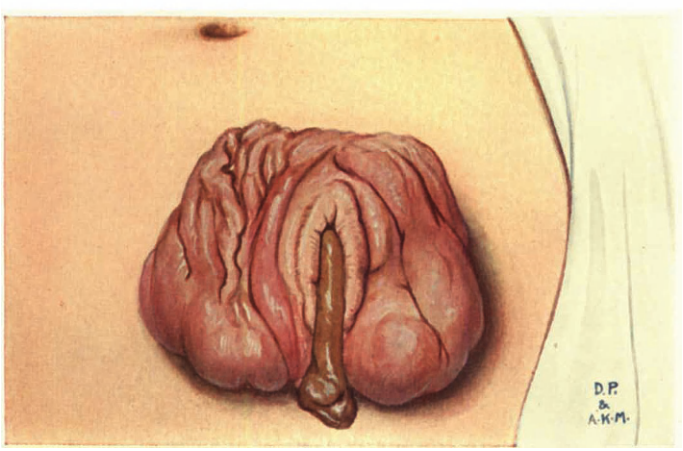

Frontispiece

NOTE ON FRONTISPIECE.

THE picture, for which I am indebted to Miss D. Pillers, and Mr. A. K. Maxwell, shows the condition in the patient referred to on page 179.

The cæcum has prolapsed through the wound in the abdominal wall, and is turned inside out to show the mucosa. Beneath the thin wall of the cæcum, the coils of small intestine are seen bulging, in incessant peristalsis.

The rough sketch at the top shows the position of the swelling on the abdominal wall.

In the upper coloured picture the sphincter is quiescent, between meals. Notice the contracted raised muscular ring.

The lower picture shows the sphincter lying relaxed, and one of the intermittent gushes of fluid ileal contents pouring through, ten minutes after a meal.

PREFACE TO FIFTH EDITION

THE rapid exhaustion of edition after edition of this modest little work has been a source of great gratification to the writer, if only because it shows that the practitioner of to-day is keenly interested in the scientific aspect of his professional work, and the advances made in physiology which may have a bearing on medical and surgical problems. It is the aim of the author and publishers to make the book strictly conform to its title, and consequently each edition presents large additions to and subtractions from its predecessor, as material ceases to be new, and fresh researches are published. It is intended that even those who hold the previous editions may find here practically a new book.

Consequently three fresh chapters appear, dealing with the physiology of muscular exercise, the functions of the kidney, and the dietetic factor in the causation of appendicitis. The chapter on the heart has been rewritten throughout by Dr. C. E. K. Herapath. Extensive alterations will be found in the chapters on food deficiency diseases, the functions of

the stomach and intestines, and the genital glands, and the rest of the book has been thoroughly revised and new matter incorporated. To make room for all this, two chapters that have appeared in former editions, and a large part of a third, are dropped out.

Nothing has given the author greater pleasure than to read in more than one review that the reviewers found the book more interesting than a novel. It speaks well for their professional keenness.

A. R. S.

October, 1922.

PREFACE TO FIRST EDITION

THESE chapters are intended for the general practitioner, the consulting surgeon, and candidates for the higher examinations in physiology.

There was a time when one man could be physiologist and surgeon too, but the rapid march of progress in each field has left a great gap between the sciences, which is continually widening. The triumphs of the surgeon are unknown to the physiologist, and the converse is equally true. Yet many of the discoveries of the past ten years which have so changed the face of physiology are fraught with vast possibilities for the clinician. This book is an attempt to sift out from the New Physiology that which is likely to be of value in the actual diagnosis and treatment of patients.

It would be a small service to lay before the practical reader mere theories or guess-work. With but few exceptions, only the established and settled conclusions arrived at by many competent and independent workers have been introduced. Part of the chapter on cutaneous anæsthetics, and a few other researches and passing suggestions for which the author is personally responsible, must stand in a different category.

An effort has been made to explain matters so simply that they may be intelligible to those having the most elementary knowledge of physiology, and all technical terms have been avoided or defined.

There are excellent manuals now published treating of the application of physiology to diseases which concern principally the consulting physician. This little book limits itself to surgical problems, and to the common every-day aspects of disease that confront us all, physicians, surgeons, and general practitioners alike.

I owe a debt of thanks to my chief, Professor A. F. Stanley Kent, for some valuable suggestions and criticisms.

A. R. S.

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The New Physiology in Surgical and General Practice.

CHAPTER I.

THE PHYSIOLOGY OF MUSCULAR EXERCISE.

THE MUSCLES IN ACTIVITY—THE HEART AND LUNGS DURING EXERCISE—THE BLOOD-FLOW THROUGH THE MUSCLES—THE ADRENALIN STORY—THE PART PLAYED BY THE CENTRAL NERVOUS SYSTEM — TRAINING AND OVER-TRAINING.

THERE is a singular fascination about the problems relating to the means by which the body is attuned to carry out vigorous athletic exercises. This is due in part to our British fondness for athletic sports, and our appreciation of a human animal that runs well or plays a game well; but there are other reasons also. When all the adaptations which come into effect to enable the body to carry out some exacting task are considered together, we find a series of changes in the various organs which present, taken as one whole, a picture of remarkable perfection and beauty. And if this perfection fails somewhere, the patient comes to us with symptoms which cannot be properly appreciated unless we understand the normal mechanism.

THE MUSCLES IN ACTIVITY.

It is by no means certain how the change in shape, accompanied by the putting forth of a powerful pull, which constitutes a muscular contraction, is actually brought about. There is a reversal of the cross-striation seen under the microscope, and it has been supposed that the dark stripes represent a spongy matter, into the interstices of which the more fluid protoplasm of the lighter stripes is sucked up during contraction. Each muscle fibre consists of a number of long slender tubes (sarcostyles), packed around with an undifferentiated protoplasm (sarcoplasm) which is itself contractile, but more sluggishly than the sarcostyles. These contain the spongy substance and the more fluid matter of the lighter stripes, and serve for very quick contraction. This histological conception, however, does not take us very far. The present view is that the actual cause of the contraction is that the sarcostyles which are embedded in the sarcoplasm present an immense area of surfaces, and that the surface-tension is altered by the action of free H-ions, which are brought to bear on it when sarcolactic acid is liberated by the chemical change which takes place in contraction. Certain facts are in favour of a surface-tension theory—for instance, the fact that a muscle contracts more vigorously when it has been stretched, and that warmth relaxes muscular tone, well seen in the dartos, or in a frog's intestinal muscle. However, all this is very doubtful and purely theoretical.

We have a certain amount of information, but very incomplete, as to the chemical changes that

occur when a muscle contracts. It uses up oxygen, and gives out carbon dioxide. Glycogen and glucose disappear and lactic acid appears, although very recent observations by the electrometer seem to show that acidity only develops during fatigue or rigor (Ritchie). What happens to the lactic acid is in doubt. According to one view (A. V. Hill) it is built up again into the molecule of the complicated chemical substance by whose 'explosion' the contraction is brought about. On another theory (Fletcher and Hopkins) the lactic acid is formed from the imperfect combustion of carbohydrate, and will afterwards be fully oxidized to CO_2 and water. As we shall see, the acidity developed has very important consequences outside the muscle itself, in causing other organs to minister to its needs.

From the chemical point of view the contraction of muscle may be compared with the explosion of a shell. In the shell there is a percussion cap, with fulminate of mercury or some similar body, which explodes at a touch and so brings about the detonation of the heavy bursting charge, T.N.T. or other explosive. In muscle there is a receptor substance, situated at the junction of the nerve-ending and the muscle protoplasm. It is on this receptor substance and not on the motor-end-plate, that curare acts. The nervous impulse induces some chemical change in the receptor substance which fires off the big molecule in the muscular protoplasm, by whose disintegration lactic acid, amongst other bodies perhaps, is liberated. It is one of the standing marvels of physiology how this explosive can be

built up again in time to yield the quickly repeated contractions of, shall we say, the expert piano-player.

For its upbuilding, muscle requires to be supplied with blood bringing oxygen, and with foodstuffs, though as is well known an excised muscle will yield quite a number of contractions before ceasing to respond to stimuli. What particular foodstuffs are most suitable has been long and hotly debated, and the question is important, because on the answer depends the proper diet of the manual labourer and the athlete. Time was when the professional boxer or University runner was fed heavily on beefsteak, on the theory that protein is the main muscle food. There is no evidence in favour of this. Calculation of the respiratory quotient during severe exercise shows a very small and rather variable rise, which is to be taken as evidence that there is generally a preference for carbohydrate (Benedict and Cathcart), and it is well known that the beating mammalian heart uses up glucose. Other evidence, however, makes it certain that muscle can utilize fat as its main source of energy. The heart, for instance, with its blood-supply intact in a 'heart-lung' preparation, may draw on fats by preference (Evans). Recent investigations by Krogh and Lindhard seem to show that work is performed more economically when the body is supplied with fat rather than with carbohydrate. It is not probable that glucose is directly converted into lactic acid during contraction (A. V. Hill). Seeing that not one foodstuff alone is drawn upon to furnish the fuel for muscular energy,

but that all are used, there is therefore no obvious advantage to be gained by feeding an athlete on any one-sided diet; but it seems reasonable to regard chocolate or sugar as a ready source of energy at the time of the contest.

When a muscle contracts, heat is evolved. As a matter of fact, the evolution of heat takes place in four stages. There is an initial rapid production, which takes place even in the absence of oxygen; then a smaller evolution all through the period of stimulation. The third is a large one during relaxation; the fourth, also large and only seen in the presence of oxygen, going on for some minutes after the muscle has relaxed. This last is evidently due to some oxidation process, perhaps lactic acid being converted into CO_2 and water. During severe and prolonged exercise, the body temperature rises a degree or two; if the day is hot and moist it may even reach 102° or more. Probably this is of advantage in that it hastens the oxidation of lactic acid.

A comparison may be made between the efficiency of a modern machine and of animal muscle. When an engine is at work burning fuel, the energy derived from the combustion may appear as work or as heat, but the latter is to be regarded as a defect, not as an advantage. It serves no useful purpose to scorch the driver on the footplate; it is a necessary evil. In ordinary, the efficiency of a muscle, that is the proportion of its energy output that appears as work, is about 25 per cent. In a trained individual working under optimum conditions it may be as high as 33 per cent. These figures are obtained with the

Atwater-Benedict calorimeter. A good modern oil-engine has an efficiency about the same, but that of a steam-engine is far lower. To secure the best muscular efficiency the subject must be 'trained', the rate of work must be neither too fast nor too slow, and there must be no fatigue. We shall return to this aspect later.

THE HEART AND LUNGS DURING EXERCISE.

The lesson was thoroughly impressed on us during the war that it is useless to have a striking force in the front-line trenches unless there is a complete mobilization behind it to supply food and munitions, and to organize transport ; and that every man and woman in a nation may have to bear a part. When muscles are in active exercise their requirements of oxygen and foodstuffs are much increased, and means have to be found to enlist the services of all the other organs to supply them.

The rate of breathing is greatly increased, and also the depth. Thus a much larger amount of oxygen is supplied to the blood, and CO_2 removed. The effective agent in stimulating the respiratory centre into activity is the increased H-ion concentration of the blood, or, in the old-fashioned parlance, the tendency to increased acidity. The respiratory centre is so sensitive to acids that there is practically no real alteration in the blood-reaction, the CO_2 being exhaled as fast as it is poured into the blood by the muscles. The increased H-ion concentration is partly due to CO_2, or rather to carbonic acid, and partly to lactic acid. After very sudden and

severe exertion, such as a hundred yards' race, lactic acid may even appear in the urine, but not after a longer, slower event, such as the London-Brighton walk. I found that riding from Bapaume to Miraumont (in 1917) over shell-pitted roads on a heavy old army bicycle led to the appearance in the urine, in my own case, of about double the normal amount of ammonia nitrogen, which is a measure of the total acids excreted. It used to be supposed that the increase of lactic acid in the blood during exercise was due to shortage of oxygen, but this can hardly be the truth, as it may occur when the exercise causes no sort of distress, as in my case, and on the other hand it does not appear when we breathe an atmosphere deficient in oxygen.

The increase in the ventilation by the lungs is strictly parallel to the severity of the muscular work done, and may be very considerable. We may inhale five times as much air during work as we do at rest, or even more. Moreover, the deeper breathing causes alveoli of the lungs which are not ordinarily brought into use to be opened up and to function.

It has been shown that a few inhalations of oxygen at the commencement of a short race may enable an athlete to improve on his own records, but it is not certain that oxygen is any better than deep air-breathing in this respect. Thus we find that the escape of acid products into the blood helps muscular activity by improving ventilation.

Not only must the oxygen supply to the lungs be improved, but the means of transport to the tissues will also need amplification; therefore the heart

must greatly increase its output per minute. This may be brought about by an increase in *rate* or an increase in the *volume* expelled by the ventricle at each beat, or by both. As a matter of fact, both occur ; the pulse-rate may rise to 160 or more, and the output per beat from the normal 70 c.c. to 150 c.c. (Krogh and Lindhard). This observation depends on the nitrous-oxide method of measuring the output ; this method has been criticized, in that the gas may not be evenly diffused in the lungs, and may not have time to finish passing through the alveoli into the blood and bring about equilibrium between the blood and the air. In more recent work by Douglas and Haldane (1922), they use the lungs as an aerotonometer, and give air containing about 7·5 per cent CO_2 to breathe (if the blood contains more CO_2, it will cause the percentage 7·5 in the expired air to increase, and if less, to diminish, and so the CO_2 in the blood of the pulmonary artery can be determined ; and, that in the pulmonary vein being already known by first estimating the CO_2 in alveolar air, the quantity of blood that passes through the lungs in a given time may be calculated if we estimate the total volume of CO_2 lost by exhalation in that time ; if the pulse is counted, the output per beat of the ventricle is obtained). They find that during rest 5 to 8 litres per minute go through the lungs ; during activity, 24 litres. The output of the heart was 120 c.c. per beat ; during exercise it might or might not rise. Direct observation with the *x* rays immediately after exercise shows a very trifling increase in diameter,

or none at all; but probably an extra 20 or 30 c.c. would not be sufficient to show. We may conclude, then, that there is an increase in output per beat, at any rate in persons in good 'training', but not nearly so much as Bainbridge, following Krogh and Lindhard, would have us believe.

And how are these modifications of the heart-beat brought about? In the first place, by better filling of the right ventricle with blood. The increased depth of breathing draws not only air but blood also into the chest along the great veins; the muscular contractions force the blood along the thin-walled and valved veins. This brings into play the two 'laws of the heart', the Starling law, and the Bainbridge law. According to the first, which was worked out on a mammalian heart-lung preparation, the force with which the heart contracts is directly proportional to the initial length of its fibres, so that if the ventricle is well filled there is a more powerful systole. The second law is that the rate of the heart-beat varies with the degree of filling of the right auricle; when this is stretched the pulse-rate is increased.

THE BLOOD-FLOW THROUGH THE MUSCLES.

It is not sufficient that the blood should be well oxygenated and the circulation stimulated; it is also necessary that the blood-flow through the active muscles should be greatly increased. Krogh has shown how beautifully this is brought about. It is possible to watch the capillaries of the frog's tongue during rest and contraction, and in the latter case

one may see, not only a dilatation and quicker flow through the capillaries that were previously visible, but also new capillaries previously invisible now open up and spring into sight. Measurements of the flow through the lip muscles of the horse show that during activity there may be five times as much blood passing as when the parts are at rest. The effective factor in bringing about this dilatation is the action of lactic and other acids on the cells lining the walls of the capillaries in the muscles. By the same means the circulation through the coronary system is improved and the heart kept fit for its greater exertions.

This, however, is not all. Not only are the muscular vessels opened up, but the general blood-pressure rises, and the splanchnic arteries are constricted, so that the more blood may be free to supply the muscles. This is effected by a stimulation of the vasomotor centre in the medulla, due partly to messages reaching it from the cerebrum—the rise may take place even before the exercise begins—and perhaps also to the direct action on the centre of H-ions in the blood. The blood-pressure usually goes up about 50 mm. of mercury, rising very rapidly at the beginning of the effort, reaching a maximum in five minutes, and then remaining steady until the end, when it falls very quickly. Douglas and Haldane believe that the flow through the tissues is so regulated that the partial pressure of oxygen and the H-ion concentration around each tissue-element are kept constant in exercise as in rest (1922).

The liberation of acids by contracting muscular

tissue has yet another service to render. It is well known that the extraction of oxygen from a solution of oxyhæmoglobin is made easier by the presence of carbonic acid—the oxygen is given up in a partial vacuum at a less reduction of pressure. So, in the presence of this and other acids in and around the muscle-fibres, the red corpuscles part with their load of oxygen more readily than they otherwise would.

THE ADRENALIN STORY.

A fascinating theory has been advanced by Cannon and others, to the effect that during excitement or exercise messages pass from the central nervous system to the suprarenals, causing an increased output of adrenalin into the circulation. Consider how beneficial this must be if it occurs. Adrenalin increases both the force and the frequency of the heart-beat ; it acts as a general vasoconstrictor, but has little such effect on the vessels in the muscles ; it dilates the bronchi ; mobilizes glucose from the liver into the circulation ; and inhibits the movements of the intestine. The vessels of the lung, brain, and heart escape from its vasoconstrictor effect. The pupil is dilated, so that if the man or animal is fighting or flying, a wide view of the periphery is provided.

There is a good deal of evidence that such a liberation of adrenalin does really take place, but the point is not quite clear. In favour of the opinion is the fact that after removal of the superior cervical ganglion dilatation of the pupil may be caused by frightening the animal (a cat). As the dilator

nerve has been destroyed, this must be due to the action of some chemical substance circulating. Electric stimulation of the splanchnic nerves is said to liberate adrenalin into the blood ; a double rise of blood-pressure follows, of which the first is due to vasoconstriction in the abdominal area, and the second to adrenalin. There are difficulties, however, in the way of accepting all this ; Stewart and Rogoff find no evidence that any increased quantity of adrenalin is poured into the suprarenal veins during excitement, and it is now known that *small* injections of adrenalin are vasodilator, not constrictor. Gasser and Meek also find no evidence that exercise is normally accompanied by an increased output of adrenalin.

THE PART PLAYED BY THE CENTRAL NERVOUS SYSTEM.

Every muscular contraction is initiated, of course, by a nervous impulse, in which at least two cells, one in the precentral cortex and another in the anterior horn of the spinal cord, take a part. These cells therefore do work, and their supply of nutriment is increased by the speeding up of the intracranial circulation that takes place in consequence of the raised blood-pressure. We know very little about the actual nature of the nervous impulse, or the needs of the nerve-cell in activity. It is certain that muscular exercise can be better performed when the whole mind is given to the task, and when the cheers of the spectators, the efforts of a competitor, or the subject's own strong determination to win,

come in to reinforce the activity of the nerve-cells and to banish fatigue.

Fatigue is principally an affair of the central nervous system. It is of course possible to tire out a muscle by repeated electric stimulation, and the more quickly if the circulation has been cut off. This local fatigue is due to the accumulation of waste products, such as lactic acid, in the muscle, which can be washed out. Whether the feeling of stiffness, which we all know so well, after a movement frequently repeated, or on the day following the first game of cricket of the season, is due to this acid liberation is very uncertain. More probably the late fatigue at any rate is caused by mechanical wear and tear of the sense organs in the tendons and joints, which are not used so smoothly and skilfully when the exercise is unaccustomed. There is very little connection between this late fatigue and actual capacity for further work.

That fatigue is primarily in the central nervous system is shown by the fact that when a muscle pulling up a weight and letting it down again has been tired out, and the voluntary contraction is no longer possible, electric stimulation of the nerve will make it contract again vigorously. If the cortex is excited until response ceases, fresh contractions can be evoked by shifting the electrodes to the spinal cord or to the peripheral nerve.

During the strenuous days of the war a good deal of attention was paid to the subject of industrial fatigue, and some definite conclusions were arrived at. Industrial fatigue is undoubtedly due to tiring

of the brain. It may be measured by the output per hour of the average factory worker, or by the effect on the patient's reaction times and blood-pressure. It is not possible to increase output by extending the hours of work beyond a certain point. The optimum, for heavy work, is somewhere about 56 hours per week. Labour on seven days a week does not give a better output than on six. By all the tests there is a curious 'Monday effect'; there is less capacity for work on Monday morning, after the weekly rest, than when the human machinery is 'warmed up'. The speed at which work is done influences the onset of fatigue. To quote Bainbridge, every mountain-climber in Switzerland thinks at the beginning of the climb that the pace set by the guide is too slow, and at the end too quick; the truth being that the man of experience has learned his optimum, and keeps steadily to it.

It is extraordinary what severe degrees of fatigue the healthy body can tolerate. One sees schoolboys at the end of a mile run, or a long 'cross-country', come in looking absolutely exhausted, in a condition like profound shock; but in less than an hour they are all right again, and suffer no hurt, whatever their mothers may think.

TRAINING AND OVERTRAINING.

Training for an athletic contest has generally been understood to include regular and gradually increasing exercise, a generous protein diet, and abstinence from tobacco and alcohol. There is no definite evidence that diet has any real influence, provided

it is adequate. The consequences of training are a definite increase in the size and power of the exercised muscles, an enlargement of the heart accompanied by slowing of the pulse-rate, a normal or rather low blood-pressure, and a modification of the first heart-sound—*l-l-lump* instead of *lub*. Together with these structural changes, there is a better functioning, less sense of fatigue, less respiratory distress during severe exertion, and less rise of the pulse-rate. The untrained man improves his circulation principally by quickening his pulse-rate, and the trained man by increasing his output per beat. In the trained man, the muscles appear to be able to get more oxygen out of a given amount of oxyhæmoglobin of the blood, and less CO_2 is evolved.

There is a well-known phenomenon called 'second wind'; during a hard game the trained man may be short of breath at first, but he settles to a comfortable and lasting state of regular breathing. It may be seen even in the untrained. It is accompanied by a fall in the H-ion concentration of the blood (Pembery and Cooke), and more or less coincides with the onset of sweating. Its causation is not simple; the establishment of a better blood-supply to the muscles probably has something to do with it.

Briggs, working on colliers climbing the slopes of the Midlothian collieries (1921), found that in the physically unfit the capacity for work was greatly improved by inhaling oxygen from a mine-rescue apparatus, whereas the fit man did not benefit, unless he was obviously overloaded. He describes a method for testing fitness by comparing the curves of the CO_2

output when breathing air and when breathing oxygen ; in the unfit, they diverge ; in the fit, they do not. A man may, however, soon pass from one category to the other as his health varies.

There was a condition known before the war as 'soldier's heart', during the latter stages of the war as D.A.H., and now as 'effort-syndrome'. The symptoms of shortness of breath and quickened pulse, which are normal during exercise, in this condition tend to persist after the exercise is over, and even when resting in bed. Even the thought of exertion will bring them on. It is not, however, usually due, as used to be supposed, merely to overstrain of a normal heart ; in most cases there has been some infection, or perhaps the after-effects of 'gassing', to start off the trouble. There is generally a large neurotic element, and the quickening of the pulse is a sympathetic effect. There is no alteration in the alkali-reserve of sodium bicarbonate in the blood of these patients (Bainbridge and Canti). It seems probable that in those cases that are not purely neurotic, the defect is a weakened contractile power of the heart due to infection, or to the exchange from a sedentary mode of life to a too strenuous one. The treatment is graduated exercises to 'train' the heart again to do a normal day's work.

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*References at the end of chapters are not meant to be exhaustive. Only a few accessible authorities are quoted, in some of which a fuller bibliography will be found.

CHAPTER II.

MODERN WORK ON THE FUNCTIONS OF THE KIDNEY.

STRUCTURE OF THE KIDNEY—THE MODERN THEORY OF RENAL FUNCTION—EFFECTS OF BLOCKING THE URETERS—NEPHRITIS—TESTS OF RENAL FUNCTION.

IT has been one of the common reproaches against physiology in the past, that when we asked for facts, it could give nothing but very evenly balanced conflicting theories. Particularly has this been so in relation to the functions of the various parts of the kidney. It cannot be said even now that all difference of opinion is at an end, but there have undoubtedly been advances towards this position.

It will be remembered that the mammalian kidney consists essentially of a large number of glomeruli, in man perhaps about two million in number, which rather resemble a child's cup-and-ball ; the ball is the glomerulus—a tuft of blood-vessels with a surface epithelium—and the cup is Bowman's capsule. The stem represents the beginning of the renal tubule, and is of course pervious. The cells of the tubule differ in appearance as we trace it along ; its length is about 2 cm. The kidney is supplied with nerves, but they are merely vasomotor in function.

Originally two theories were held as to the part played by the glomeruli and tubules in the secretion

of urine ; the Ludwig theory, which in its first form is now defended by no one, and Heidenhain's theory that the glomeruli secrete the water with its dissolved salts, NaCl and the like, and that the tubules add the urea, uric acid, pigment, and any foreign substances, such as drugs, which are excreted in the urine. It has always been a moot point whether the glomeruli secrete or merely act as a filter, even amongst those who in general adhered to the Heidenhain theory.

The modern theory, which now secures a wide degree of acceptance, holds that the glomeruli filter out a fluid from the blood which is simply plasma minus protein, the driving force being the blood-pressure in the capillary tuft. As this fluid passes along the tubule, the cells abstract a solution of more or less constant composition, being a watery solution containing sodium chloride, glucose, and a little potassium and other salts. That is to say, the substances which are of value to the body are retrieved, but those which are not wanted, such as urea, pigments, sulphates, etc., are allowed to pass out into the ureter.

A table taken from Cushny may make this clearer. A careful scrutiny of this table will show that the great bulk of the water which is passed through the glomeruli is retrieved, about 61 litres being returned to the body for each litre of urine excreted. According to the theory this must of course be so, because urea in the plasma is 0·03 per cent, and in the urine 2 per cent. Thus 67 litres of plasma must be distrained upon to yield the daily output of urea. The

COMPOSITION OF PLASMA AND URINE.

	67 Litres Plasma Contain		62 Litres Filtrate Contain	61 Litres of Re-absorbed Fluid Contain		1 Litre Urine Contains	
	Per cent	Total		Per cent	Total	Per cent	Total
Water	92	62 lit.	62 lit.	.. ..	61 lit.	95	950 c.c.
Colloids	**8**	**5360** gr.	.. ..	.. ..	.. ..	.. ..	.. ..
Dextrose	0·1	67 ,,	67 gr.	**0·11**	**67** gr.	0	0
Uric Acid ..	0·002	1·3 ,,	1·3 ,,	**0·0013**	**0·8** ,,	**0·05**	**0·5** gr.
Sodium	0·3	200 ,,	200 ,,	**0·32**	**196** ,,	**0·35**	**3·5** ,,
Chloride	0·37	248 ,,	248 ,,	**0·4**	**242** ,,	**0·6**	**6** ,,
Urea	0·03	20 ,,	20 ,,	0	0	**2·0**	**20** ,,
Sulphate	0·003	1·8 ,,	1·8 ,,	0	0	**0·18**	**1·8** ,,

absorption of this water and its contained dextrose and salt is due to the vital activity of the renal tubule-cells, and takes place against a powerful resistance in the shape of the osmotic pressure of the urea-containing fluid in the tubules, which increases as the fluid concentrates. The cat can absorb against a resistance of 50 atmospheres or more; the human kidney is not so powerful, but it is said to be able to concentrate sugar to 20 per cent, which would mean a resistance of 25 atmospheres.

It has always been regarded as an argument against the Ludwig hypothesis, of which the modern theory is a development, that it seems wasteful to have to filter nearly 70 litres of fluid through the glomeruli in order to provide one or two litres of urine. But, after all, this is not so unusual in physiology. The liver pours out a pint or so of fluid into the duodenum every day, whereof nearly the whole of the water and salts, except only the bile pigment, is re-absorbed. The kidney of birds passes a clear watery fluid down the ureters, but in the bowel almost all the water is absorbed, leaving only a white paste of urates. Let it be remembered, too, that on the theory that the tubules excrete, even so they must have 70 litres of plasma brought to them in the lymph bathing the cells, to furnish the necessary urea. Cushny makes a calculation from the blood-flow through the kidney of the cat, and the ascertained number of tubules in a cat's kidney, that it is only needful for each capsule to pass out 0·015 c.c. per hour, of which the tubule, 3 cm. long, will have to absorb 0·014 c.c. This seems well within the capacity of the apparatus. About

60 litres of blood pass through the cat's kidney in a day; 12 litres are filtered off by the capsule, and 11·9 restored by the tubules.

It will not do to suppose that the glomerulus filters a dilute protein-free plasma to which the tubules add urea, because in that case the urine must contain sugar. We are driven to conclude, either that the capsule exercises a selective action, or that the tubules re-absorb sugar. The great advantage of the modern view is, that instead of having to believe that the cells both of the glomerulus and also of the tubules are capable of acting as skilled analytical chemists and selecting a great variety of substances to excrete, and another great variety to hold back, it is only necessary that the capsule should act blindly as a filter (keeping back, however, the proteins), and that the tubule-cells should absorb a certain fluid of more or less constant composition under all circumstances, but in such quantity as the body may require. Thus, on a salt-poor diet, or in such a condition as pneumonia, when there is a great output of chlorides into the exudate in the lungs, almost all the NaCl will be absorbed; ordinarily, all the sugar is retrieved, but in diabetes it is not wanted and is allowed to escape. After heavy sweating the water is largely taken up again by the tubules; after copious drinking it is allowed to reach the ureter. Certain unwanted substances such as urea and sulphates escape entirely, or almost entirely.

It will not be necessary to discuss at all fully the rather complicated experiments which have been interpreted in favour of the one theory or the other.

The original arguments put forward in support of the view that the tubule-cells select and excrete various substances were based on the classical researches of Heidenhain and Nussbaum and modifications thereof, and on the three following propositions: (*a*) That a urine more dilute than plasma can sometimes be got; (*b*) That a very brief asphyxiation, as by nipping the renal artery for ten seconds, will induce cessation of the flow of urine for an hour, which was taken to show that some vital structure and not a mere filter had suffered; and (*c*) That during diuresis the oxygen CO_2 exchanges are often increased, as though more living-cell activity were going on. To consider these *seriatim*: Heidenhain found that dyes such as indigo-carmine (Na sulphindigotate) injected into the blood, after slowing down the current of urine by a high division of the spinal cord, were to be recognized in the tubules and in their cells, but not in the glomeruli; this was taken as evidence that urea goes the same way. But indigo-carmine, and still more other stains, *may* be found in the glomeruli; the cells of the tubules get stained, not early, but many hours after the injection, and may retain the colour long after the urine is normal again. This looks as if the cells were absorbing, not excreting, the dye. The blue stain in the lumen of the tubules is denser as we pass towards the ureter; this suggests that it becomes precipitated as the water is gradually absorbed by the tubules. Thus Heidenhain's experimental results are rather better explained on the hypothesis that the dye was excreted in very dilute form through the capsule.

Nussbaum tied the renal arteries of the frog; this cuts off the blood-supply of the glomeruli, but leaves the tubules nourished by blood from the renal portal vein. The secretion of urine ceased, but it was possible to restore it by injecting urea intravenously, though the flow was very small and a lot of urea was present. This was taken to prove that the water comes from the glomeruli, and the urea from the tubules. Some perfusion experiments on the frog's kidney give a certain amount of rather dubious evidence in the same direction. When the tubules are poisoned by mercuric chloride perfused through the renal portal vein, and the kidneys then perfused with normal saline, the urine escaping is just the same as the saline in composition. To all this it may be objected that it is not safe to argue from the frog to the mammal, and that it is not certain that the fluid obtained is urine at all, and not a mere diffusion fluid.

That a urine more dilute than plasma may be obtained, e.g., after heavy drinking, or in diabetes insipidus, was taken as proving that the tubules could excrete water at need. The fact of the matter may be, however, that the tubules absorb under these circumstances not, as usual, a saline solution of such a composition that some of the *salt* is left behind in the lumen to be excreted, but a saline solution of such composition that some *water* is left for excretion. Thus the urine becomes more watery than the plasma. In ordinary, of course, there is rather more salt in the urine than in the blood.

It is true that a brief asphyxiation will render the

kidney impermeable for an hour, and that albumin may be present in the urine afterwards, but there is no difficulty in believing that the delicate animal membrane lining the capsules may be spoiled by lack of oxygen, and rendered impermeable, perhaps by some intracellular precipitation.

With regard to the oxygen consumption during diuresis, this varies with the cause. Diuresis due to an injection of normal saline has no effect on the gaseous exchanges; that due to sodium sulphate, urea, or caffeine is generally accompanied by an absorption of oxygen and output of CO_2. The explanation given by advocates of the modern theory is that the cells of the renal tubules have to work hard against the osmotic pressure of the sulphate in the lumen, to concentrate the fluid by retrieving the water; the same holds good for urea. When saline is given, however, the NaCl can be absorbed in the ordinary way, and does not accumulate in the tubules to make the work of the cells harder. The diuresis without increased gaseous exchanges tells strongly against any theory of vital excretion.

Some points in favour of the modern theory may now be mentioned. Nishi has shown in cats, dogs, and rabbits, that dextrose can be found in the cortex, but not in the medulla; this suggests that it is present in the glomerular filtrate, but absorbed lower down in the tubules.

Starling estimated the osmotic pressure of the blood proteins, and found it about 30 mm. of Hg. The lowest blood-pressure which allows the kidney to form any urine is about 40 mm. of Hg. The significance

of this relationship lies here: in the capsule, two forces are working against each other, the capillary blood-pressure driving the filtrate out, and the osmotic pressure of the blood proteins (which are not able to pass and therefore load the scales in favour of the blood as against the filtrate) pulling it back. The fact that the secretion fails to come through when the blood-pressure drops to the level of the counter-pull is strong evidence that there is no vital factor, but only the ordinary physical forces of filtration pressure and osmotic pressure, at work in the production of a flow through the capsule.

When the ureter is partially obstructed so as to raise the pressure in the tubules, the result is to reduce the amount of water; the chlorides fall in about the same proportion, but though less urea is excreted the percentage rises. Thus, in one experiment (Lepine and Porteret) the following figures were found:—

	Urine in c.c.	Urea		Chloride	
		Total	Per cent	Total	Per cent
From free ureter ..	73	0·146	0·2	0·35	0·48
From blocked ureter ..	11	0·121	1·1	0·04	0·40

Sulphates behave like urea. The deduction to be drawn is, that on account of the raised pressure and consequent delay in the tubules, such constituents of the filtrate from the glomeruli as are capable of re-absorption by the tubule-cells are taken up in larger

amount than usual, but not the unwanted urea and sulphate. These observations have been confirmed on man in a case of ectopia vesicæ, by blocking one ureter (Allard). Cushny attaches more importance to the effect of the raised pressure reducing the amount of filtrate through the capsules than to any effect in the tubules.

We have now passed in review the more controversial part of the subject of our chapter, and shall proceed to consider how the functions of the kidney are modified by various physiological and pathological changes.

EFFECTS OF BLOCKING THE URETERS.

We have already considered the chemical changes in the urinary secretion when the ureter is blocked. There is some important clinical evidence to discuss.

As is well known, the passage of urine down the ureter is brought about by rhythmical peristalsis of the ureter, and every skilled observer with the cystoscope is familiar with the periodic gush of fluid seen coming through the orifice into the bladder, usually occurring every few minutes. If a human kidney and ureter are excised, and the ureter is kept in oxygenated Locke's fluid, after a while the peristalsis starts again and can be watched. The renal pelvis also contracts at intervals, and apparently there is a sphincter guarding the pelvi-ureteric junction. It has been suggested that certain cases of distention of the renal pelvis in man, causing acute attacks of pain, may be due to some interference with the proper working of this sphincter (Pannett).

Ligature of the ureter, whether of purpose in animals or accidentally in man, produces rather variable consequences. In man, it does not seem to do much harm ; as a rule no hydronephrosis (dilatation of the renal pelvis with watery urine) is developed, and even after a fortnight the kidney may recover if the ligature is removed (Caulk, cases from the Mayo clinic). In animals, the results are sometimes similar, the kidney quietly atrophying ; but in dogs there is frequently some degree of hydronephrosis. An intermittent or partial block in man also produces a hydronephrosis. Probably what happens is that after the ligature or other obstruction interposes, the pelvis fills up to its limit with urine ; if this cannot escape, the kidney ceases to function and gradually atrophies. If, however, some gets away, the pelvis remains distended and a little more urine can be formed, and so in time the walls of the pelvis yield to pressure and the distention extends far beyond its original limits. If the tubule-cells degenerate from pressure, the urine will be more watery than usual, and in an old hydronephrosis this is generally the case.

A word may be said here on the subject of renal reflexes. It is quite clear from clinical evidence that irritation of one kidney or ureter, as by a stone or the passage of a ureteral catheter, may give rise to reflex suppression of urine from the other kidney. Probably this is due to arterial cramp. The increased flow of urine which sometimes follows a partial obstruction of one ureter may also be a reflex. It ought to be widely recognized that a too effectual use of the catheter may be fatal to an old man. If a patient

comes up with a very distended bladder, due perhaps to enlarged prostate, and a zealous dresser draws off the whole of his urine with a large instrument, the kidneys are apt to cease functioning for ever. This may be a reflex, but in a case which came under my notice the autopsy showed great dilatation of the ureter in its whole course, and what seemed to have happened was that the sudden fall of pressure in the bladder had, on account of the loss of the valve-like protection of the sphincters at the upper and lower ends of the ureter, been transmitted to the pelvis of the kidney, which is not built to experience such rapid changes, and the tubules and glomeruli, already not far from bankruptcy, had finally succumbed. In such cases one should only take away about half the urine at a time.

A personal experience that may be mentioned as showing how readily infection of the renal pelvis from the bladder may occur was the following. The right kidney had been removed for severe hæmaturia about three weeks before, but on account of the patient's exceedingly anæmic condition, and the intervention of an attack of paroxysmal tachycardia to which she was subject, healing did not take place. On more than one occasion urine, which had evidently ascended the ureter from the bladder, was found coming out of the wound.

NEPHRITIS.

The main features that characterize this condition are the reduction in the quantity of the urine, the albuminuria, and the tendency to œdema. Casts

may be present. In some types of renal disease, the contracted granular kidney for instance, and the chronic interstitial nephritis that accompanies enlargement of the prostate or stricture, the quantity of urine is excessive, and the specific gravity low. The microscope shows more change, as a rule, in the cells of the renal tubules than in the glomerulus, but this does not prove that the permeability of the latter may not be altered. Quite a small change in the cells might allow of the passage of more or less water than usual, and some of the serum proteins might be able to get through. Egg albumen injected into the circulation is normally excreted by the kidney, and so is free hæmoglobin. Compression of the renal artery for a few seconds causes albumin to appear in the first urine secreted afterwards. The albuminuria of heart disease is probably of similar origin, the glomerular cells being in each case partially asphyxiated. In all these conditions, and in nephritis, protein has been demonstrated in the glomerular cells. Tube-casts seem to be masses of protein precipitated by absorption of water as the solution passes down the tubules, in many cases picking up desquamated cells by the way. The same change that allows the passage of albumin also impedes the filtration of water.

An attempt has been made by Schlayer to poison different parts of the kidney by means of differential poisons, and then to work out the changes that result. Cantharidin and arsenic act principally on the glomeruli and the vascular tufts therein, and uranium, mercurials, and bichromates principally on the tubules. None of these is absolutely specific. In

uranium poisoning there may be general œdema in rabbits, especially if they are given much water and chlorides. These drugs usually cause at first a diuresis, which is followed by a fall in output of urine and the presence of albumin.

General œdema is due to lessened excretion of water and chlorides, which latter accumulate in the tissues and so by their osmotic power abstract the water from the plasma into the tissues; hence the modern chloride-starvation theory of treatment.

The increased urine excretion in contracted granular kidney and in the early stages of renal bankruptcy from the obstruction presented by an enlarged prostate is probably due more to changes in the general circulation than in the kidney itself; but this is not very clearly understood.

TESTS OF RENAL FUNCTION.

It is often of great importance, both in medical and surgical cases, to obtain some numerical criterion of the functional capacity of a damaged kidney. This is especially desirable when an operation is contemplated such as removal of the prostate, whether in one stage or by a two-stage operation.

A great number of tests have been proposed, some of which are fallacious, as the cryoscopy method (I have seen a life lost through depending on this test), and others are too complicated for clinical use. The following may be referred to as the best available in ordinary practice.

1. *The Two-hour Test* (Mosenthal). — A normal kidney is capable of wide variations in its labours;

it can at need excrete a concentrated urine or a dilute one, in response to the intake of fluids or solids. A damaged kidney cannot excrete so much; it has no margin; it must always be doing its little best. If the urine is collected every two hours for twenty-four hours (not necessarily during sleep), the normal kidney will excrete a urine with a specific gravity that varies exceedingly from period to period, the variation being over 8 or 9 points (e.g., from 1·016 to 1·027). Also the night urine is only about one quarter of the day urine in quantity. If, however, the kidneys are unsound, the specific gravity will keep very constant; it may for instance be always about 1·016; further there is not much difference between the day and night output. In carrying out the test the patient should be given at least four pints of water in the twenty-four hours, and a fairly high protein dietary, with 5 grm. of salt at lunch.

2. *The Urea-concentration Test.*—The patient is given 15 grm. of urea at a dose, and the urine secreted during the next two hours is collected and the urea estimated. If the urine contains 2 per cent or more of urea, the kidney is normal. Under 1 per cent indicates grave deficiency; under 1·5 per cent moderate deficiency. One caution is necessary: the patient must not have been drinking a great deal of fluid just before the test, or a too low value may be obtained. I once saw a patient with defective kidneys drop off into a deep slumber just after the dose, but he recovered well from an operation for resection of part of the bladder for cancer.

3. *The Blood-urea Test.*—The normal amount of

urea in human blood is about 25 mgrm. per 100 c.c. A figure over 40 mgrm. signifies that the kidneys are damaged. One sometimes finds figures over 120 mgrm. ; any surgical proceeding under such circumstances is likely to end in disaster.

4. *The Phenolsulphonephthalein Test.*—This test is reliable, but requires care in the technique, and a colorimeter is necessary, which lessens its usefulness clinically. A dose of 6 mgrm. is injected into a vein, and the urine drained away by a catheter into a test-tube containing a drop of 25 per cent NaOH solution ; when it turns red, the time is noted. The catheter is passed again after two hours, and the urine drawn off, rendered pink with NaOH, and made up to one litre with water to compare in the colorimeter with a standard solution of the dye. If blood is present this reaction is interfered with. Normally, the colour begins to come out in the urine in five minutes, and 60 to 85 per cent of the dye is excreted in two hours.

I have recently given up this method in favour of the urea-concentration and blood-urea tests, which are more universally applicable and less troublesome. The specific gravity examination can easily be employed even in country practice without any laboratory estimations. In prostate cases kidneys which are nearly bankrupt may be restored to a large extent by relieving the back-pressure, either by tying in a catheter, or by draining the bladder.

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CHAPTER III.

FOOD DEFICIENCY DISEASES.

CARBOHYDRATE, PROTEIN, AND FAT DEFICIENCIES—VITAMIN B — GROWTH — SCURVY — RICKETS — THE CAUSATION OF GOITRE.

THIS chapter is not a discourse on the phenomena of starvation. It rather aims at setting forth the consequences that may be expected when some one more or less essential ingredient of the food is omitted from the dietary.

In a Report of a Committee of the Royal Society on the "Food Requirements of Man", issued in 1919, it is observed that as a general rule the brain-worker requires from 2200 to 2600 calories as the energy value in heat units of his daily food, whereas the labourer needs 3300; but in the case of the brain-worker the food will need to be lighter, more digestible, and to contain more protein, so that it will cost more in proportion.

There is not much that is new to be related concerning the ill-effects of carbohydrate starvation. Except as a therapeutic measure, it seldom occurs. It leads to loss of flesh, as in the well-known systems of dieting for obesity, and to an increase in the formation of β-oxybutyric and diacetic acids in the blood.

Chittenden's work at Yale University showed that

it is possible to maintain life, and apparently both mental and physical efficiency, on a diet containing less than half the amount of protein allowed in the standard dietaries. Hindhede, of Copenhagen, by supplying an ample total calorie value of food (4000 calories per day), was able to maintain his laboratory attendant in health for 150 days on a diet of nothing but potatoes, margarine, and onions, containing only 4·425 grm. of nitrogen a day. It is very doubtful, however, whether the results would be satisfactory over a longer time. It has been demonstrated that the mental and physical efficiency of the various races of India, many of whom live very near the protein-starvation level, varies directly with the protein allowance in their dietary. The Royal Society Committee report that the diet of the average man should contain not less than 70 to 80 grm. of protein daily, and that some of it should be of animal origin.

There is a disease common in the Mediterranean countries and in the countries bordering on the Gulf of Mexico called pellagra, characterized by a rash like severe sunburn on the exposed parts, gastro-intestinal disturbances, and nervous symptoms. It is apt to attack its victims every spring, but to improve later in the year, and may recur over many years. Its causation has long been in doubt; bad maize, and many other conditions, have been blamed. Evidence is now accumulating from many sources that the real cause is protein-starvation, aided, it may be, by some personal idiosyncrasy as in other food deficiency diseases. During the war,

Wilson, in charge of Armenian refugees at Port Said, observed that 10 per cent developed pellagra in a year. The only etiological factor appeared to be a diet grievously deficient in protein; they were living principally on vegetables, which furnished 92 per cent of their proteins, and the total was only equivalent to 22 grm. per diem of caseinogen. A better dietary, with proteins to the equivalent of 41 grm. of caseinogen, abolished the disease. The same was seen in Turkish prisoners of war. Evidently all proteins have not the same biological value in warding off this ailment, perhaps on account of variations in their amino-acid content.

Goldberger in America was in charge of an asylum with numerous cases of pellagra amongst the inmates, and found that an extra allowance of animal food rapidly cured them. His work was verified by two representatives of Johns Hopkins University sent to report on it. Of eleven adult male convicts who volunteered for the experiment, pellagra was induced in six by systematic protein-starving for seven and a half months. Their diet contained from 41 to 54 grm. of protein daily, mostly from cereals (wheat, maize, etc.). Return to a more normal diet cured them. Chick and Hume have induced symptoms resembling pellagra in three monkeys by reducing the protein intake; one of them was dramatically cured by caseinogen. Sunlight exaggerated their skin-lesions, as in man. Tryptophan feeding seemed to delay death in one monkey. There is still a possibility that bad maize may be a factor, and, according to McCarrison, deficiency in vitamin B.

Some very interesting information bearing on the relative value of the different amino-acids in proteins is furnished by the observations of Hopkins and others on young growing rats and other animals. It is well known that both for young animals and adults, tyrosin and tryptophan are necessary for life, as apparently the body cannot manufacture the benzol-ring. Tyrosin is closely allied to adrenalin, and is probably its necessary precursor. Gelatin is defective, because it does not contain these aromatic amino-acids, and will only support life if they are added. Zein, the protein of maize, contains neither lysin (a di-amino-acid) nor tryptophan, and if fed to young rats is inadequate to maintain life. If tryptophan is added, they live, but do not grow. If lysin is then added, they both live and grow. Gliadin, the principal protein in wheat flour, contains no lysin, and is therefore not suitable as a main source of protein for growing animals, though useful for adults. It is the supreme virtue of caseinogen, the principal protein of milk and cheese, that it contains all the most necessary amino-acids in suitable proportions.

A colossal experiment in fat-starvation was carried out during the war on the population of Germany and the other Central European states. There was a high infantile mortality, general loss of flesh, bodily and mental torpor, and increased liability to tuberculosis. Rickets became a widespread scourge among German infants. Another consequence of prolonged fat deficiency was a chronic affection of the conjunctivæ in infants (xerophthalmia). This has also been experimentally induced in animals.

There seems to be a close relation between the assimilation of fat and the capacity for bodily work. " Where vigorous muscular exercise has to be undertaken, it is essential that the diet should contain not less than 25 per cent of its energy in the form of fat " (Royal Society Committee Report).

Another condition that came to light at the end of the war was what is called famine-dropsy. It was seen in the great Indian famine of 1877–8, and again in various districts on the Continent where there was prolonged semi-starvation during the war. For instance, von Joksch reports that in 1917, 22,842 persons developed it in Bohemia, and 1028 died of it. It appears to occur when the diet contains less than 1400 calories, and deficiency in fats and carbohydrates is said to be more important than protein-starvation. Men suffer more than women or children. The symptoms are slow pulse, polyuria, dryness of the skin, great wasting, and dropsy, but not albuminuria. It is readily cured by rest in bed and a more generous diet; cod-liver oil is particularly valuable. The œdema may be related to that resulting from a vitamin defect, to which we shall presently refer.

VITAMIN B.

For generations it has been a fundamental axiom of dietetics that a proper food allowance should contain proteins, carbohydrates, fats, salts, and water. Tables, such as Ranke's, have been drawn up and copied from book to book, setting forth the proper proportions of each to maintain health.

During the past ten years, however, important evidence has been adduced to show that these five proximate principles by themselves are inadequate, and that a mysterious something more is necessary.

One of the first reforms leading up to the marvellous emancipation of modern Japan from her mediævalism of half a century ago was concerned with a problem of this sort. The Japanese navy was reduced to complete ineptitude by the prevalence of beri-beri—a form of peripheral neuritis—amongst the crews, as many as a quarter of the men being afflicted. Baron Takaki, lately returned to his own country after a study of modern medicine, found that the dietary was very imperfect, and instituted an improved ration with complete success. Beri-beri was until recently a terrible scourge amongst the inhabitants of the Malay States; was often seen in coolies at English seaports; and has broken out in an asylum in Dublin. Improving the quantity of food in the prisons of the Straits Settlements failed to limit the disease.

The outstanding feature of the incidence of beri-beri in the Straits was, that while the Tamils were exempt, the Chinese suffered severely. Rice is the main article of diet with both races, but with this difference, that whereas the Tamils store their rice and boil it in husk, the Chinese use husked white rice such as we are accustomed to in this country, though, of course, with us rice is a very much less important item in the daily dietary. The Chinese are extremely prone to beri-beri; the Tamils very seldom suffer. This cannot be due to any racial

peculiarity, because Tamils in prison and fed on husked rice are just as liable as the Chinese.

The explanation originally given was that the bare rice grain had become contaminated in some way; but experiments by Casimir Funk and others have brought out another aspect of the case. It is possible in pigeons to produce a peripheral neuritis closely resembling beri-beri by feeding exclusively on polished rice, and when small quantities of husk are added the birds rapidly recover. The essential constituent of the husk which has this effect is only present in small quantity, but it can be isolated in crystalline form, and on analysis appears to belong to the pyrimidine group. It is not the coarse fibrous husk that contains so much of the anti-neuritic substance, but the thin film or 'silver skin' just covering the grain, wherein also lies the embryo. Wheat embryo, wheat bran, yeast, and egg yolk also contain fair quantities of this element; milk and meat only hold traces. Cellular organs such as liver, brain, and sweetbread contain a good deal. Some is present in most fruits and vegetables. From 100 kilos of yeast 2·5 grm. of the crystals were obtained. It is absent from polished rice, white flour, butter, and the refined foods of modern food industries.

There is clinical evidence in support of this experimental work. Research in the Philippines has shown that the infant of a mother fed on polished rice is likely to develop beri-beri, but that it is rapidly cured either by fresh cow's milk or by an extract of rice-husk. The substitution of parboiled for polished

rice in a Siam prison has brought down the death-rate from 113 to nil.

McCarrison shows that it is not only the nerves that are affected by a diet restricted to polished rice. The thymus, testes, ovaries, and spleen all atrophy, and in a less degree the pancreas, heart, liver, and kidney. The suprarenals, on the other hand, become hypertrophied, and there is usually œdema, which seems to run parallel to the degree of enlargement of the suprarenals. Doubtless this accounts for the 'wet' form of beri-beri, and perhaps for 'famine œdema' already referred to.

McCarrison has shown, further, that if monkeys are fed on a diet of autoclaved rice, the vitamin we have so far been considering having been destroyed by the heat, characteristic changes occur. The stomach is dilated, intestines are thinned and ballooned, and intussusceptions develop. The mucosa is congested, and the mesenteric glands are enlarged. Gastric ulcers are occasionally seen. The colitis resembles that so often seen in man, and there is a close mimicry of the condition known as chronic intestinal stasis. The symptoms are loss of appetite, diarrhœa or dysentery, and general weakness. It is well worth consideration how far colitis and intestinal stasis in the human subject may be due to a prolonged deficiency in the diet of the necessary vitamin. Cases are on record of speedy improvement when articles of food containing it in plenty, such as 'marmite', brown bread, glandular organs, and fresh fruit, were added to the daily menu.

GROWTH.

The principle having once been established that a dietary to maintain health must contain, in addition to the five well-known elements—proteins, carbohydrates, fats, salts, and water—traces of other so-far unrecognized chemicals, a new field is opened for exploration, and several diseases come up for a similar explanation. The new chemical bodies which appear to be thus needful are called 'vitamins'.

Hopkins has shown that something of the sort is necessary for ordinary growth. Young rats fed on purified protein, carbohydrate, fat, salts, and water, absolutely cease to grow, even if the quantity supplied is correct. If the experiment is prolonged, the animals die. If only a teaspoonful of milk is supplied daily, growth becomes normal. We now know that *two* vitamins are necessary for growth; one of these is called fat-soluble A, and is contained dissolved in the fat of milk, and the other is water-soluble, and appears to be identical with, or closely allied to, the antineuritic vitamin, called water-soluble B. Considerable research has been done lately on the fat-soluble A. It is shown by Halliburton and Drummond, using young rats, that none of the vegetable margarines which have come into such extensive use of late contain it. It is present in milk, butter, cream, animal fat, especially in the liver, cod-liver oil, and the higher-priced (oleo-oil) beef-fat margarines. Lard contains little if any; it has been spoiled in the process of preparation. The fat-soluble vitamin in mother's milk is derived in considerable part from cow's milk or cream she

has taken as nourishment. These observations go to show the national importance of providing milk and animal-derived fats both for young children and also for nursing mothers. In the last resort, the cow obtains it from grass; it is present in most green leaves and young shoots. Tomatoes are specially rich in it. There is much more present in cow's milk in the spring and early summer than later in the year, or in the winter. Skim milk does not contain it, nor do white flour, meat extracts, and refined foods. Pork fat contains little, as the pig does not eat much green food.

Even sarcoma-cells require vitamins, and if they are withheld, Jensen's rat sarcoma only develops at a quarter its usual rate. At Romney there are two fields, apparently identical, but the animals pasturing in the one put on flesh, and in the other they become thin.

SCURVY.

It has been known for centuries that scurvy is a deficiency disease; but exactly where the deficiency lies has always been uncertain. Nowadays it is very rare in adults in this country, though the writer has seen one case affecting a lonely man who was trying to live on his old-age pension. A few cases occurred in France during the war. I saw one quite severe example of the disease at a casualty clearing station. The man had been a long time in the trenches, and had had no fresh food.

Much more commonly the disease is seen in young infants fed upon boiled, stale, or artificially-prepared milk. It was very prevalent amongst troops in

Mesopotamia during the earlier periods of that campaign, but disappeared when the fruits and fresh vegetables of Baghdad became available.

Some most interesting and important points have lately come to light with regard to scurvy. It should be remembered that the swollen gums, loose teeth, hæmorrhages from the mucous membranes and beneath the skin and periosteum, and grave anæmia, are signs of an advanced degree of the food deficiency. There are less characteristic symptoms long before these develop—lassitude, inability to think or work, and general debility. When these signs appear in a body of men, undeclared scurvy should be thought of. Latent scurvy often occurs in babies ; the child ceases to thrive, feeds badly, becomes peevish, and there may be a few petechiæ, tenderness of the femurs, and inflamed gums. Suitable dieting rapidly cures the condition (Hess).

It has been an article of faith for nearly a century that lime- or lemon-juice and fresh vegetables are the main preventives of scurvy, and yet there have been curious gaps in the evidence. Up to the beginning of the eighteenth century, both the British Navy and the mercantile service had suffered terribly from the disease, and many expeditions were ruined in consequence. In the days of Robinson Crusoe the antiscorbutic properties of lemons and fresh fruit and vegetables were known, but the supineness of the authorities was such that often no trouble was taken to provide sailors with them until about 1803, when the Navy began to get a regular supply of lemon-juice from Malta. It was often called 'lime-

juice'. After about 1865 the juice of Montserrat limes came to be used instead, and this has been the main standby in the Army and Navy ever since. From 1803 onwards there has been very little scurvy. The use of fruit-juices became compulsory in the merchant service after 1844, and was equally successful. Of course, shorter voyages and better food supplies generally have led to less and less need to place reliance on lime- or lemon-juice under ordinary circumstances. In several Arctic expeditions, such as Sir James Ross's in 1849, the lemon-juice supplied was thoroughly bad, and the company suffered severely from scurvy. Thus far the evidence is clear. There have been, however, several occasions when no fresh vegetables and no fruit-juice have been used for long periods, but fresh meat in large quantity has been eaten, and no scurvy has occurred. This was so with Nansen's expedition across Greenland, and with one of the subsidiary parties in Shackleton's expedition to the South Pole. The Hudson's Bay Company people live almost entirely on fresh meat and fish, and they never show signs of the disease. Yet fresh meat has failed to avert scurvy (as in the Kaffir campaign of 1846–7) when plenty of other food is taken at the same time. Evidently the amount of vitamin in fresh meat is low, and unless it is eaten in great quantity it proves inadequate. Also, the traditional Army stew probably destroys much of the vitamin by long cooking.

During the war, doubts have grown up as to the preventive value of lime-juice. This has led Miss

Alice Henderson Smith to bring to light many most interesting facts about the history of the disease in the records of Arctic and Antarctic exploration. There is a remarkable contrast between two expeditions, that of Sir Robert McClure in the *Investigator* in 1850, and that of the *Alert* and the *Discovery* in 1875. McClure went to seek for Sir John Franklin; his ship was north of Alaska for twenty-seven months after leaving England before the first case of scurvy occurred, in spite of great hardships and many months on half rations. In the *Alert* and *Discovery*, north of Greenland, there was a severe outbreak of scurvy in eleven months, though on full rations. The *Alert* had sixty cases and three deaths out of a company of 122. The food-supply of the *Alert* and of the *Investigator* was practically the same, except that on the latter lemon-juice was used, and on the *Alert* lime-juice. In each case the officers took great care to see that the juice was really drunk.

Finally, an investigation has been made experimentally by Chick and Hume at the Lister Institute, which shows that lemon-juice has four times the antiscorbutic power of lime-juice. Oranges are as good as lemons, and the fruit is better than the bottled juice. The antiscorbutic power of fresh meat is low; about four pounds a day is needed in man, whereas an ounce of lemon-juice will do. The most interesting discovery is that germinating peas and beans develop a high proportion of the vitamin. If they are soaked in water for twenty-four hours, then spread out to germinate for two days, and cooked not longer than an hour, they are powerfully

antiscorbutic. What suffering it would have saved if this had been known before ! The *Alert* and *Discovery* brought back unused 6000 pounds of dried peas !

During the war there was a good deal of scurvy amongst Serbian soldiers in Macedonia, and Wiltshire was able to test the relative curative value of lemon-juice and of germinated beans by allotting a ward full of scorbutics to be treated by each method. In spite of the fact that the soldiers rather resented being fed upon 'pig-food', its therapeutic virtues were, if anything, rather superior to those of the fruit-juice.

Swedes, potatoes, and cabbage, unless cooked too long, all contain the antiscorbutic vitamin. Canned fruits and vegetables are almost useless. Beer had a great reputation in the old Navy ; native Kaffir beer certainly protects, but the 'high-dried kilned malt' used by Sir John Franklin's expedition, and modern brewed beers, are of no value. The largest quantities are contained in fresh orange- or lemon-juice, onions, and raw cabbage juice. This vitamin is known as water-soluble C.

Fresh milk contains the vitamin, but it is lost on boiling for more than five minutes. It disappears in stale or dried milk. Probably this vitamin may fail at the end of prolonged lactation, thus accounting for a few authentic cases of scurvy in breast-fed babies. In ordinary, sufferers from infantile scurvy have been fed on stale, artificial, sterilized foods. The disease is rapidly cured by giving fresh unboiled milk and fruit-juices. Infants reared on boiled milk ought to have a little orange- or grape-juice (though

this is not quite as good) every few days. They like it. Also, the milk ought not to be boiled more than a minute. If no other source of vitamin is supplied, animals have to be given a great deal of milk to avert scurvy.

The vitamins that prevent beri-beri and scurvy are both water-soluble, but they are not identical. The antineuritic body is not so readily destroyed by heat, and it keeps better. Vitamin A is the most stable, and C the least; it can best be carried in the form of tinned tomatoes, or peas that are ready to be germinated.

RICKETS.

Few diseases have given rise to a greater volume of discussion and research, during the past few years, than rickets. It is probably in part at least a deficiency disease. The infants have usually been fed upon a diet containing too much starch and sugar, and too little fat and protein. The observations of Bland-Sutton at the London Zoo rather point to the deficiency of fat as being the more important. A lioness there was unable to suckle for long, and litter after litter of cubs had died of rickets. Investigation of the diet showed that they were fed upon London cab-horse, which naturally did not supply any fat, and their little teeth were not able to crush the bones and obtain the marrow. When they were given milk, cod-liver oil, and pounded bones they did excellently. It is well known, of course, that cod-liver oil, cream, and fresh milk are the best treatment for rickets.

There is much difference of opinion at the moment whether rickets is due principally to deprivation of a fat-soluble vitamin, as the above observations and the researches of the Mellanbys would indicate, or to lack of fresh air and exercise, as is maintained by Noel Paton and other workers in the Glasgow school. At the Glasgow Zoo, cod-liver oil does not prevent rickets; the only zoo free from it is said to be Hagenbeck's at Hamburg, where the animals are allowed great open spaces and natural conditions. Investigation of the home surroundings of children of the hospital class in Glasgow shows little difference as to bottle-feeding and breast-feeding, or the amount of fat in the dietary, between the healthy and the rickety. If the rooms were small, crowded, high up, and ill-ventilated, and the children seldom taken out, the proportionate incidence of rickets was high. In the markedly rachitic children, 3·93 persons inhabited each room, and the cubic feet of air-space per person was 422; in the non-rachitic, there were 3 persons per room, and the air-space was 625 cubic feet. The homes of the rachitic were poorer and less well cared for. Of the rachitic, only 30 per cent were properly exercised; of the healthy, 86 per cent.

In Nasik, a town in the Bombay Presidency, there are two distinct classes in the population; in Class 1 are the Brahmins, well-to-do Hindus, and better-off Mohammedans, all of whom seclude their women and girls in purdah, which involves close confinement, but a good and rich dietary. In Class 2 are the lower castes and outcasts, who do not maintain

purdah, but get a food-supply much poorer in fats and the fat-soluble vitamins than their more prosperous neighbours. The incidence of rickets, however, is much heavier amongst the females of Class 1 than in Class 2. In 1073 children of purdah mothers there were 24·9 per cent of active or obsolescent rickets; in 2305 children of non-purdah mothers only 4·8 per cent (Hutchison). All babies are breast-fed for twelve months. Seventeen cases of late rickets were seen, all in females about thirteen years old; of these all but one were purdah girls, although the bulk of the clinical material belonged to Class 2.

There is some animal evidence in the same direction. Puppies kept in the laboratory are much more prone to rickets than those allowed to run wild in the country. The *x*-ray signs of rickets at the growing ends of a puppy's long bones are very well shown. In some cases the country puppies were given less fat than the laboratory ones. A particular instance is quoted of two identically fed puppies, one belonging to an active boy and the other to his invalid cousin; the latter developed rickets, because it was more cooped up.

Noel Paton believes that the cause of the defective bone formation in rickets is an error of the metabolism of the phosphorus-containing fats (lecithins), probably in the liver; and that this is accompanied by an increased conversion of cholin into guanidin bodies, thus explaining the liability to tetany and convulsions in rickety babies. The blood of rachitic children is deficient in phosphorus, but not

in calcium. McCollum and his collaborators in America advance evidence that a disproportion between the calcium and the phosphate ratio in the diet is more important than the fat-soluble vitamin.

The Mellanbys and others maintain the vitamin hypothesis. E. Mellanby has used a much larger number of pups, over 200, and finds that a diet containing bread, meat, oatmeal, linseed oil, yeast, orange-juice, and an *inadequate* amount of milk causes rickets constantly in a few months. Giving more milk, or animal fats, prevents rickets. Fast-growing pups show symptoms more markedly than slow-growing. Calcium salts make no difference. Mrs. Mellanby shows that on such a diet, adequate in all other respects, but lacking animal fats, the puppies' deciduous teeth are lost late, the permanent teeth erupt late and are badly placed, the enamel is defective, and the calcium content low. If plenty of milk or cod-liver oil is given, the teeth are normal.

Mellanby replies to the Glasgow school, that the milk allowance for their dogs was always rather low, so that the difference between confinement and exercise might turn the scale when animals were already near the margin, by differences in appetite and assimilation. When pups have plenty of milk, confinement does not make them rickety. The amount of fat in the dietary of the Glasgow children was very near the minimum, and there was, as a matter of fact, less in the diet of the rachitic families ; also, if children eat a lot of bread they tend to

neglect the articles that contain the vitamin. In Greenland, where the Eskimo children are cooped up all the winter in huts, but get plenty of animal fat, rickets does not occur.

There is no doubt that cod-liver oil is a powerful preventive of rickets, and also that it cures the disease when established, both in young animals and in children. It is far more potent than milk or milk fats. In an American negro baby clinic, of thirty-two infants given 54 oz. of cod-liver oil in six months, only two were rachitic ; of sixteen given none, all but one became rickety.

In his later publications, Dr. E. Mellanby does not plump so whole-heartedly for the single factor of defective fat-soluble **A** vitamin in the diet. He sets forth the etiology of rickets in the following order : " A deficiency of calcium and phosphorus in diet ; a deficiency of fat containing the anti-rachitic vitamin in diet ; excess of bread, other cereals, and carbohydrates ; absence of meat ; excess of the protein moiety of caseinogen free from calcium ; confinement." He thinks the commonest cause in children is deficient vitamin and excess of bread.

There are grave objections to the view that the fat-soluble growth vitamin and the anti-rachitic vitamin are identical. Puppies with rickets do not cease to grow, nor do children in every case. The faster the growth, the worse the rickets. Green leaves are specially rich in fat-soluble **A**, but so far as the little evidence available serves us, they do not prevent or cure rickets. In rats, McCollum and Shipley found that to induce rickets it was necessary

to deprive them of fat-soluble vitamin *and* of phosphorus compounds.

Evidence is accumulating that sunlight and fresh air alone will often suffice to prevent and cure rickets. This has been confirmed by Hess in America, and by Dr. Chick working with the starveling children in Vienna. In the United States, rickets is a winter disease, and gets well of its own accord in the summer. Artificial light allowing ultra-violet rays to pass is a potent cure. The relative liability of the negro to the disease is explained by the pigment in his skin neutralizing to some extent the rays of the sun. We have probably overdone the splint treatment for bow legs and knock-knee; it would be better to straighten the bones under an anæsthetic, and get the child running about in the open air as soon as possible.

In constructing a diet table for children it ought to be remembered that such a deficiency of vitamins as may produce scurvy, beri-beri, rickets, or stunted growth represents a *gross* deviation from the ideal, and that much chronic ill-health and liability to infection may result from less exaggerated deviations.

THE CAUSATION OF GOITRE.

Like rickets, goitre is a condition in which the causative factor is not simple. The principal facts are as follows:—

1. Certain drinking-waters will produce it, as the Kropfbrunnen on the Continent, and the waters of Gilgit. Boiling the water, or filtering it through a Berkefeldt filter, abolishes the danger. McCarrison

advances evidence that fæcal contamination of the water is an important factor.

2. A diet deficient in iodine will induce goitre; this is well seen in sheep in inland districts, and is cured by giving an iodiferous rock salt. The gland enlarges to catch more iodine to manufacture its active principle.

3. Confinement in dirty cages is another factor, probably due to the same cause as that which contaminates the drinking-water. If plenty of iodine is supplied, goitre will not appear under these circumstances.

4. Excess of fat in the diet will induce goitre. This has been demonstrated both by McCarrison on pigeons in India, and by Mellanby in this country. Butter has most effect; cod-liver oil does not act, probably because of the iodine it contains. There is evidently a fat-thyroid-iodine balance; too much fat, or too little iodine, will make the thyroid enlarge. Oleic acid is particularly active in determining this.

The observations just described are too recent for us to appraise their clinical significance, but are already leading to most encouraging results in the treatment of thyroidism and exophthalmic goitre. At a recent surgical congress I heard the opinion expressed by a surgeon who had seen some of the results of the newer methods, that surgical specialists in Graves' disease will soon be out of a job! The treatment advised is to cut out the fats as far as possible from the dietary, especially the milk fats, and to give small doses of potassium iodide. It seems surprising that so simple a method

has not been tried before, but the wasted appearance of the patient has encouraged fat-prescribing rather than fat-deprivation.

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CHAPTER IV.

THE DIETETIC FACTOR IN THE CAUSATION OF APPENDICITIS.

THERE can be no doubt that appendicitis has become very much commoner than it used to be. The first case described in medical literature is that of Mestivier in 1759, and the first English record is Parkinson's in 1812. It was not till 1886, when an epoch-making paper on the subject was issued by Fitz of Boston, that the condition began to attract general attention; it was Fitz who gave it its name. It is not certain who first made a diagnosis in the living patient and deliberately removed the appendix; the claimants are Kronlein in 1884, Treves in February, 1887, and Morton of Philadelphia later in the same year.

It was not till 1901 that deaths from appendicitis were classified separately in the Registrar-General's mortality tables for England and Wales.

Following is the death-rate from appendicitis per million living, for England and Wales:—

Year	.. 1901	1902	1903	1905	1910
Death-rate	38	45	52	57	66
Year	.. 1911	1913	1915	1917	1918
Death-rate	75	68	67	67	72

At first there was more appendicitis in the towns than in the rural districts; nowadays there is no

difference. The mortality per case is considerably lower to-day than it was fifteen years ago; taking this into account, there must be quite five times as many cases recognized now as compared with 1901. The food privations of the later war period made no difference in the frequency of the disease; amongst the troops there was certainly no more, and perhaps less, appendicitis than in the civilian population of the same age.

I have carefully gone over the figures of the Bristol Royal Infirmary to study the incidence of the disease. There has been a remarkable rise, especially between the years 1895 and 1905, as shown by the following table:—

CASES OF APPENDICITIS (ACUTE) AT THE BRISTOL ROYAL INFIRMARY.

Year	Cases of probable or certain appendicitis	Additional very dubious cases	Total in-patients treated
1880	4	2	2591
1885	2	1	3370
1890	4	6	2913
1895	15	—	2910
1900	23	—	2865
1905	64	—	3762
1910	58	—	4149
1915	75	—	3481
1917	98	—	3907
1918	113	—	4021

Mr. Sherren has shown that the sudden rise in the number of cases treated at the London Hospital was also between 1895 and 1905.

It may be objected that this rise is not a real one,

but that the older practitioners did not recognize the disease. This is certainly incorrect; the rise is quite authentic. I have gone over the notes of all abdominal cases, medical, surgical, and gynæcological, with great care, to see how many could be forced into a diagnosis of appendicitis; but, as the table shows, it is very, very few. The old doctors *were* on the look-out for the disease; often one reads in the notes that there was no tenderness over the right iliac fossa. The unpublished records of private practitioners who were in a large way of business before 1890 show that they, too, saw very little appendicitis, as compared with other abdominal diseases.

The distribution of this ailment in the community is interesting and instructive. It is very uncommon in poor-law patients, in the residents in Portland Prison, and in orphan institutions, in all of which the diet is plain and old-fashioned. It is very common in the United States, and in the northern countries of Europe. Amongst the poor and the country folk of Southern Europe it is comparatively uncommon. Amongst negroes, Asiatics, Egyptians, and Polynesians it is almost unknown, unless—a very significant exception—they have taken to European food and ways of living.*

Another very valuable fact is that though the disease does not seem to be recorded in wild animals, it is very common in apes in captivity. At the London Zoo there have been two cases in gibbons

* Figures in support of all this are given in my paper referred to at the end of the chapter.

and one in a chimpanzee; Weinberg reports that 10 out of 61 post-mortems held on chimpanzees in captivity showed appendicitis.

We have, then, to seek a cause for appendicitis which will cover the foregoing facts—the sudden rise in its incidence in England, the immunity of the native races unless they take to European food, and the persisting liability of Europeans to the disease when they themselves go to the tropics. It is quite clear that it must be some food factor which has brought this visitation upon us.

A study of Government Blue-books dealing with the various imports into this country brings to light the very interesting fact in this connection that it was during the years 1890 to 1905 that England ceased to feed herself, and came more and more to rely on food brought by ship over the seas. The principal imported foodstuffs are wheat and other cereals, meat, butter, tea, coffee, cocoa, sugar, rice, bananas, oranges, currants, and raisins. Most of these can be exonerated without going into the question here; nor can the suggestion be accepted that the method of milling has anything to do with the problem. By plotting a chart for the increased consumption per head of the population alongside a curve for the increase of appendicitis, one can dismiss butter, tea, coffee, and rice from further consideration. A case has been made out against bananas by one or two writers, but the curves do not correspond, especially those of the war period; and though the natives of the West Indies eat plenty of bananas they do not get the disease. Nor can oranges be blamed.

When, however, we come to plot the curves for imported beef and mutton alongside the appendicitis curve, the correspondence is so close that it is quite certain that there must be *some* connection, whether it be immediate or indirect (*see Fig.* 1).

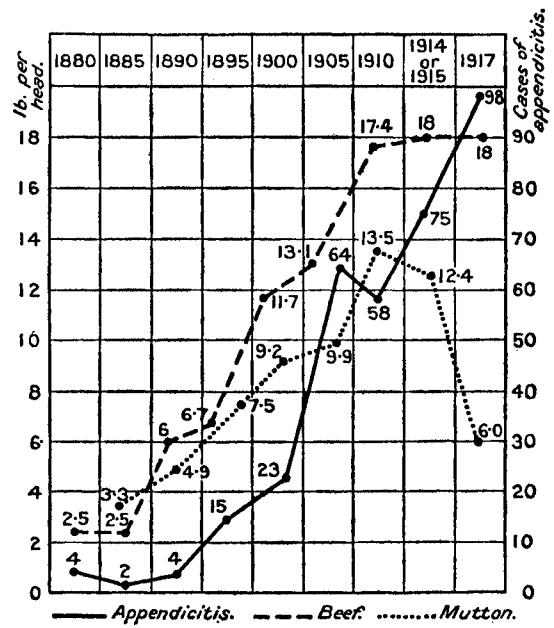


Fig. 1.

One is at first disposed to accept the theory that disease of the appendix is the direct consequence of too much meat-eating. But this view can scarcely bear examination. It is true, and must be carefully borne in mind in arriving at our conclusion, that

those races, the Chinese, Indians, and African negroes, who are more or less vegetarian in their diet, do not suffer, nor do the Polynesians, who live on fish and vegetables; whereas the meat-eating people of Europe and America very often develop the disease.

There is unfortunately no adequate information as to the incidence of the trouble in populations like the Eskimos and Paraguayans, who live almost entirely on flesh, at any rate in the remoter districts. But in spite of all this, there is evidence against the meat theory. It would not explain, for instance, the frequency with which apes in captivity get the disease. Again, in some countries where a fair amount of meat is eaten, such as Persia, Abyssinia, and Madagascar, there is practically no appendicitis. And although it is true that there was a great rise in the use of imported beef and mutton into Great Britain just at the time when we began to be aware of the increase in the number of cases of appendix trouble, it does not follow that the average Britisher only began to get a meat diet somewhere between 1890 and 1905. Figures can be quoted to show that while the consumption of beef and mutton from overseas has increased, the flocks and herds in these islands have remained practically stationary on a rising human population, so that there has been a fall in the use of meat produced at home. Also, there used to be a big trade in importing live beasts for slaughter, which almost died out about 1905. The curve shown in *Fig.* 2 exhibits the consumption per head of the population of all forms of imported

meat in pounds per annum, and if it is remembered that the use of home-grown meat was falling, it will be seen that there is not so very much difference between 1890 and 1917, after all. During the year

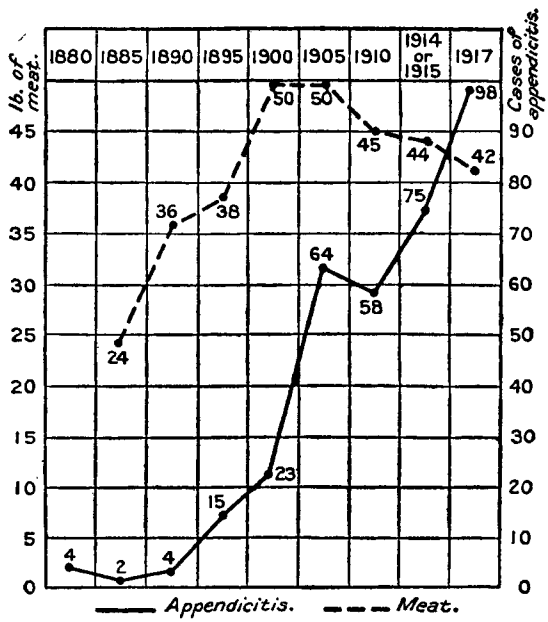


Fig. 2.

1921, about 47 per cent of the meat eaten was imported.

But the problem may also be considered from another point of view. Granted that in the 'hungry forties', and long afterwards, the poor of England did not often see meat on their tables, there has

always been a minority of well-to-do farmers and others who were able to obtain quite as much as people do now. Our old songs sang the praises of the 'Roast Beef of Old England', and contemporary records tell us of gluttonous feasts. It was an old saying in the country that 'a goose is a fool of a bird, too much for one, and not enough for two!' In 1889 the official ration for soldiers in the British Army was 12 oz. of meat daily, and Brigade-Surgeon Maunsell weighed 1232 rations, and found that the average amount of cooked meat issued, exclusive of bone and dripping, was 7 oz. 1 drachm daily per man. In a report to Parliament, also in 1889, the manager of Pearce's Dining-rooms in London showed that the firm fed 30,000 carmen daily, and they consumed every day for dinner 5 oz. of meat, weighed uncooked without bone. Clearly, there were millions of people in England eating as much meat as anyone does to-day, and far more than civilians could get in 1918, during the war hardships. If meat-eating were the cause of appendicitis, there should have been plenty of it before 1890, and it should have died out in 1918.

The question of course arises, that perhaps it is the preservation of the meat that leads to trouble. But anyone who served overseas in the army or navy will testify that a principal difference between the diet of home-life and that of active service was the quantity of preserved meat we ate—bully beef, pork and beans, veal loaf, frozen beef or mutton, or Maconachie ration was our daily fare. Therefore, if the increase in appendicitis is due to these things,

the army should have suffered very badly. There is no evidence that this is so; what evidence there is points all the other way. Preserved meats are much used in institutions, where we have seen that the incidence of appendicular trouble is less than in the average community. Nor can such a diet be accused of causing the condition amongst apes in the Zoo. If it is maintained that it is frozen meat, and not tinned, that is to blame, why do Europeans in the tropics so frequently suffer, where there are no refrigerators in which to store frozen meat pending distribution?

It looks as if we had been led to an impasse, and we may turn aside for a moment to inquire whether the introduction of boric acid and the other food preservatives can be blamed. It seems very unlikely. They came into general use too early, 1880 to 1895. For the past ten years scarcely any boric acid or other preservative has been used in milk or butter, though they are still present in bacon and in cream. Appendicitis is often seen in Denmark, where such agents are forbidden by law; also amongst Europeans in the tropics, and in the farming class, neither of whom would be likely to be treated to much boric acid in their food.

Where, then, shall we look for a solution of our problem, which seems at first so clear in its data? As it does not work out well as the direct result of something *added* to the diet, let us consider the possibility of its being a deficiency disease.

That it is related to the great modification of dietary that took place between 1895 and 1905,

when Great Britain ceased to grow the bulk of its own food and began to import most of it, seems too firmly established to be questioned. Other countries have modified their feeding along the same lines, some earlier, some later. In this country, the official figures show an enormous increase in the consumption per head of a great variety of imported foodstuffs, not only of meat, which we have considered, but also of rice, tea, fruits, and potatoes, which rose from 2 million cwt. in 1890 to 3½ million in 1905. Meanwhile there was a huge increase in the quantity of wheat brought in from overseas—60 million cwt. in 1890, and 97 million cwt. in 1905.

What does all this mean? It means, infallibly, that the older home-grown foodstuffs have been more or less crowded out by the newer, more tasty, or more nourishing imported articles. Swedes, turnips, carrots, parsnips, leeks, asparagus, cabbage of all sorts, rhubarb, lettuce, celery, the coarser fruits and vegetables, oatmeal porridge, rye, barley—in a word, the cellulose-containing foods—have been superseded in the dietary. It is not necessary to prove that the average Britisher eats less, absolutely, of any or all of these than his forefathers. This is probably true, but it would be difficult to bring it to a mathematical demonstration. The point which is mathematically proved is that, *relatively to the total food eaten*, cellulose consumption has fallen. This is bound to be so, since it is a fact that more meat, rice, cocoa, wheat, and potatoes have been taken per head. Modern white bread contains less cellulose than the older browner breads. If in 1890

a man took porridge for breakfast; soup, turnips, cabbage, and potatoes for dinner; and brown bread and butter and lettuce for tea, the percentage bulk of cellulose in his daily diet must be reduced if he has now added bacon to his breakfast, Australian meat to his dinner, and cakes to his tea, even if he does not drop out the porridge, greens, and brown bread and butter and lettuce.

Let us see how this suggestion will fit our facts.

1. The time factor is correct. It was between 1895 and 1905 that the foreigner began to feed us, and that we imported appendicitis with his food. Since then, there has been little change in either.

2. The cellulose foods would survive longer in the rural districts than in the towns, but to-day there is little difference in the diet of town and country. Appendicitis was at first a town disease, but now there is no difference in its local distribution.

3. In prisons and institutions for orphans, etc., the older and cheaper foods are still used, and are less diluted.

4. Apes in captivity do not have the coarse fibrous food to which they were accustomed in the wild state.

5. During the later stages of the war, in spite of various privations, there was no great return to the old coarse foods. People ate less, but of the food to which they were accustomed. Soldiers were protected by their pork and beans, and Maconachie ration—and as a matter of fact they often got fresh vegetables.

6. The national distribution of the disease is much

in favour of the theory. Those races that eat coarse vegetable foods are not liable, but if they turn to European diet they lose their immunity.

7. There is some direct experimental evidence in favour. Von Knierien showed as long ago as 1885 that rabbits fed on a cellulose-free diet develop inflammation of the cæcum, which may be fatal. This does not occur in carnivores, whose cæcum is usually small. Apparently the effect is mechanical, as horn-shavings suffice to avert the trouble. Cellulose is of course almost unaffected by the digestive processes.

The cellulose content of some foodstuffs is given in the following table (Bunge) :—

PERCENTAGE OF CELLULOSE IN SOME DRIED FOODS.

Wheat flour	0·4	Spinach ..	8·1	Asparagus..	17·0
Rice ..	0·7	Green peas	8·7	Cabbage ..	18·0
Wheat ..	2·9	Carrots ..	8·8	Strawberries	19·0
Potato ..	3·1	Apples ..	10·0	Melon ..	22·0
Lentils ..	4·1	Radish ..	12·0	Pears ..	25·0
Beans ..	4·1	Cauliflower	13·0	Raspberries	47·0
Onions ..	5·0	Cucumber.	14·0		

REFERENCE.

A. RENDLE SHORT.—*Brit. Jour. Surg.*, 1920, Oct., 171.

CHAPTER V.

RESEARCHES ON BLOOD.

RECOVERY OF BLOOD AFTER HÆMORRHAGE—BLOOD TRANSFUSION—THE FOUR BLOOD GROUPS—FATE OF RED BLOOD-CORPUSCLES—FUNCTIONS OF THE SPLEEN AND LIVER—COAGULATION OF THE BLOOD—PURPURA HÆMORRHAGICA—HÆMOPHILIA—ANAPHYLAXIS.

THROUGHOUT the war hæmorrhage was a terrible bugbear, and the study of the blood and its problems received a new impetus. Hæmatology had made greater advance in America than in the British Isles, and the valuable assistance of American medical officers, coming at a time when we were all thinking about such problems, led to a better understanding of many important facts.

We shall consider first the process of natural recovery from a big hæmorrhage. It has long been known that within a few minutes the blood remaining in the vessels becomes diluted by taking up watery fluid from the tissues, and that the arteries contract down on the reduced volume so as to maintain the blood-pressure and provide an efficient filling for the heart on the venous side. We now know that there is active spasm of the veins also, so much so that there may be serious difficulty in getting an intravenous infusion to flow. I have several times during a blood transfusion been

compelled to use the internal saphenous vein at the groin on this account.

There are several modern methods of estimating the total blood-volume. The best is by the use of an innocuous dye called 'vital red', introduced by Keith, Rowntree, and Geraghty. A sample of the patient's plasma (10 c.c.) is first obtained, citrated, and centrifugalized—or another person's plasma will do. Then a dose of the dye, well diluted, is given intravenously (3 mgrm. per kilo of body weight). Two samples of blood are then taken three and six minutes after from the two arm veins; these are citrated and centrifugalized. The original plasma diluted with three parts of saline is then mixed with the dye solution to match the coloured plasma, withdrawn after injection, in a colorimeter. From this the plasma-volume in the body can be calculated. To obtain the whole-blood-volume, a hæmocrit must be used. In normal persons the plasma-volume is one-twentieth the body weight. This is a higher figure than that obtained by the older, less accurate, and more dangerous carbon-monoxide method, but it agrees well with the results got by another procedure—that is, by calculating from the difference in the blood-count before and after transfusing with a known volume of gum-acacia solution.

In obesity the plasma-volume is relatively low, and in chlorosis relatively high; it is also high late in pregnancy.

After a severe hæmorrhage, the total blood-volume may fall to 60 per cent of the normal, and yet recovery

may take place. Insisting on the patient taking large quantities of fluids by the mouth and per rectum greatly hastens the rate of recovery. In a few cases the capillary hæmoglobin-count was higher than the venous (30 per cent and 26 per cent); as the patient improves, the difference passes off (Robertson and Bock).

During the process of regeneration, the red marrow, which is normally confined to the flat bones, the bodies of the vertebræ, and the ends of the long bones, encroaches upon the yellow marrow in the shafts of the long bones to some extent. A few nucleated reds may turn up in the peripheral circulation. A much more constant sign of blood-regeneration is the appearance amongst the red corpuscles of reticulated cells, best seen after staining with cresyl-blue, which may be used instead of Hayem's fluid for the blood-count. In normal blood these cells amount to 1 per cent; during active blood-regeneration they may reach 20 per cent.

Kerr, Hurwitz, and Whipple have made a study of the restoration of the blood-serum proteins. If after a big bleeding the red corpuscles are centrifugalized off, suspended in Locke's fluid, and returned to the circulation (in dogs), it takes some weeks to restore the protein to normal. If the animal is starved, recovery is retarded. If plenty of meat is given, however, the restoration will be speeded up, and a 50 per cent depletion may be recovered from in five to seven days. There is some evidence that the new protein is supplied by the liver. In a dog in which

the liver has been partly cut out of the circulation by an Eck fistula, recovery of the serum protein after bleeding is slow and poor. In phosphorus poisoning, reduction of the liver protein and serum protein go together.

BLOOD TRANSFUSION.

It has passed into a hackneyed phrase to speak of 'infusing new blood' into a committee or business undertaking; but until the last two years of the war the procedure was more metaphorical than literal in Great Britain. In America, blood transfusion has made immense strides. There is no doubt, now that so many medical officers have learned its value in France, that it will become a well-established method of treatment in this country.

It is well known that animal's blood, or preserved serum, cannot be used, as violent toxic symptoms are produced if any considerable quantity is injected.

The principal indication for blood transfusion is a severe hæmorrhage of whatever origin. For this condition the benefit is very striking—much more lasting than that seen after a saline transfusion.

Traumatic shock apart from hæmorrhage is also improved by injecting blood. For these purposes one needs large quantities; about a pint is a usual dose. Blood transfusion is very probably the best remedy we know for pernicious anæmia, but it is not a permanent cure. It appears to act not so much by directly increasing the volume and oxygen-carrying power of the blood, but by stimulating the

red marrow to renewed activity, and so to bring on a remission. A first transfusion, in my experience, is more valuable than a second, unless the second follows within a week or two of the first. Possibly at a later date anaphylaxis comes into play. Yet another indication is continuing hæmorrhage from hæmophilia, as we shall see. For these two diseases, half a pint will be sufficient as a dose.

Many different methods are in use for giving the blood. I have described these in some detail elsewhere. Direct arm-to-arm transfusion by connecting the donor's artery with the patient's vein is unsatisfactory in that one does not know how much blood passes; it may be little or none. Some prefer to use unmodified blood kept from clotting by withdrawing from a vein into a paraffin-lined receptacle and injected as quickly as possible. Others prefer to use citrated blood, which is much easier to handle. I have given much larger doses of citrate intravenously to wounded soldiers than we now consider necessary, and no harm resulted. Hedon finds that 4 grm. is safe for a dog. I have several times given 8 or 9 grm. to men. It is a curious point that the injection of citrate does not alter the coagulation time of the receiver's blood; this has been verified by myself and others. It is also interesting that taking a pint of blood from a healthy donor does not produce any symptoms. In America there are professional donors who are willing to give blood every three weeks or so.

A very interesting research has been published by Abel that bore excellent fruit during the war.

He found in animals that a big hæmorrhage can be replaced just as efficiently by the animal's red blood-corpuscles washed and suspended in Locke's fluid as by fresh whole blood. The plasma proteins do not seem to matter. Rous and Turner carried the matter further, and showed that red corpuscles kept in a citrate-dextrose solution may be preserved in an ice-chest for several weeks, and will still function if injected into an animal of the same species at the end of that time. If they are kept too long (three weeks in a rabbit, over four weeks in a man), they do no harm, but are rapidly removed, so that if the receiving animal is bled, and then transfused with the preserved corpuscles, the blood-counts show first the rapid fall due to the bleeding, then the rise to normal following transfusion, then in the course of a few days a rapid fall to the post-hæmorrhage level. If the corpuscles have not been kept too long and are still functioning, this secondary fall does not occur.

Captain O. H. Robertson was sent to the casualty clearing station where I was working just before the battle of Cambrai, to apply these results to man. Forty pints of blood (including a pint from a well-known surgeon) were taken and stored in ice, in a citrate-dextrose solution. It takes about a week for the corpuscles to settle; the supernatant plasma is then decanted off. The results were just as good as those obtained by using fresh blood. Needless to say, it might be dangerous to inject *plasma* which had been kept any length of time.

Miss Ashby has shown that after a transfusion of

blood the injected red corpuscles survive at least thirty days in man. This was determined by transfusing a patient belonging to *Group II* with *Group IV* cells, and then testing by agglutinins for the *Group IV* cells at various dates afterwards.

Blood transfusion in man is not completely devoid of risks to the receiver. There is the possibility of conveying disease, such as syphilis, if the donor is not healthy. A rigor may follow, or vomiting, or a rise of temperature. If the transfusion is given too fast, the patient may complain of a feeling of distention and bursting inside the chest. The most serious danger, however, arises from the use of an incompatible blood. If the donor and the patient do not belong to the same blood groups, there may be hæmolysis of the injected corpuscles, resulting in vomiting, dyspnœa, an urticarial rash, a quick weak pulse, and perhaps convulsions or coma. These may come on during the transfusion, and may be followed by hæmoglobinuria. In a few cases death has resulted. If the transfusion is stopped immediately, serious trouble may be averted. This brings up the importance of testing out the donor beforehand. If this precaution is not taken, alarming reactions may be expected in 5 to 10 per cent of the cases.

THE FOUR BLOOD GROUPS.

Strange to say, the blood of different individuals, even of the same family, are not always compatible. Shortly after birth the blood takes up the characters of one of four groups, and these apparently persist

throughout life unchanged. The blood of a person of a particular group may safely be given to another person of that group, but not necessarily to someone belonging to another group. The incompatibility lies in two directions : the one plasma will (1) hæmolyse and (2) agglutinate the corpuscles of a patient of another group. It seems to be established that a blood which will hæmolyse another will always agglutinate it ; this is convenient, because it is simpler to test out the agglutination reaction than the hæmolysis.

According to Moss, there are four classes of bloods, designated as *Groups I, II, III,* and *IV*. The relative frequency of these groups and their suitability as donors, are given in the following table :—

Donor	Percentage frequency	Suitable if patient belongs to
Group I	5	Group I
,, II	40	,, I, II
,, III	10	,, I, III
,, IV	45	,, I, II, III, IV

When the blood of a *Group IV* donor is given to a *Group I, II,* or *III* patient, the plasma of the donor has a tendency to hæmolyse and agglutinate the corpuscles of the patient ; but the plasma of the patient does not so act on the corpuscles of the donor, and it is found in practice that what matters is the effect of the patient's plasma on the injected corpuscles, not the reverse. This is no doubt because the bulk of the patient's blood is so much greater than that of the transfused blood.

The best method of determining the blood group of a donor is by the use of preserved stock sera belonging to *Groups II* and *III*. To make the test, a glass slide is taken, and two *large* drops of the test-serum placed one near each end. Then the donor's ear is pricked, and a *small* drop of blood taken with a match-stick and mixed with the *Group II* serum. Another drop is mixed by another match-stick with the *Group III* serum. The result may be as follows :—

Blood corpuscles agglutinated by	Donor is
Group II *and* Group III serum ..	Group I
,, III serum but not Group II serum	,, II
,, II serum but not Group III serum	,, III
Neither serum	,, IV

The agglutination is quite obvious to the naked eye in about five minutes.

In choosing donors, we may use either one belonging to the same group as the patient, or a *Group IV* donor. *Group IV* individuals are the universal providers. Thus, if a *Group IV* donor is available, it is not necessary to know what group the patient belongs to. On the other hand, if both patient and donor belong to *Group II*, the bloods will be compatible.

If one has not the two group sera in stock, it is necessary to test the patient's serum against the donor's corpuscles directly. Draw off a few c.c. of the patient's blood and allow it to clot in a tube. Obtain a *large* drop of quite clear serum, add a trace

of citrate, and then mix in a *small* drop of the donor's blood. If agglutination occurs in five minutes, the donor is unsuitable; if there is no agglutination, the donor's blood may be used for that patient.

FATE OF RED BLOOD-CORPUSCLES.

Some of the older text-books hazard a guess that red blood-corpuscles usually live about three weeks, but since even transfused corpuscles in man are surviving after a month it is probable that the ordinary life of a corpuscle is much longer. The normal fate of red cells in man, monkeys, and cats, according to Robertson and Rous, is to fragment in the blood-stream, and the fragments are swept up by the spleen. The poikilocytes and microcytes of grave anæmia do not appear to be preformed in the red marrow, and they are the result of breaking up of circulating red corpuscles. Often they show the reticulum which is characteristic of young cells.

In the dog, rat, and guinea-pig, whole red corpuscles are taken up by the spleen.

FUNCTIONS OF THE SPLEEN AND LIVER IN RELATION TO THE BLOOD.

It has been known for years that the spleen must have *some* relation to the formation or destruction of blood-corpuscles. The way in which it enlarges in blood diseases such as leukæmia, pernicious anæmia, von Jaksch's anæmia, splenic anæmia, chronic malaria, and other tropical blood-parasite infections, is proof of this. Spleen pulp cells can be seen in the act of immolating damaged red

corpuscles. The sponge-like structure of the spleen, too, and the absence of capillaries, render it a very efficient corpuscle-trap. The endothelial cells lining the spaces within the spleen which the blood has to traverse are capable of amœboid movement, and may wander freely, and ingest corpuscles. But when we seek for further evidence, it becomes very dubious and uncertain, and a good many of the published observations are demonstrably incorrect.

The whole subject has recently been re-investigated with care and restraint by Pearce and his fellow-workers, taking account both of experimental and clinical observations.

Splenectomy in dogs gives rise to the following changes :—

1. A mild secondary anæmia of the usual type, reaching its maximum after a month, and recovering later. Why this occurs is unknown, except that injection of spleen extract into a normal dog causes a brief rise of the red count by stimulating bone-marrow. This may furnish some experimental basis for spleen-extract therapy in anæmia.

2. A brief polymorphonuclear leucocytosis. Many other leucocyte variations have been described, but they are inconstant.

3. Increased resistance of the red corpuscles to hæmolytic agents. We do not know why.

4. Reduced liability to jaundice and hæmoglobinuria after the administration of hæmolytic agents. This may be due to three factors. The animal being anæmic, the death-rate amongst the red cells is low, and the liver, the grave-digger in

ordinary when the spleen is gone, is not likely to be overworked even when the death-rate rises somewhat. Again, the corpuscles are more resistant. And thirdly, as the spleen and splenic vein are gone, the liver receives less blood.

The point is interesting, because we know that there are two varieties of splenomegaly associated with anæmia and jaundice. One variety is congenital, the other is acquired. In each, splenectomy cures the anæmia and the jaundice. Probably the spleen contained a hæmolytic toxin.

In spite of older statements to the contrary, there is no constant difference in the cell-counts of the blood of the splenic artery and splenic vein, and no free hæmoglobin in the vein. Nor does splenectomy in normal dogs cause metabolic changes. In man, splenectomy for a very large spleen reduces the excessive output of uric acid and urobilin.

Diversion of the splenic vein into the inferior vena cava, to avoid the liver, has approximately the same effects in every way as splenectomy.

In most cases after removing the spleen the yellow marrow in the shaft of the femur becomes red, signifying increased production. This takes about six months. The reason is unknown. The hæmolymph glands contain an excess of endothelial cells, and if a hæmolytic agent is given, these cells are abnormally full of red corpuscles in process of digestion. Probably this is compensatory. A new induced anæmia in a splenectomized animal is badly recovered from.

Banti's disease is supposed to be a chronic inflam-

mation of the spleen with great enlargement (going on later to fibrosis) and excessive function, so that too many red corpuscles are destroyed. Splenectomy in the early stages cures the anæmia.

Radium has an extraordinarily powerful effect on the spleen enlarged by disease. After an application or two, a spleen that nearly filled the abdomen may be reduced to quite moderate proportions.

Probably everyone feels that in discussing the functions of the spleen, the proved facts seem small and unimportant in relation to the size of the organ, and its constancy in the animal kingdom. As Sir Berkeley Moynihan pointed out in his Bradshaw Lecture for 1920, the reason perhaps is that organs cannot be isolated and regarded as totally independent in their functions ; we have learned how the appendix and the stomach are interdependent, and maybe the spleen ought to be considered principally as a member of the reticulo-endothelial system of the body described by Aschoff. Whenever the tissue that surrounds capillaries is loose, it is composed of reticulate cells supporting the endothelial cells, and the same meshwork arrangement is reproduced on a large scale in the spleen pulp and the liver, where certain large star-cells (of Kupffer) are to be regarded as endothelial, and phagocytic in function. After splenectomy, they increase ; in hæmolytic diseases, they are full of iron pigment. Red bone-marrow has an analogous structure. Probably all these structures have a co-ordinated function. One such function is to manufacture antibodies. After splenectomy, animals are much more easily killed by the

injection of cultures or toxins, and it is difficult to immunize them.

Not much has been added to our knowledge of the blood-destroying functions of the liver. After Eck's fistula, the liver-cells atrophy considerably, and bilirubin is considerably reduced in the bile, which suggests that the liver is normally active in blood destruction, and does not merely sweep up dead and degenerated red corpuscles. Splenectomy does not alter this effect (Whipple and Hooper).

COAGULATION OF THE BLOOD.

We are still far from a clear conception of the exact pathology of hæmophilia, purpura, and the hæmorrhagic tendency in jaundice, but it will be only by a sound understanding of the normal processes of coagulation of the blood that we shall be able to comprehend the abnormal.

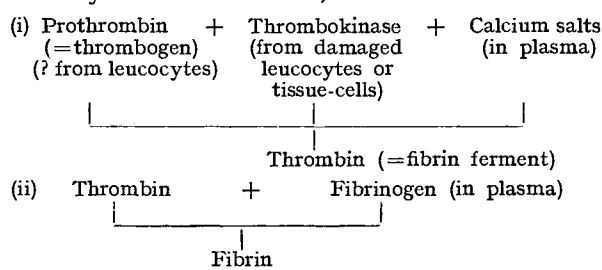
The phenomena of blood-clotting are beautifully designed to avoid two opposing evils : if no provision was made for fibrin formation, every injury would be fatal ; but on the other hand, if all the essentials for the process were already present in the plasma, the circulation would immediately be brought to a standstill by intravascular thrombosis. Therefore coagulation is made to be dependent on contact with damaged cells, either tissue-cells or leucocytes, and in particular with the nucleoprotein constituting their nuclei, while the intact lining endothelium of the blood-vessels has the power of preventing clotting. We have all been told that a length of jugular vein containing blood may be tied at each end and hung

up for a week, and no clotting occurs until damaged tissue-cells are added. Thus we find that the very incision or laceration which excites the hæmorrhage provides also the wherewithal to stop it. The nucleoprotein furnished in this way by the tissues is called *thrombokinase*.

Next, we know that *calcium salts* are needful for clotting, and if they are withdrawn by oxalates or citrates, no fibrin will be formed. An excess of calcium salts, however, delays clotting.

Concerning *thrombogen* or *prothrombin* we cannot speak so confidently. It is intimately associated with, and hard to separate from, fibrinogen, but is probably derived eventually from the leucocytes and platelets. Hydrocele fluid, which does not contain any corpuscles, will not clot until blood or fibrin is added.

The actual mother substance of the fibrin is of course the *fibrinogen*, a protein in the plasma. There is really a double reaction, thus :—



According to J. Mellanby, the name *fibrin ferment* is a misnomer, as a particular weight of thrombin will liberate only a certain definite quantity of fibrin

from fibrinogen, whereas a ferment knows no limits to its activities.

We have yet one more provision to refer to. The cells lining the blood-vessels, and the leucocytes themselves, are not immortal. When they die, thrombokinase is shed out, and so thrombin would be formed and induce local clotting. This does actually occur in phlebitis and other forms of venous or arterial thrombosis. In the physiological state, however, the liver secretes into the blood an *antithrombin* sufficient in amount to deal with small formations of thrombin, but not sufficient to interfere with the natural process of arrest of hæmorrhage.

Recent research suggests that antithrombin is the product of interaction of two other substances, called *heparin*, which is derived from the liver, and *proantithrombin*. Both are said to be present in the blood. The heparin activates the proantithrombin when it is needed (Howell).

So far we have followed, as in our previous editions, the commonly accepted hypothesis of Morawitz, but it must be admitted that recent work tends rather to weaken than to support it. Vines, in a complicated research, maintains that a calcium-lecithin-nucleoprotein compound will coagulate blood rendered incoagulable by hirudin, cobra venom, or potassium fluoride, and he believes that this compound is thrombokinase, and the nucleoprotein not really essential.

Pickering and Hewitt are more revolutionary; they find that the addition of tissue extract to bird's blood *in vitro*, very slowly and in weak dilution,

gives a negative phase, rendering the blood incoagulable, thus making all antithrombin theories needless. One is reminded of the experiment published by Wooldridge many years ago, that intravenous injection of tissue-extract in small quantity renders the blood incoagulable, but in larger quantity gives rise to intravascular clotting. Like him, they believe that thrombin is formed *after* and not *before* coagulation occurs. It will not cause intravascular clotting.

Foster and Whipple teach that fibrinogen is derived, not from the marrow, but from the liver. It is not altered in red bone-marrow diseases, such as aplastic anæmia, but is profoundly reduced in liver diseases, such as phosphorus or chloroform poisoning.

Considerable variations take place in the readiness with which the blood coagulates, and it is often easier to understand *why* than *how* this is brought about. For instance, at the end of pregnancy clotting is rapid ; in the diseases mentioned above it is deficient or slow. After a hæmorrhage, the fibrinoplastic (clot-forming) power rises quickly. Information may be obtained by means of the *coagulimeter*, a standard capillary tube into which the blood is sucked up so that the time which it takes in solidifying may be measured. It requires some care in practice to avoid variations in the calibre, variations in temperature, the inclusion of lymph or clots, etc.

Associated with deficient coagulability there is often a tendency to effusions of plasma through the capillary walls on account of the low viscosity of the

blood. The symptoms of such a tendency to effusion are liability to chilblains, headaches, nettlerash or patchy œdema, and transient or functional albuminuria.

The conversion of fibrinogen into fibrin is only the first stage of a more prolonged process, just as the very similar conversion of caseinogen in milk into solid casein is only one step in the process of breaking it down to simpler substances such as peptones and aminoacids.

The fibrin is not a permanent body. Even in blood-clot kept at about 40° C. it undergoes partial resolution into simpler and soluble substances, under the influence of ferments already present in the clot, called *fibrinolysins*. It is probable that these, as well as leucocytes, play an important part in determining the resolution of fibrin collections in the human body, such as may be found not only in bruises and thromboses but also in the lymph-clot which is the precursor of adhesions in the pleural and peritoneal cavities. It is well known that these adhesions may disappear spontaneously to a remarkable degree. Any value which thiosinamine and its derivative fibrolysin may have, given hyperdermically to absorb young fibrous tissue, may possibly be due to the production of ferments such as these.

PURPURA HÆMORRHAGICA.

English physiologists have expressed a good deal of doubt as to the very existence of platelets as preformed elements in the blood. It is said that the number to be found in a stained film depends

upon the method of preparation, and that when blood stands and clots it deposits platelets in plenty. It is also said that they are never visible in the living circulation in the web of a frog's foot or in dog's omentum. American hæmatologists, on the other hand, seem to have no doubts as to their existence preformed in the living blood.

Lee and Minot, whilst admitting that they do not occur except in mammals, say that platelets are visible in the circulating blood of the rabbit or guinea-pig. They are derived from the mega-karyocytes of the marrow. The number of platelets present runs parallel with the coagulability of the blood, and, in particular, blood-clot will not retract firmly so as to plug vessels unless platelets are present in normal numbers. Benzol reduces the platelet count, and may lead to a tendency to bleed. In purpura hæmorrhagica, and the hæmorrhagic type of some fevers, the platelets are few or absent in the blood.

An observation that is interesting in itself, and that may also throw light on the platelet problem, is published by Lee and Robertson, and also by Ledingham and Bedson. If the platelets are separated out from guinea-pig's blood by sedimentation, and injected into some other species, such as the rabbit, an antibody is formed in the rabbit's serum destructive to guinea-pig's platelets. If some of the serum thus obtained is injected into a guinea-pig, a condition closely resembling purpura hæmorrhagica is produced. There are bleedings from the nose, bowel, and other mucous membranes,

and purple patches of hæmorrhage in the skin and conjunctivæ. The animal may die. Few or no platelets are to be found in its blood.

It is not suggested, of course, that the disease in man is produced just in this way, but the experiment raises the probability that the underlying cause of purpura hæmorrhagica may be a toxin destroying the platelets, which as we have seen are markedly reduced. The blood in this disease may begin to clot in normal time, but the coagulum is soft and will not retract firmly.

HÆMOPHILIA.

Of all the many conditions in which the hæmorrhagic diathesis is present, hæmophilia is at once the most interesting, the best understood, and the most tragically dangerous. We will not stay to speak of the curious problems of its inheritance, nor of the well-known tendency to bruising, joint effusions, and bleeding after the most trivial injuries. One or two of its peculiarities, however, deserve a word of mention, as they may throw a light on the production of the hæmorrhagic tendency. For instance, the locality and the nature of the injury have some significance. In a few cases, wounds below the neck may not bleed to excess, whereas abrasions of the most trifling description affecting the lips, cheeks, or gums may baffle all attempts to stanch the flow. Again, needle pricks, if small, do not bleed, probably because the elastic skin seals the opening; it is even safe to withdraw blood from a vein. Further, it is not true that the hæmorrhage never stops. It

may cease with or without treatment, sometimes permanently, sometimes only to come on again later. If a subcutaneous hæmatoma develops, the wall is lined by well-formed clot, but the central portion contains blood which shows no tendency to coagulation in spite of the contact with clot. It is the capillaries, rather than the arteries, which continue to ooze.

It will be a matter of opinion whether under the generic name of hæmophilia we should include cases that arise every now and then, in either sex, of a congenital and persistent tendency to bruise and bleed from every slight abrasion, apart from any family history of a similar kind. There is no doubt that the symptoms and course of some of these cases are identical with ordinary hæmophilia,* and they are nearly as common. Bulloch states that the characteristic joint affections never occur except in the hereditary class.

Up to a certain point modern observers are agreed as to the cause of hæmophilia. Ever since Sir Almroth Wright, nearly twenty years ago, showed that the coagulation time in these patients is very greatly delayed, all students of the disease who have carefully fulfilled the proper conditions have been able to establish his discovery. Normal blood in a Wright's coagulimeter tube clots in 5 to 10 minutes; hæmophilic blood may take anything from 15 to 90 minutes to solidify, although the eventual yield of fibrin is copious and firm. Addis has shown

* See instances given by Squire, *Brit. Med. Jour.*, 1910, i, 1168; and Osler, *Lancet*, 1910, i, 1226.

that the coagulation time is exactly related to the severity of the tendency to bleed, the mildest cases yielding the shortest times, and the severe cases the longest. It is true that a few who have used the blood shed out during an actual hæmorrhage have found no delay in the coagulation time ; but apart from other fallacies, such as the danger of including fibrin ferment, the mere fact of the continued bleeding makes the blood clot more rapidly both in bleeders and in ordinary people, as Wright and Addis have shown.

Another abnormality in the blood is a frequent deficiency in polymorphonuclear leucocytes.

We may take it that the rival theory, that of the undue fragility of the vessel walls, is now definitely abandoned. Morawitz and Lossen have both shown that the œdema obtained by dry-cupping is no greater in hæmophilics than it is in normal individuals.

So far, then, there is substantial agreement. When we seek to go further, and to inquire just which we are to blame of the various elements that take part in regulating the coagulation of the blood, the problem becomes complicated.

Theoretically, the delay might be due to :— (1) Deficient quantity or quality of the fibrinogen ; (2) Deficiency or excess of calcium salts ; (3) Deficient quantity or quality of the thrombokinase ; (4) Deficient quantity or quality of the prothrombin ; (5) Excess of antithrombin.

In the examination of these factors we follow the researches of Addis. The main point to determine is whether the delay is in the first or the second of

the two reactions involved—that is, in the conversion of prothrombin into thrombin, or in the conversion of fibrinogen into fibrin. It proves that the former is at fault; the latter is quite normal. Hæmophilic fibrinogen is as readily clotted by normal or by hæmophilic thrombin as is normal fibrinogen, and normal fibrinogen is easily clotted by thrombin from a bleeder. But hæmophilic blood must stand a long time before prothrombin is converted into thrombin.

Taking up the points, then, in order:—

1. *The defect is not in the fibrinogen,* because it is readily clotted if isolated and treated with thrombin. Moreover, when clot does at last form during a hæmorrhage, it is as firm and abundant as in ordinary blood.

2. *The defect is not in the calcium salts,* because analysis shows no abnormality in quantity, and the addition of these salts to drawn hæmophilic blood, though it may hasten the time of clotting, does not bring it to normal.

3. *The defect is not in the thrombokinase.* Here Sahli joins issue with Addis, because the addition of washed leucocytes to hæmophilic blood rapidly causes it to clot. These may, however, bring in prothrombin as well as thrombokinase, and Addis shows that solutions of thrombokinase, derived by crushing up testis in saline, have far less effect on hæmophilic than on normal blood unless very concentrated extracts are used. Again, there is just as much thrombokinase in the serum of a bleeder squeezed out after coagulation as in that of a normal person.

4. *It is in the prothrombin that the defect lies.* A

very little normal plasma, or a few washed corpuscles from a normal person, restore the coagulation power forthwith.

Addis believes that he had directly proved the point by the adoption of the following method for isolating the prothrombin, and at the same time he has established that in the hæmorrhagic diathesis it is deficient not in quantity but only in character. He prepared a solution of fibrinogen from normal or hæmophilic plasma in the ordinary way by precipitating it by passing a stream of carbon dioxide through plasma kept from clotting by citrate or oxalate. Fibrinogen so obtained, as Mellanby shows, always carries with it prothrombin, and in the presence of calcium salts and thrombokinase would liberate thrombin. Addis, however, added instead a trace of thrombin, which clotted the fibrinogen and left its prothrombin in solution. When a trace of prothrombin so obtained from a normal blood was added to hæmophilic blood, this promptly coagulated. (The criticism would of course be that there was some unused thrombin present as well, too much having been added to the fibrinogen.)

Thus, the exact pathology of hæmophilia would be, in Addis's opinion, a congenital defect in the constitution of the prothrombin, whereby it yields thrombin much too slowly. Possibly the leucocytes are ultimately at fault.

The practical deduction we shall see later.

5. *There is no excess of antithrombin* in the plasma of the bleeder. If there were, the addition of a trace of normal blood would not cause hæmophilic blood

to clot as it does, because any thrombin in the former would be overpowered and destroyed by the anti-thrombin in the latter.

To sum up, the secret of hæmophilia lies in a defective quality of the prothrombin, such that it takes much longer than usual to develop into thrombin. No evidence is yet to hand to show whether the hæmorrhagic tendencies in scurvy, purpura, pernicious anæmia, and occasionally in jaundice have the same explanation.

It is important to bear in mind the fact that certain cases of jaundice may ooze to death by capillary hæmorrhage after operation; most of us can recollect instances of this calamity. It has been recommended to give drachm doses of calcium chloride for three days before the operation, but probably a more useful proceeding would be to take the coagulation time by means of a Wright's tube, and to refuse to operate on any cases showing serious delay.

It will be gathered that unfortunately the underlying causes of hæmophilia do not lend themselves to direct remedy. We cannot, except by one drastic proceeding, influence the quality or quantity of the more complicated and specialized fibrinoplastic elements in the blood, and we can use only those means which in a general way are understood to increase the coagulability.

Sometimes the ordinary surgical means such as rest, pressure, plugging, or adrenalin may be successful. It is usually advised not to stitch wounds, for fear of bleeding from the punctures, but if these

are made with a small, round-bodied needle, the elasticity of the skin will prevent oozing. Therefore, if tight stitching would obviously bring useful pressure to bear, it should be resorted to, but only in the skin, not in mucous membranes.

It has been advised, and the advice is physiologically sound, to apply normal human blood to the oozing point. Unhappily even if a mass of clot is formed over the wound, it soon gets pushed away by the collection of unclotted blood beneath it. For the normal arrest of hæmorrhage it is necessary either that clotting should take place inside the bleeding vessel or that it should fill the wound so tightly about this vessel as to present a complete block to the flow. It is often impossible to get the remedy near enough to the actual rent in the artery or capillary to bring this about, and the shape of the wound may not lend itself to filling up tightly with firm clot. Nevertheless the method is simple and painless, and has sometimes succeeded.

Styptics such as ferric chloride, tannin, or alum may be applied to the wound, but they are painful and lead to much sloughing, so it is well first to give a brief trial to fresh normal blood applied by wool pledgets, and to Wright's physiological styptic (thrombokinase), composed of one part of minced thymus in ten parts of normal saline. This produces a firm clot, but does not act as quickly as the escharotic styptics.

Internally, Wright gives calcium salts, preferably the lactate, but admittedly this is a bow drawn at a venture, because the calcium is often absorbed very

badly, and may already be at the optimum in the blood. The first difficulty may be obviated in some patients by using magnesium lactate or carbonate. The doses of any of these drugs should be 60 gr. for adults, and 15 gr. for children, at once, followed by 10-gr. doses three times a day for three days for adults, with a corresponding reduction for children. Calcium salts reverse their effect after three days. According to Mason, calcium chloride is better absorbed than the lactate.*

Weil recommends the injection of horse-serum, conveniently obtained as diphtheria antitoxin. It probably increases the rate of blood-clotting, but apparently not until many hours have passed, and consequently it often fails in practice.

There remains one last resort in the most desperate cases, and no patient should be allowed to die of hæmophilia without its being attempted. We have seen that there is only one way to restore prompt coagulability to hæmophilic blood, and that is to supply normal blood.

Goodman has published a well-written, almost dramatic description of his treatment of a Jewish boy, age two and a half, a well-known bleeder and member of a bleeder family, who was moribund from hæmorrhage from a cut inside the cheek, which had oozed incessantly for two days. Pressure, adrenalin, styptics, calcium salts, and horse-serum (antitoxin) had all been tried in vain, and finally the child lay motionless and pallid, scarcely breathing, with

* *Jour. of Biol. Chem.*, 1921, xlvii, 3.

hæmoglobin down to 12 per cent, and hæmorrhage continuing.

Goodman decided to inject normal human blood. A donor, not a relative, was tested by Wassermann's test for syphilis, and declared free. Under novocain anæsthesia his radial artery was connected by an Elsberg cannula with the child's femoral vein. There were some initial difficulties in getting a good flow, and hot cloths had to be applied; finally the basilic vein was substituted for the femoral on account of differences in the level of these patients. Transfusion was continued for twenty-eight minutes. During this time colour gradually mounted up in the cheeks of the little sufferer, the breathing became audible once more, the almost watery blood acquired its normal hue, and the hæmoglobin rose to 70 per cent. Most significant of all, the bleeding was completely and permanently arrested, and there was no hæmorrhage from the incisions.

ANAPHYLAXIS.

It is well known that when certain proteins are injected into an animal's blood-stream, so far from antibodies being formed, there may be an increased sensitiveness developed, so that a second injection months or years afterwards may produce severe or even fatal symptoms. A few cases are on record in which second injections of horse-serum containing diphtheria or other antitoxin have caused most alarming illness or death. Now that so many men who were wounded in the war and given a dose of antitetanic serum are about in the community, it is

possible that there may be trouble one day when one of them is given diphtheria antitoxin or some other preparation of horse-serum protein. It is also well known that if the second dose is given within a week, this sensitization (anaphylaxis) does not occur.

The symptoms in severe cases are due to intense swelling of the mucosa of the bronchi, causing suffocation and convulsions. In mild cases they resemble those of ordinary serum sickness—an urticarial or measly rash, joint pains, and the like.

Evidence has accumulated that anaphylaxis may explain some other conditions besides serum poisoning. It occasionally happens after tapping or operating on a hydatid cyst that there may be violent urticaria, or in a few cases fatal suffocative symptoms (intoxication hydatique). This is an anaphylactic phenomenon.

Some cases of asthma and hay fever appear to be due to the inhalation of a foreign protein of animal or vegetable origin to which the patient is supersensitive. Sometimes the foreign protein is conveyed in the diet, and white of egg would seem to be the commonest offender. In yet other cases it is of bacterial origin. A careful history may help to detect the source of the trouble, and if the skin is scratched and a solution of the suspected substance —grass pollen, egg-albumen, milk, or whatever it is— painted on the scarifications, there will be swelling and redness. It may then be possible to avoid the article, or to obtain an acquired immunity by starting

with exceedingly minute doses (say 1 mgrm. of egg-albumen) and increasing very cautiously. It is necessary to keep a large variety of extracts to test out these cases—foods, animal hairs, plant pollens, bacterial proteins, etc. Often a patient may react to several different irritants. Coke records a case of a girl of nine, who had asthma continually for six years in London, but was free for nearly a year at Exmouth. Her skin reacted to horse, dog, and cat hairs. She kept a cat in London, but not at Exmouth. She was in hospital six weeks without an attack, but on being given the ward cat to play with, awoke that night with bad asthma. In another case, a girl was very sensitive to dog hair. She got rid of the dog, and the asthma went. Then she went to the seaside, and had a bad attack the first night. It transpired that the previous lodgers had four dogs, which used to sleep on the rug that covered her bed.

Sometimes it is possible to tell *why* the sensitiveness occurs. In a case of Schloss's, a boy had albumen-water for diarrhœa when only a few days old, and at that age egg-albumen can be absorbed, so he was sensitized. At fourteen months he had his first spoonful of egg, and it nearly killed him.

Intractable eczema in children may be caused in the same way, and yield to similar treatment. The testing out may need to be quite elaborate, using milk protein, fat and sugar separately, egg-albumen, and watery extracts of various foodstuffs filtered, precipitated with alcohol, washed, and applied in powdered form. According to White, in two-thirds

of the cases a positive result was obtained to some foodstuff or other.

There is an interesting case on record in which, after receiving a blood transfusion from a donor who was subject to horse-sensitiveness, a patient was seized with asthma, for the first time in his life, on going for a drive in a horse-drawn carriage during his convalescence (Ramirez).

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CHAPTER VI.

THE HEART.

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DEVELOPMENT AND STRUCTURE OF THE HEART—MODES OF EXAMINATION OF THE HEART — HEART RHYTHMS — PROPERTIES OF CARDIAC MUSCLE — THE NERVOUS SYSTEM OF THE HEART—THE WORK OF THE HEART—ARTERIAL BLOOD-PRESSURE—CARDIAC IRREGULARITIES.

AT the beginning of the third week of fœtal life the heart consists of a straight muscular tube, demarcated into four parts: (1) The sinus venosus; (2) The primitive auricle; (3) The primitive ventricle; (4) The bulbus cordis. The beat begins in the sinus venosus, and is carried on by a peristaltic wave through the various chambers of the heart in the order given above. A little later the tube becomes bent upon itself, one bend occurring at the junction of the auricle and ventricle; the other involves the ventricular portion of the tube, which assumes a V form. As a result of these bends the auricle takes up a position dorsal to the ventricle; the shorter curvature of the ventricular bend becomes absorbed, and one large ventricle is formed. At this time septa appear which divide the primitive auricle and ventricle into two, and the right and left auricles grow out from the dorsal portion of the primitive

auricle, while the right and left ventricles grow out from the ventral and lateral portions of the primitive ventricle. The sinus venosus gradually comes to lie in the dorsal wall of the right part of the primitive auricle, and when the right auricle grows out it takes the sinus venosus with it, so that it comes to lie in the wall of the right auricle. The bulbus cordis becomes incorporated chiefly in the left ventricle.

The auricular canal, which is the connection between the primitive auricle and the primitive ventricle, becomes surrounded by an upgrowth of the base of the primitive ventricle, and very little of it remains in the adult heart; but part is carried down in the interauricular septum.

The embryological heart muscle has the property of conducting the stimulus from the sinus venosus to the bulbus cordis, and a remnant of this muscular tube continues to act as the conducting path in the adult heart, so that to understand this it is necessary to trace this path as it appears in the adult heart. The sinus venosus has been seen to move across and to lie eventually in the wall of the right auricle, its structure lying chiefly between the superior and inferior venæ cavæ. From here the path runs down the auricular canal, of which the interauricular septum is the chief remains, though part is incorporated in the wall of the right and left auricles.

The ventricles are mostly new structures, being formed as evaginations from the primitive ventricle, the remains of which are chiefly in the interventricular septum whch grows from the apex upwards and takes most of the primitive ventricle with it.

If we now examine the recent histological work on the conduction path, we find that it agrees with what has been shown should be its path from the morphological aspect.

The place of origin of the heart-beat has been proved to lie at a point in the sulcus terminale below the junction of the superior vena cava and the right auricular appendix, and a patch of specialized tissue is found in this position which is known as the sinu-auricular node.

From this node the stimulus spreads into the auricular muscle, causing its contraction, and then passes down the interauricular septum to another larger node of similar tissue which lies in the posterior part of the interauricular septum below and to the right of the opening of the coronary sinus. This is known as the auriculoventricular node. From this a bundle of pale muscular fibres similar to Purkinje muscle passes downwards and forwards to the interventricular septum, and at the undefended space it divides into right and left branches. The left branch pierces the septum and comes to lie on the left surface of the ventricular septum just beneath the endocardium, while the right branch remains on the right surface of the septum. Both branches pass down to the apex of their respective ventricles and there break up into a large number of small fibres which are distributed to the papillary muscles and to the muscles in the walls of the ventricles. This is the path by which the stimulus passes from the sinus node to the ventricles: some workers have suggested that there is a direct path

between the sinus node and the auriculoventricular node, but no such path can be demonstrated anatomically.

In birds there is no auriculoventricular bundle and node such as has been described above, but the stimulus is conducted by a muscular connection which lies in the posterior part of the auriculoventricular groove in the region of the left superior vena cava. A similar path has been described in this position in man, and also another lying in the right auricular wall almost on the extreme right lateral aspect of the heart slightly towards the posterior surface. So far as is known, these paths do not convey stimuli in man.

MODES OF EXAMINATION OF THE HEART BY GRAPHIC METHODS.

Much of the recent physiological work on the heart has been stimulated by clinicians who by means of special instruments, the polygraph and the electrocardiograph, have classified the irregularities of the heart.

The polygraph is an instrument by means of which simultaneous records of the venous and arterial pulses may be obtained, with the addition of a time-marker, so that the actual time-intervals of the various events in the cardiac cycle may be worked out.

The venous pulse is obtained from the jugular bulb, which lies just above the clavicle, 1 to 1½ inches external to the sternoclavicular synchondrosis. The right side is usually preferable to the left. It nor-

mally consists of three waves of positive pressure, *a*, *c*, and *v*, and two waves of negative pressure, *x* and *y* (*see diagram*).

The *a* wave is caused by the auricular contraction. As soon as this is over there is a fall, *x*, due to the blood rushing into the dilating auricle; this fall is interrupted by *c*, a wave caused by the sudden systole of the ventricle closing the auriculoventricular valves with a snap and communicating a shock to the

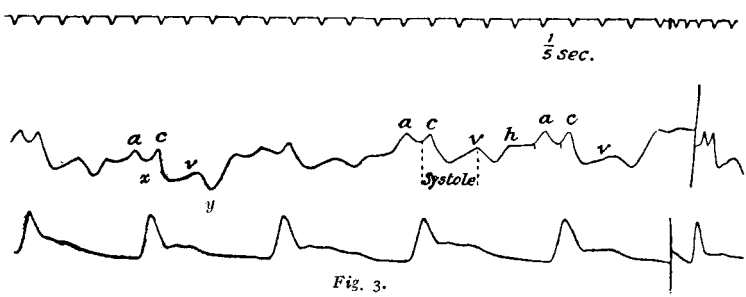

Fig. 3.

auricle and jugular vein; it occurs at the commencement of systole, and marks the onset of ventricular contraction in the venous pulse.

During ventricular systole the auricle fills and the pressure in the jugular vein rises, causing the *v* wave. As soon as systole is ended, the auriculoventricular valves open and a sudden drop occurs (*y* in diagram), as the blood rushes into the ventricle. Consequently the summit of *v* or the commencement of *y* marks the end of ventricular contraction. The *v* wave is commonly notched or in two portions. This division of *v* marks the closing of the arterial valves.

A tracing of the radial pulse is taken at the same time to serve as a record of the ventricular action. It should be noted that the radial pulse occurs $\frac{1}{10}$ second after the carotid pulse. Let us now discuss how a tracing should be read and what evidence may be obtained from it.

As soon as the machine is stopped, each pen should be moved so as to mark on the paper the point at which each lever stopped. These marks are called ordinates, and are important for measuring. With a pair of calipers the distance between the ordinate and the commencement of a radial upstroke is measured. By means of the time-marker $\frac{1}{10}$ second is added on to this distance to allow for the earlier onset of the pulse in the neck. If one end of the calipers be now placed on the venous-pulse ordinate, the other will mark the onset of ventricular systole in the venous pulse, and a wave will be found commencing its upstroke at this point. This is the *c* wave. Having marked this on the tracing, a wave will be found about $\frac{1}{5}$ second previous to this, and this will be the *a* wave. Shortly after the *c* wave will be found the *v* wave, and the summit of *v* will synchronize with the dicrotic notch in the radial; in other words, the distance from *c* to the end of *v* is the length of the ventricular systole. The commencement of *v* is not a fixed point, as it depends on the venous pressure; the higher the pressure the earlier it will appear, as the auricle will fill more quickly. In cases where the *a* wave is doubtful, owing to diastole being very short, as in rapidly-beating hearts, the fixation of the summit of *v* will

often help in determining which is the *a* wave and which the *v*.

The interval between the commencement of *a* and *c* is normally $\frac{1}{5}$ second, and is used as a measurement of the time taken for the stimulus to reach the ventricle from the sinu-auricular node. Any increase of the *a–c* interval, as it is called, is looked upon as an indication of delay in the conductivity of the auriculoventricular bundle.

In slow-acting hearts a fourth wave (*h* in diagram) may sometimes be found; this occurs in early diastole, and is accompanied by the third heart sound. It is caused by the sudden rush of blood into the dilating ventricle floating up the cusps of the auriculoventricular valves and momentarily closing them.

The venous pulse is thus normally composed of three waves to every systole of the ventricle, and this is known as the auricular type of venous pulse.

In some conditions the *a* wave may entirely disappear, so that the venous pulse consists of only two waves, the *c* and *v*, and these may be fused into one broad wave. These waves fall entirely in the ventricular systole; hence it is called the ventricular type of venous pulse.

The ventricular type of venous pulse occurs in the following conditions:—

1. In rapidly-beating hearts where the *a* wave falls on the preceding *c* or *v* waves. If conduction be impaired and the *a–c* interval long, it is easy for the *a* wave to occur coincidently with the preceding *c* wave.

2. In conditions of marked increase in venous pressure in the right auricle and great veins—the polygraph may fail to record the *a* wave.

3. In atrioventricular rhythm where the auricle and ventricle are beating synchronously.

4. In auricular fibrillation, where the auricle no longer contracts in a normal manner. As will be seen later, the heart is completely irregular, and small irregular waves may be sometimes detected in the venous pulse due to the fibrillary contractions of the auricle.

The electrocardiograph is a more exact method of registering the action of the chambers of the heart, and is of use in analysing conditions which are not clear in polygraphic tracings. Great strides have been made in experimental physiology and in diagnosing abnormal rhythms in man by means of its use.

The instrument consists of a very delicate string galvanometer which works on the following principle. If an electrical conductor in the shape of a fine thread be placed between the magnetic poles of a powerful electro-magnet, it is found that, should minute currents be passed through the fibre, a deflection of the fibre occurs relative to the strength of the current. Also, if the current be passed in one direction it will cause a deflection to one side, while reversing the current produces a deflection to the opposite side. The fibres are made of very fine silvered quartz or fine-drawn platinum.

In the Cambridge pattern instrument the poles

of the magnet are drilled through the centre and a telescope is placed in position, so that, should the light from an arc lamp be thrown through the telescope, the shadow of the string may be focused on a moving photographic plate or paper, and any deflections of the string will be reproduced. A time-marker is arranged to mark $\frac{1}{5}$ or $\frac{1}{30}$ second on the photograph, and in this way an accurate timing of any movements of the string may be determined.

Cardiac muscle, like all muscle, gives rise on contraction to differences in electrical potential, and as a wave of contraction passes through the heart, a wave of electronegativity passes with it. If the base and apex of the heart are joined up to a string galvanometer, minute currents pass through it and cause certain deflections of the string.

It is found that these currents may also be led off from the limbs of patients ; thus we may get tracings from right and left arms, right arm and left leg, and left arm and left leg. These are respectively known as leads I, II, and III. Lead II is the one most commonly used, but in cases of difficulty help may be obtained from all three.

An electrocardiogram taken with lead II is shown in the accompanying figure.

We see that there are waves marked P, Q, R, S, and T. P is caused by the auricular systole, and is in an upward direction. Q, R, S, and T are caused by ventricular systole. Q and S are in a downward direction, but are very variable. Q is hardly shown in the figure ; S is larger than usual, but it may be absent.

R is the largest deflection, and is very quickly over. T is a small slow deflection, and marks the end of systole.

This form of electrocardiogram occurs when the contraction of the chambers of the heart takes place in the normal sequence and the conduction of the excitation wave follows the normal course. Variation in either of these two points causes changes in the forms of the waves: thus, if a contraction commences in the base of the auricle instead of in the upper part, the P wave is inverted.

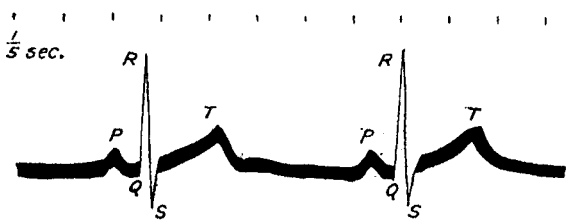

Fig 4.

The ventricular complex is normal so long as the impulse reaches the ventricular muscle by means of the auriculoventricular bundle; but if a contraction starts in the ventricular muscle, an abnormal complex appears which varies according to the place of origin of the abnormal beat. In the same way, if one of the branches of the auriculoventricular bundle be blocked, the stimulus reaches the muscle of that ventricle by some abnormal path, and a variation in the complex is produced.

For the various types of complexes associated with abnormal beats, the reader is referred to text-books.

The P–R interval, corresponding to the *a–c* interval of polygraphic tracings, may be very accurately measured, and is found to vary in normal persons from 0·12 to 0·18 second.

Most of this time is taken for the stimulus to traverse the auriculoventricular node. Any increase of this interval means delay in conductivity in some part of the auriculoventricular bundle.

HEART RHYTHMS.

It has been stated that the normal rhythm of the heart starts in the sinu-auricular node, which has been termed the 'pacemaker' of the heart. The proof of this lies in experimental work on animals. The region of the node is the first point in the heart to become electronegative.

Electrocardiographically the complex of auricular activity in normal beats is identical with the complex obtained in a beat originated in this region by a mechanical stimulus, and a similar complex can be obtained from no other portion of the auricles.

In a normally-beating heart, cooling the region of the sinu-auricular node slows the rate of beat, warming it accelerates it, and this is the only part of the heart which reacts in this way. If, however, the sinu-auricular node be cooled with ice-cold water, a different rhythm starts, which has been proved by the electrocardiograph to originate in the auriculo-ventricular node, and called the atrioventricular rhythm.

In dogs the auriculoventricular node has an upward prolongation which extends round the

coronary sinus, and is divided into an auricular portion and a ventricular portion. The former is the prolongation in the neighbourhood of the coronary sinus; the latter lies further forward. Each of these portions has been found capable of originating a rhythm of its own. It is known that a rhythm can originate from the auriculoventricular node in man, but no auricular portion of the node has as yet been described.

Other methods, such as excising, clamping, or poisoning the sinu-auricular node, have been found efficacious in producing an atrioventricular rhythm. If the auriculoventricular node be put out of action, a rhythm starts in the Purkinje fibres below the node, producing what is known as the idioventricular rhythm. So that there are three main pacemakers of the heart which may replace each other when the necessity arises, each successive rhythm in the order described being of a slower rate than the previous one. This arrangement prevents the rhythm in action being interfered with by a rhythm of a lower order; but if, owing to disease, a pacemaker of a lower rhythm becomes more irritable than that of a higher rhythm, the lower rhythm may assert itself and replace that of the higher. In the same way, any particular portion of the musculature of the heart may have its irritability so increased that a rhythm may start, having its origin in this irritated focus. In slow-acting hearts with a sinus rhythm we do occasionally see an escaped beat or a short series of beats belonging to a lower rhythm appearing in a tracing.

PROPERTIES OF CARDIAC MUSCLE.

Heart muscle carries on its work by means of five special functions. These are: (1) Stimulus production; (2) Conductivity; (3) Excitability; (4) Contractility; (5) Tonicity.

Ordinary muscles remain immobile till some nerve-cell discharges a stimulus which is conducted by a nerve-fibre to the muscle, which then responds to the stimulus with a contraction. Heart muscle, if suitably nourished, will contract rhythmically even when isolated from the body and with all its nervous connections cut; therefore it is certain that it receives its stimulus from within. We know that, the stimulus commences at the sinu-auricular node. If this structure be minutely studied, we find that in the words of its discoverer, "it consists of pale cardiac muscle-fibres with which the nerves appear to become actually continuous. This tissue, apparently intermediate in nature between muscle and nerve, is characteristic of the sinu-auricular node". It therefore appears that these modified muscle-cells have, during development, taken to themselves one of the properties of nerve-cells, namely the originating of impulses. It differs, however, from an ordinary nerve-cell inasmuch as, instead of sending out a rhythmic series of stimuli such as causes a tetanus in an ordinary muscle performing voluntary movement, it originates one stimulus causing one contraction.

In the same way the muscle of the auriculo-ventricular bundle has developed the property of conducting an impulse as nerve-fibres do. The rate

of conduction has been estimated at about 5 metres per second, which is much nearer the rate of conduction by muscle than nerve, nervous impulses being conducted more quickly.

Excitability and contractility are properties of all muscles, and are very intimately connected; the former consists of the power to receive a stimulus, and the latter the power of contraction on its receipt. The latent period between excitation and the commencement of contraction is about 0·001 second in both skeletal and cardiac muscle.

It used to be thought that the heart muscle differed from skeletal in that submaximal contractions could be obtained in the latter but not in the former. But these submaximal contractions are in reality maximal contractions of some of the muscle-fibres, while a stronger stimulus causes contraction of more fibres, and so on up to the maximal contraction. This fractional response is probably impossible in cardiac muscle. The interlacing of cardiac fibres and the wide ramification of the Purkinje system of conduction fibres ensure that contraction is carried out by every fibre in the cardiac muscle.

These two kinds of muscle also differ markedly as to their refractory period—the time after a contraction during which the muscle is unable to respond to another stimulus. In skeletal muscle this is very short, about 0·0015 second, whereas in cardiac muscle it is about 0·4 second. It is, of course, owing to this property that tetanization of cardiac muscle is impossible.

The tone of muscle may be defined as the tension

in its fibres while relaxed. No muscle relaxes to its utmost extent, but is kept in a state of partial contraction or tension. The tone of skeletal muscle is kept up by means of a reflex nervous path having a centre in the spinal cord, and it is controlled by the central nervous system. Any break in this reflex arc causes loss of tone and complete relaxation of the fibres of the muscle concerned.

In cardiac muscle this is not the case, for the perfused heart beating in the laboratory contracts perfectly well when it has no nervous connections. Cardiac muscle cannot be overdistended while the pericardium is intact. The ideas on the tone of cardiac muscle have altered of late years, and will be fully described in the paragraph on the work of the heart.

The volume of the ventricles and therefore the amount of stretching of its fibres will be seen to depend upon the venous pressure and not upon the tone of the muscle fibres.

THE NERVOUS SYSTEM OF THE HEART.

Although the heart can beat normally under suitable conditions when removed from the body, it is to a great extent controlled, during life, by the central nervous system. The medulla, from which all the vital functions of the body are controlled, is the home of cardiac control. Here are situated the vagus nuclei, both motor and sensory, and the vasomotor centre is intimately connected with it. Stimuli from the heart, great vessels, and all parts of the body, are continually arriving there by means

of the afferent fibres of the sensory nerves, and as a result of these messages the heart is slowed or accelerated. The efferent nerves controlling the heart are the vagi and the sympathetic.

The impulses reaching the heart from the vagus are inhibitory, causing: (1) Slowing or stopping of the heart-beat; (2) Lowering of conductivity or contractility; (3) Alterations in tonicity. It has been shown in animals, and to a certain extent in man, that the vagi of the two sides differ in their action. The right vagus appears to act mainly on the pacemaker of the heart—the sinu-auricular node—thereby slowing or temporarily stopping the heart. The left vagus acts more on the auriculoventricular node, producing delay in the *a–c* interval, or even heart-block, partial or complete. It is thought by many that stimulation of the vagus may cause a weakening of the contractions, but it is a difficult matter to determine, as lengthening of diastole tends to increase the contractile power of the heart muscle.

In dogs' hearts in which, by cooling the sinu-auricular node, auriculoventricular rhythm has been obtained, this rhythm is markedly slowed by stimulation of the vagus. The idioventricular rhythm is entirely out of the control of the nervous system.

The tone of the heart has repeatedly been shown to be affected by stimulation of the vagus, though the results are somewhat contradictory; sometimes the tone is increased, at others it has been depressed. Changes of tone from drugs which have been proved to occur by means of the vagi, are prevented by atropine, which paralyses the vagi.

The sympathetic fibres are supplied from the rami communicantes arising from the upper dorsal, and possibly from the lower cervical, nerves. They are carried to the heart by means of branches from the cervical and stellate ganglia. Their action is the direct opposite of the vagi; their stimuli accelerate and augment the beat of the heart and increase conductivity. Some workers have also been able to show differences in action between the right and left accelerator fibres, the right being concerned mostly with the sinu-auricular node and causing acceleration of sinus rhythm, while the left may produce auriculoventricular rhythm, with or without tachycardia. The experiments, of course, only refer to animals, though it is likely that the same effects may occur in man.

The rate of the heart-beat appears to depend on the balance of sympathetic and vagal action. Each is continually in activity, and factors which increase the one usually depress the other; but in certain marked alteration in rhythms, one function may be completely inhibited, allowing full control to the other.

The afferent system of sensory fibres passes up to the medulla in the vagi. It has been shown that each beat of the heart sends impulses up to the medulla by means of these fibres; in addition there are some special fibres from the root of the aorta and the left ventricle, called the depressor fibres; stimulation of these causes general dilatation of the blood-vessels throughout the body, producing a marked drop in blood-pressure, thereby giving

instantaneous relief to a heart beating against a pressure too high for its powers.

There is no doubt that pain does arise in the heart itself, but the precise nature of the pain-provoking stimulus, and the path by means of which it is linked up with the afferent cardiac nerves, has not yet been demonstrated.

THE WORK OF THE HEART.

The efficient working of the heart is indicated by the circulation of sufficient blood to all parts of the body for the need of the individual both at rest and during exercise. For the proper carrying out of this there must be a correlation between the heart, the central nervous system, the lungs, and the muscles themselves. The circulation is maintained by the output of the heart and the rate of the beat. The output of the heart depends upon two factors: (1) The efficient filling of the ventricles, and (2) The contractile power of the cardiac muscle.

The amount of blood passing into the ventricles during diastole varies directly with the pressure in the great veins in the thorax. It has been considered in the past that the 'tone' of the ventricles, resisting dilatation, had a large influence on the volume of the ventricles at the end of diastole, but Bainbridge has shown that the ventricular muscle fully relaxes during diastole and that the filling entirely depends upon the venous inflow. It must be admitted that there is no such thing as the 'diastolic tone of cardiac muscle', but that the fitness for contraction developed by the heart muscle during diastole is the indication

of its tone. Loss of tone means that during systole there is a lessening of contractile power.

Starling has shown that the force with which healthy heart muscle contracts depends upon the amount of stretching that its fibres have undergone during diastole, and has given this principle as a law which is known as Starling's law of the heart. This is 'that the force with which the heart contracts is directly proportional to the initial length of its fibres.'

As the ventricle is a hollow muscle, the longer its fibres the bigger the volume of the chamber; hence the more the ventricle is dilated during diastole, the more powerful will be its resulting contraction.

During exercise the body needs a great deal more blood than during rest: to effect this the heart has to increase its output largely. This may be done either by increasing the output per beat or by increasing the output per minute through quickening the pulse-rate. In reality both these methods are used together. The increase of the output per beat depends upon the 'law of the heart'. During exercise the increased respiratory effort and the action of the muscles, squeezing more blood into the veins, increase the venous pressure; this results in the ventricles being more distended with blood during diastole, and more blood is pumped into the aorta owing to the increased force of the beat. This does not take place instantaneously, but is extended over a few beats, the diastolic volume gradually getting larger till the output equals the inflow. The greater dilatation of the ventricles is a strictly

normal physiological process, and is only limited by the size of the pericardial sac, the function of which, as was pointed out in 1898 by Barnard, is to prevent overdistention of the heart.

Increase of the rate of beating will also increase the output of the heart, provided that the cutting short of diastole does not prevent the proper filling of the ventricles. If the venous inflow be slow, the increase of rate will greatly lessen the output per beat, and will have very little effect on the output per minute ; but if the venous pressure be large, so that filling of the ventricles is completed early in diastole, increase of the rate will almost proportionately increase the output per minute and will not lessen to any great extent the output per beat.

If the contractile power of the ventricle be poor, through lack of nutrition, fatigue, or disease, exercise will increase the venous inflow and cause increased filling of the ventricle; but the ventricular muscle will not be able to increase its contractile power, with the result that the chamber will be unable completely to empty itself during systole. An increase of rate will now markedly increase the output per minute, and will be able to compensate for the lessened contractility of the ventricle. With further weakening of the muscle, contractile power becomes less still, and the increase in rate cannot keep up the necessary output ; the output becomes less than the inflow, with the result that the venous system is overcharged and the ventricle is full of blood and cannot empty itself.

This is pathological dilatation, which is therefore

seen to be an overdistention both during systole and diastole. The circulation fails from weakening of the muscle, and the picture of heart failure develops.

It can now be understood what the reserve force of the heart really is. It is the ability of the heart to increase its power with an increased flow of blood from the great veins. It varies greatly in different individuals. In an untrained man the contractile power of the ventricles is not increased by the stretching of its fibres to nearly the same extent as in a trained man ; and therefore to enable a man of sedentary occupation to take even a moderate amount of exercise the pulse-rate will have to be increased largely to keep up the output, while in a trained man the heart can increase its output to a large extent solely by increasing the output per beat.

It has been estimated that during work the output may be increased to 20 litres per minute, whereas during rest the output varies from 3 to 5 litres per minute. The reserve force of the heart can be largely increased in young and healthy adults by means of training.

BLOOD-PRESSURE.

The arterial blood-pressure is the means whereby the intermittent force of the heart-beat is converted into a more steady pressure for the keeping up of the circulation, and also for the supply of more or less blood according to the needs of the individual.

The blood-pressure is very intimately linked up with the heart reflexes, so that the alterations in the rate of heart-beat, in the output of the heart, or in

the need of special tissues for blood, may find the cardiovascular system ready to ensure that the pressure is sufficient for the emergency. In a normal heart at rest the blood-pressure varies inversely as the rate of the heart-beat. This was put forward by Marey, and is known as Marey's law. Increase of blood-pressure in the aorta is followed by slowing of the pulse-rate, which thereby lowers the output and compensates the rise of pressure. Bainbridge has also pointed out that increase of pressure in the venous side of the heart increases the rate of beat, so that the extra amount of blood arriving at the heart may be dealt with. During work neither of these laws holds good, as the pressure has to be considerably increased and kept up until the work is concluded. The blood-pressure depends upon two factors, (1) the output of the heart, and (2) the peripheral resistance.

The former has already been discussed. The latter depends upon the constriction or dilatation of the arterioles. The vasomotor system of nerves may constrict or dilate certain areas, lessening or increasing the amount of blood passing to them. Constriction of one area decreases the amount of blood passing to it, and thereby raises the pressure to some extent by decreasing the capacity of the whole system. It also allows more blood to be available for other parts of the system, and if there be a dilatation of the arterioles in any area, a very much increased blood-supply is ensured to this part. During exercise there is a constriction of the splanchnic area and a dilatation of the vessels in the active

muscles, whereby the blood-supply to the muscles is very much increased.

The correlation of the cardiovascular system to changes in the activity of the individual is carried on in the medulla, where the vagus and the vaso-motor centres lie. The commencement of exercise, or perhaps the idea of its inception, calls forth a psychical influence on these centres, causing a bracing up of the body generally, with increase in pulse-rate and some increase of blood-pressure; the rest is carried on by automatic reflexes reinforced by psychical influences calling forth a special effort as a result of encouragement or a competitive spirit.

The increase of blood-pressure that occurs during exercise ensures that there shall be a larger supply of blood to both the central nervous system and to the heart itself, for in no tissues can an increase of work be undertaken unless there be an increase in blood-supply.

CARDIAC IRREGULARITIES.

Cardiac irregularities may be classified according to the site of origin of abnormal action in the neuro-muscular elements of the heart, and fall, therefore, into the following groups: (1) *Irregularities of nervous origin*; (2) *Defects in conductivity*; (3) *Increased excitability*; (4) *Defects in contractility*.

1. *Irregularities of Nervous Origin.*—Experiments have proved that stimulation of any sensory nerve affects the heart-rate. In life, any emotion, movement of the body, or activity of organs sends impulses to the brain by the sensory nerves, but

they are too small to bring about changes of the heart-rate. Forced movements, and great emotions —such as fright, anger, or pain—produce impulses that do affect the rate. Stimuli which are normally not strong enough to cause changes in rate may do so in conditions of nervous instability, or in children. Thus ordinary breathing, swallowing, yawning, digestive activity, or smoking may cause irregularity of the heart. This irregularity is named *sinus arrhythmia*, inasmuch as it is caused by alteration in the rate of stimulus production in the sinu-auricular node.

This type of arrhythmia may also occur in meningitis, or other conditions of increased intracranial tension, in tumours pressing on the vagus, or from drugs such as digitalis. Occasionally cases are met with in which standstill of the whole heart for some seconds has been caused by vagal inhibition, and one case has been recorded where cerebral anæmia from this condition caused loss of consciousness and convulsiform movements such as occur in the Stokes-Adams syndrome. Sinus arrhythmia is easy to detect in polygraphic tracings. The venous pulse shows that each beat is of normal sequence. After a series of rapid beats there may be a pause suggesting the pause after a premature beat; but on accurate measurement of the pulse periods, the succeeding ones will be seen to get gradually shorter till another series of rapid beats will occur.

The respiratory rhythm can usually be seen in venous tracings, and the periods of quick and slow beats may be seen to correspond with inspiration

and expiration. Respiratory sinus arrhythmia is extremely common in children.

2. *Defects in Conductivity.* — These may occur either from nervous influences—for we have seen that the vagus may decrease conductivity of the bundle—or from pathological lesions in, or in the neighbourhood of, the conduction fibres. The commonest of these are gumma, aneurysm, tumour, acute inflammatory conditions, fibrosis, or calcification. The delay may be of any intensity, from a mere lengthening of the *a–c* or P–R interval to complete block.

In some cases of rheumatic heart disease, polygraphic tracings or electrocardiograms show an increase of the *a-c* or P–R intervals; if the process goes a stage further, a ventricular contraction may be observed to fail occasionally owing to conductivity not having recovered in time to carry the stimulus to the ventricular muscle. This is beautifully shown in tracings; the *a–c* interval is gradually increased with each successive beat until a ventricular contraction fails. The next *a–c* interval is normal, or almost so, owing to the long pause enabling the bundle to recover its function; but then the steady increase starts again till another contraction is missed, and so on. If a heart such as this beats more slowly, the longer diastole gives the auriculoventricular bundle more time to recover, and the heart-block decreases; but if it accelerates, the block immediately becomes more intense.

With a more serious defect in conductivity the ventricle may drop out more frequently, and may

only respond once to two, three, or more beats of the auricle, causing a 2–1, 3–1, 4–1 heart-block.

If a complete block occurs, the idioventricular rhythm is called into action, while the auricles continue to contract at the dictation of the sinu-auricular node. There is often a pause of some seconds before the idioventricular rhythm starts; the length of this seems to depend on (*a*) The suddenness with which the block occurs; and (*b*) The healthiness of the ventricular muscle. The more suddenly the block occurs, the longer the ventricles take to start their own rhythm, and healthy muscle appears to respond more quickly than diseased muscle. The loss of consciousness and the convulsions which occur, depend on the length of the ventricular pause, for they are caused by the cerebral anæmia resulting from the absence of the pulse.

The idioventricular rhythm arises somewhere between the auriculoventricular node and the ventricular muscle, for the electrocardiogram shows a normal ventricular complex, proving the beat to have arisen somewhere in the Purkinje system of fibres. It is regular, and, as a rule, about 30 per minute, though it may be slower or quicker; one case is described where the rate was 60 per minute. The reason for this variation is not clear. It has been proved that the cardiac nerves have no effect on this rhythm, so that it must depend on the excitability of the focus giving rise to the stimulus.

The regularity of this rhythm is sometimes interrupted by premature beats occurring at a certain time-interval after each beat. These are ventricular

premature beats arising in the ventricular muscle, as shown by the electrocardiogram, which gives an abnormal complex of that type. The pause between the premature beat and the next idioventricular beat is always of the same length as that of a cycle where no premature beat occurs.

The auricles are unaffected, and their rate of beat is still governed by the sinu-auricular node, the ventricular beats being quite independent of the auricles. In fact, cases have been described where the ventricle has been beating independently, and the auricles have been fibrillating or fluttering.

It has been mentioned that during the inception of the idioventricular rhythm there is a pause in the ventricles of some seconds; in some cases this recurs at varying periods and is of varying length. Patients often die during one of these, but again in many cases the rhythm goes on perfectly regularly, and may remain so for years, till the patient dies of some intercurrent affection. These periods of asystole are thought to be caused by a progressive lesion, such as acute inflammation, ulceration, or tumour, spreading down the bundle and invading the area originating the stimulus; the ventricular rhythm will then stop until some part lower down takes on the function of stimulus production; if, however, the lesion is an unirritating one such as fibrosis, scarring, or calcification, the rhythm will remain quiescent after the initial damage.

There is no difficulty in recognizing heart-block, partial or complete, by means of tracings or electrical curves. In partial block it will be seen that no

c or *v* wave occurs during the radial pause, but that the *a* wave is present in the situation expected in the venous pulse. The *a–c* interval, where the ventricle contracts, will also be seen to be longer than normal. In complete block the *a* waves are as a rule well marked, and will be seen to occur regularly quite independent of the ventricles, which beat slowly and regularly unless disturbed by premature contractions. These can be easily recognized in the radial pulse.

The Stokes-Adams syndrome may be confounded with standstill of the whole heart associated with vagal inhibition; but the absence of *a* waves during the pause, and the normal sequence of *a*, *c*, and *v* waves, when a contraction does occur, discloses its mechanism.

Some cases of complete heart-block have been described where no abnormality has been found in the conduction system after death; and again, others have been recorded where, although no dissociation occurred during life, severe pathological lesions have been demonstrated in the auriculo-ventricular node and bundle which would appear to have completely destroyed the bundle. These cases cannot be accounted for by our present knowledge.

Partial heart-block is in many cases due to vagal depression of conductivity. This may be shown by injecting $\frac{1}{60}$ gr. of atropine, which paralyses the nerve-endings of the vagus. If due to this cause, the heart-block passes off as soon as the rate quickens and conductivity is restored. It has been thought

that this might account for some of the cases of complete heart-block with no demonstrable lesion; but in one case at least atropine made no difference to the block, and yet no lesion was found after death.

Partial heart-block has been recorded in a number of cases of rheumatic carditis, and also in pneumonia, influenza, and diphtheria. It usually passes off after a few days.

Complete heart-block occurs in acute rheumatism, typhoid fever, pneumonia, diphtheria, ulcerative endocarditis, and in gonococcal septicæmia.

Most examples of heart-block, of all degrees, are, however, met with in chronic disease such as cardiosclerosis and cardiac syphilis.

3. *Irregularities from Increased Excitability.*—Any part of the cardiac musculature which is in a state of increased excitability may give rise to a stimulus which causes contraction. Thus a premature contraction may arise from any part, and may therefore be auricular, ventricular, or nodal. If the irritation be severe, it may lead to a short series of beats from this situation, and in extreme conditions may cause a long series of abnormal beats, or in other words the normal rhythm may be replaced by a rhythm starting from the irritable focus, and paroxysmal attacks of tachycardia occur.

Single premature contractions may arise from the initiation of a stimulus in any part of the musculature of the heart; thus they may start in the auricles, ventricles, or in the auriculoventricular bundle or node.

The site of origin may be determined from polygraphic tracings.

In auricular extrasystoles a premature *a* wave is found, followed by a small *c* wave, which coincides with the small beat in the radial. The *a–c* interval is usually prolonged owing to the conductivity not having perfectly recovered from the passage of the last stimulus; the earlier in diastole the premature beat occurs, the more prolonged the *a–c* interval will be. If the ventricles beat prematurely, the auricles contract at their normal time, receiving a stimulus from the sinu-auricular node, and the ventricular beat occurs independently of the auricular.

When polygraphic tracings are studied, it will be seen that the ventricular beat may occur synchronously with the auricular, or the *a* wave may be found slightly after the *c* wave. In these cases the stimulus from the auricular beat falls on the ventricle during its refractory period, and the ventricle does not contract: hence there is a pause till the next auricular beat. From beat to beat, excluding the premature contraction, will therefore be equal to two normal beats. This is what is known as a fully-compensated pause, and is characteristic of ventricular premature contractions.

If the premature beat occurs early, or if the heart-rate is slow, the auricular contraction occurs at an appreciable interval after the premature beat, and the stimulus may fall on the ventricle after the refractory period is over, in which case the ventricle will contract, and a normal rhythm is seen, save that

one premature contraction of the ventricle occurs between two normal beats. This is termed an interpolated premature contraction.

If the venous pulse in premature ventricular contractions be studied, we find either one large wave corresponding to both *a* and *c* waves when the contractions occur simultaneously, or the *a* wave, though in its normal situation, as ascertained by measurement, may follow the *c* wave of the premature beat.

We have seen that a fully compensated pause is characteristic of ventricular premature contractions; in premature auricular contractions the pause is not compensatory. This is said to be due to the fact that, if a stimulus arises in the wall of the auricle, it passes back to the sinu-auricular node and discharges its stimulus-producing material; consequently there is a pause till the next stimulus is produced at the sinu-auricular node; the complete pause will therefore be a normal pulse period plus the time taken for the premature stimulus to reach the sinu-auricular node. If the premature beat arises in the sinu-auricular node itself, the pause is found to be exactly a normal pulse period.

Beats may originate in the conducting mechanism of the heart, either as escaped beats of a lower pacemaker or as premature contractions. The latter are frequently found arising from the auriculo-ventricular node. The stimulus is conducted both ways—back to the auricles and forward to the ventricles—and these chambers contract almost or quite simultaneously.

In polygraphic tracings there is one large wave due to both *a* and *c*, as in some premature ventricular beats, but in this case both *a* and *c* will be premature. The auricle may beat shortly before the ventricle, but the *a*–*c* interval is 0·1 second or under. There will be no sign of an *a* wave in its normal place as there is in the premature ventricular contractions.

Electrocardiograms of premature contractions are even more satisfactory than polygraphic tracings for diagnosing the site of origin. An auricular premature beat will give an abnormal auricular complex, while all ventricular premature beats will give abnormal ventricular complexes, and the type of complex will locate the position of the focus initiating the beat. Auriculoventricular or nodal premature contractions usually show an inverted auricular complex occurring just before the R of the ventricular complex.

The cause of premature beats is not certainly determined. We know from experiment that electrical stimulation and other methods will produce them, but they occur in healthy as well as in unhealthy hearts. There is some reason to think that overdistention of a cardiac chamber may provoke it to premature contraction. For instance, auricular premature contractions are very common in mitral stenosis, where the auricle has difficulty in emptying itself and is therefore fuller than in health; but one cannot exclude the possibility of disease in the auricular wall.

Again, in any case with frequently recurring premature beats of one type, the time relation of

the abnormal beat to the preceding one is usually the same. This points to some causal connection between the previous beat and the premature one.

Nodal premature beats cannot be due to over-distention; they are not met with nearly so frequently, and are probably due to some functional or organic irritative lesion in the auriculoventricular node or in the blood-vessels supplying it.

Premature beats are common in adults and older people, but not in young children. Acceleration due to exercise tends to diminish them in healthy hearts, but to increase them in hearts showing signs of overwork. The general opinion is that in health they have no significance, but that in hearts whose reserve power is failing they indicate disease in the muscle, and that they may lead on to more and more frequent premature beats then to short runs of premature beats, and finally to long paroxysms of abnormal rhythms.

A few cases have been followed through where electrocardiograms of a premature beat of a certain type have been demonstrated, and later on paroxysms of tachycardia have been shown to consist of a series of beats identical with the original premature beats. Thus there can be little doubt that premature beats may lead on to prolonged abnormal rhythms. The paroxysms may originate from the auricle, the ventricle, or auriculoventricular node.

Auricular flutter and fibrillation are abnormal rhythms of quick rate which arise in the auricle. They may start in short paroxysms, but more often are permanent once they have been originated.

Sir Thomas Lewis, in the Oliver Sharpey Lectures of 1921, has described the mechanisms of these abnormal rhythms. The basis of this mechanism depends on the following discovery, which has been known for some years:—

If one imagines a circular ring of muscle which is stimulated to contract at one point, a contraction will occur and pass round each side of the ring until the wave of contraction meets at the reverse side of the ring, when the contraction ceases. If, however, this ring of muscle has been made to contract repeatedly just before the experiment, it is found that during the partial recovery of refractoriness the wave of contraction may be stopped from passing up one side of the ring while it passes up the other side. This wave will then pass completely round the ring, and when it reaches its starting-point it will, provided the muscle has sufficiently recovered from its last contraction, start again round the ring, and so on indefinitely. The only condition necessary for the continuance of this phenomenon is that the time of partial recovery from the refractory period must be a little less than the time taken for the contraction to pass round the ring of muscle; in other words, there must be a gap between the muscle in an absolutely refractory state and the advancing wave of contraction. The time taken to complete the circuit depends upon (1) the length of the circle, (2) the rate of the contraction wave, and (3) the length of the refractory period. It is found that in rapidly-beating hearts the rate both of the contraction wave and the refractory period is about

half that of the normal, so that the time taken depends mostly on the length of the path. Lewis has found that this is what occurs in experimental flutter and fibrillation in dogs, and, as the electrocardiographic curves obtained during these experiments are identical with those obtained from men suffering from these conditions, it is justifiable to assert that this is the mechanism of these abnormal rhythms in man.

The difference between flutter and fibrillation is mostly in the length of the path. In flutter the path is longer and the gap is composed of muscle in which the partial refractoriness has almost passed away ; there is no hindrance to the path of the wave round the ring, so that each circuit takes the same time. In fibrillation the path is shorter and the gap is narrower; consequently the muscle is more disinclined to contract than in flutter, in other words, the partial refractoriness is nearer the absolute. In fibrillation the auricular muscle is more degenerated than in flutter. The result of these two factors is that the wave of contraction finds difficulty in passing round the ring of muscle, and has to discover a path for itself amongst fibres, of which some are impassable, while others can be passed only with difficulty. No two circuits are the same, and the time taken to complete the circuit is not constant. For these reasons the auricular rhythm in flutter is regular, while in fibrillation the rhythm is irregular ; in flutter the auricular rate is about 300, in fibrillation about 450, per minute. As the wave of contraction passes round the circle, it spreads

centrifugally into the remainder of the auricular muscle, so that in flutter there is regular contraction of the auricles of about 300 per minute. In fibrillation the surrounding muscle is stimulated irregularly and much more rapidly. Some of the muscle will be refractory and there will be no co-ordinate conduction from bundle to bundle; hence there will be no co-ordinate contraction of the auricles, but the muscle will be quivering from the irregular contraction of individual bundles of fibres, giving the muscle the appearance of the fibrillary tremor which is met with in progressive muscular atrophy.

Lewis has shown that in flutter the ring of muscle which is acting in this way is often the muscle surrounding the superior and inferior venæ cavæ, while in fibrillation the wave of contraction circles round one of the veins. In auricular flutter the ventricle does not respond to every auricular beat, as heart-block of varying grade may be present, thus acting as a protective mechanism; for the heart would rapidly fail if the ventricles tried to contract at a rate of 300 per minute. This fact causes a difficulty in diagnosis, as is shown in the following case seen by us not long ago:—

A woman suffering from mitral stenosis with a considerable amount of heart failure gave a history of periodic attacks of palpitation and a feeling of very rapid heart action. Her heart was beating at 72 per minute, and was perfectly regular. It was thought that these attacks were due to paroxysmal tachycardia, but an electrocardiogram showed that the auricular rate was 216 per minute. The case

was one of auricular flutter, and the attacks were due to the grade of heart-block decreasing and the ventricle taking up the auricular rate.

This case demonstrates that for accurate diagnosis it is essential to use graphic methods. Occasionally rapid movements of the veins in the neck may give a clue to this condition, and the waves are often shown in venous curves, but in the majority of cases certainty of diagnosis can only be attained by the electrocardiograph. Probably all cases with attacks of tachycardia where the quick rate is a multiple of the slow rate are due to this condition.

The heart is not always regular, as the grade of heart-block may vary from time to time or from beat to beat. This may disclose the nature of the irregularity, as the varying pulse periods bear an arithmetical relationship, being all multiples of one auricular contraction period.

In auricular fibrillation the ventricles contract in a continuously irregular manner, both as to rhythm and force; thus no two beats of the same length occur consecutively, nor is there any true relationship between beats or groups of beats as in auricular flutter. A longer pause is often followed by a small beat, while a short pause may be succeeded by a larger beat.

This ventricular irregularity is caused by the irregular stimuli arriving from the fibrillating auricles. The pulse-rate is usually about 140 per minute, but in cases where some degree of defective conductivity is present a varying number of the irregular stimuli may be blocked by the conducting

bundle, and the ventricular rhythm may be slowed, though being still absolutely irregular. If the block be complete, the ventricular rhythm will be regular and about 40 per minute. The point of origin of this regular rhythm is probably the auriculo-ventricular node, which dominates the ventricles but not the auricles as they are fibrillating. It cannot be the idioventricular rhythm, for it is too rapid and there is never a pause, as is seen at the onset of this rhythm in complete heart-block. This condition is easily diagnosed; the absolutely irregular pulse is characteristic. A tracing shows the ventricular type of venous pulse with absence of the *a* wave. During the longer diastoles, small irregular waves may be sometimes seen. These are caused by the inco-ordinate contractions of the auricles.

An electrocardiogram shows normal ventricular complexes as the stimulus is conveyed to the ventricle by the bundle. There is no P wave, but small irregular deflections are seen all through diastole, corresponding to the small waves sometimes present in the venous pulse.

Auricular flutter and fibrillation commonly occur in the later stages of rheumatic heart disease—more particularly mitral stenosis—but have been known to occur during the first attack of rheumatism; they also occur in hypertrophied hearts where the muscle is degenerated. Attacks may be paroxysmal at first, but more often they remain permanently when they have once started. Flutter or fibrillation may last for a great number of years, but the symptoms of heart failure are usually present.

Fibrillation of the ventricles occurs in cases of chloroform poisoning, and also in experimental occlusion of the coronary arteries. It is possibly the cause of death in many cases of sudden failure of the heart.

Paroxysms of *ventricular tachycardia* are rare, but are of interest physiologically, inasmuch as a retrograde beat of the heart is set up after the first four or five beats, and the auricle then responds to a stimulus conducted backwards from the ventricles, the sinus rhythm being for the time in abeyance. At the end of the paroxysm there is a pause, and then the sinus node takes on control. The condition can only be diagnosed with certainty by the electrocardiograph, which shows an abnormal type of ventricular complex.

Paroxysms of *nodal tachycardia* also occur, each beat of which is the replica of a nodal premature beat. The paroxysms start and end suddenly, and there is a pause between the offset of the abnormal rhythm and the onset of sinus rhythm.

In studying the effect these rhythms have on the heart and circulation, one must take into account the state of the heart prior to the attack. If the reserve force of the heart is fair, a paroxysm rarely gives rise to any signs of heart failure till it has lasted some considerable time ; but this also depends to a great extent on the rate of the tachycardia. A rate of over 200 will cause signs very much more quickly than one under ; but most patients, provided they lie down during the attack, show very few signs of distress, and very rapidly regain their accustomed

activity after the attack is over. If the heart be failing before the onset of the attack, it very soon places the patient in a critical condition. The contractile power becomes exhausted, the ventricles are not properly emptied, the circulation accordingly slows; there is stasis of blood in the veins and capillaries; tenderness and enlargement of the liver occur; cyanosis and œdema appear; and death will ensue unless the paroxysm ceases.

4. *Defects in Contractility.*—Pulsus alternans is stated to be due to a defect in ventricular contractility. It consists of an alternation of small and larger beats, the rhythm being regular. It is found: (*a*) In hearts failing against a high blood-pressure; (*b*) In rapid rhythms, such as paroxysmal tachycardias; (*c*) In some cases after premature beats.

A continuous pulsus alternans is a sign of weakening of the ventricular muscle, and is a danger signal except in rhythms of over 140 per minute, where it is very frequent. Recently a group of cases showing this rhythm was described (Windle). Of 13 cases in which the onset of pulsus alternans was noted, 9 were fatal, in periods of from one month to two years; 4 were still under observation, and the longest period that it had existed was twenty-three months. Of 18 others where this symptom was noted on the first examination, 12 died within nine months, 1 in twenty-one months; the remaining 5 were still alive, but the longest period of observation was eighteen months. Of the fatal cases, some did not seem very ill at the time of onset of this sign, which is therefore always of grave omen.

We may now sum up the prognostic significance of the various cardiac arrhythmias with the following proviso: an arrhythmia *per se* does not necessarily alter the prognosis at all, but must be considered in conjunction with all the other features of the case.

Sinus arrhythmia may be considered as a normal phenomenon in children and young adults.

Heart-block is nearly always a sign of grave disease, but the immediate prognosis of a complete and stationary block is relatively good.

Premature contractions in otherwise normal hearts mean nothing; but where heart disease exists, and the loss of reserve cardiac power is serious, the development of premature contractions increases the gravity of the prognosis.

Auricular flutter and fibrillation are abnormal rhythms occasioned by serious disease; but provided an accompanying block keeps the ventricular rate slow, the immediate prognosis of the case is not altered by their onset.

In 50 per cent of cases treatment may re-establish a normal rhythm; if this be not possible, the prognosis is bad unless the digitalis group of drugs slows the heart. These drugs will have to be taken continuously to prevent the onset of heart failure from ventricular exhaustion.

Pulsus alternans is of grave prognostic significance.

CHAPTER VII.

SURGICAL SHOCK.

WHAT IS SHOCK?—THE PHENOMENA OF SHOCK—EXPERIMENTAL MEANS OF INDUCING SHOCK-LIKE CONDITIONS—THEORIES AS TO ITS NATURE—PREVENTION AND TREATMENT—INTRAVENOUS SALINE TRANFUSION.

NO scientific problem more interesting to physiologists and clinicians alike came before the notice of the profession during the war than that presented by surgical shock. It was so frequent, so deadly, and withal so elusive, that an immense amount of study was devoted to the subject from many different points of view. Real progress has been made; some more or less settled conclusions have been arrived at; ancient theories have disappeared. Yet it cannot be said that we are much nearer the solution of some of the most important problems of all. This is rather surprising, seeing that we had the best young brains of Europe and America enlisted in the research, and such material as the world has never furnished before, and pray Heaven may never furnish again. Who of us that saw it will ever forget the dimly-lighted, silent tents or huts that formed the 'shock-ward' at a casualty clearing station on the night after some great battle?

One reason for the difficulty has been a difference of understanding as to what we mean by 'shock'.

The patients who came down from the field ambulances were very 'bad', often dying, or they became so within a day or two; but cases of pure shock were rather rare, and much of the 'bad'-ness was not due to shock at all. The following conditions have to be excluded or allowed for before we can agree that shock is present :—

1. *Considerable loss of blood.* Loss up to a pint does not by itself do any harm to a healthy young man, as we know from its slight effects on donors for blood-transfusion. A small loss will, however, jeopardize the life of a man with grave bodily injuries.

2. *Concussion* of brain, spinal cord, or thorax.

3. *Toxæmia from intestinal paralysis* and consequent absorption. Grave symptoms coming on a day or two after a severe abdominal injury or operation are usually due to this cause, not shock.

4. *Syncope from mental effects*, such as fainting from a slight or severe wound. This is a transient condition, and the patient recovers in a few hours, often in a few minutes.

5. *Toxæmia from acute infections.* During the war, streptococcal or gas-gangrene infections of wounds, especially wounds of the muscles of the buttock or leg, gave rise to shock-like symptoms coming on usually on the second, third, or fourth day.

When all the above have been deducted, there is still something left, but at a casualty clearing station one or other of these factors would account for more than half the phenomena of so-called 'shock'. In civil practice, where hæmorrhage and virulent

infections are less in evidence, shock is relatively infrequent ; but when it occurs it usually does so in a purer form. The best examples of uncomplicated shock are seen within the first twenty-four hours of an abdominal injury, after such an operation as amputation at the hip-joint or Wertheim's pan-hysterectomy for cancer, and in big smashes without an open wound. In burns, the picture is complicated by blood-scorching.

Surgical shock, then, is a condition of depressed vitality due to injury, but apart from the above-mentioned more tangible causes.

THE PHENOMENA OF SHOCK.

The well-known signs, such as pallor, loss of muscular power and tone, some blunting of the mind, quick weak pulse, subnormal temperature, reduced urine, etc., need merely be mentioned in passing. They are familiar. The knee-jerks are generally normal, but in profound shock they may disappear.

The most convenient sign of shock for demonstration purposes and for the sake of comparison with other cases is the fall of blood-pressure measured by the sphygmomanometer. If the systolic pressure falls below 90, the condition is serious. It is probable, however, that shock may be present before the blood-pressure falls, though it is difficult to recognize its presence, except that the patient may 'look bad'. This is important, because we all know that a man may be sent off the operating-table with a good pulse, but already his life is in danger, and a few hours

later he collapses and dies more or less suddenly. On the other hand, a fall of blood-pressure does not necessarily prove shock. Turning a patient on his stomach to excise a wound in the back after performing a laparotomy for gunshot injury used to cause a serious fall of blood-pressure, but this was quite probably due to syncope, and rapid recovery sometimes took place, though of course syncope is occasionally fatal.

Great attention has been paid to the condition of the heart and blood-vessels in shock. It is universally admitted that the heart is not primarily at fault. It responds gallantly to every call upon it, and becomes quite active after a big transfusion.

The ancient controversy as to whether the arteries are dilated or contracted in shock may be taken as settled—they are contracted. Indeed, there was never any evidence to the contrary—only theories. The superficial veins are contracted, and often in a state of active spasm, especially in the hæmorrhage-shock combination. It may be quite difficult to find the vein for transfusion purposes, and having found it one may be able by considerable force to drive fluid an inch or two along it, but the spasm prevents it from going any further. This may obtain when it is quite certain that the cannula is in the lumen, not in the vein wall. I have more than once, for this reason, had to resort to the saphena vein at the groin, to give a blood-transfusion, and even that may be found extremely contracted. I have seen the condition in pure shock apart from hæmorrhage.

It has been theorized for years that the abdominal

vessels are dilated in shock, and that most of the blood in the body collects there. Surgeons nearly all agree that this is not true. In laparotomies for acute abdominal catastrophes and for early gunshot injuries, one seldom if ever notices conspicuous congestion of the blood-vessels apart from peritonitis. Nor is the liver found engorged either at operation or post mortem.

The condition of the capillaries opens up some new and very interesting problems. The main difficulty in accounting for the phenomena of shock is how to reconcile the falling blood-pressure with the mechanical facts of the case—the heart is beating strongly; the arteries and veins are contracted; the blood has not collected unduly, either in the abdomen or elsewhere. As we shall see, Dale has discovered that a shock-like condition may be produced in animals by a drug called histamine, and here also the heart is sound, the arteries are contracted, but the blood-pressure falls. In histamine poisoning the capillaries appear to be dilated though the arteries are contracted. Some other chemical substances act similarly. Apart from drugs, there is evidence that the calibre of the arteries and the capillaries may vary independently one of the other. A few hours or days after section of the sciatic nerve in a cat, the pads of the foot on the operated side are paler (= capillary contraction), though that paw is *warmer* than the other, not only to the touch, but also to exact measurement, for if both paws are immersed in water in test-tubes, the water on the side of the denervated paw is warmed up more quickly

than the other(= arterial dilatation with capillary contraction on the operated side). This opens up the possibility that the capillaries may be dilated in shock, which if true might account for the fall in blood-pressure.

A good deal of attention has lately been paid to the behaviour of veins and capillaries. The older physiology confined its studies too exclusively to the arteries. Donegan has shown that the veins differ somewhat in their innervation and response to stimuli. The subcutaneous veins are supplied by the sympathetic, and contract when it is stimulated. The veins of the mesentery are influenced reflexly in much the same way as the splanchnic arteries. The veins of the muscles, and the inferior vena cava, appear to be independent of nerve control. Adrenalin contracts the subcutaneous and mesenteric veins, but not those of the muscles, or the vena cava.

Krogh's study of the capillaries of the frog's tongue shows that they have a tonus of their own ; they are not forced open by arterial vasodilatation, nor are they controlled to any considerable extent by nerves. They are relaxed by local stimulation, by heat, or by minute traces of adrenalin. When the muscles contract, the capillaries are widely dilated, and some channels previously collapsed and invisible become pervious to the current of red blood corpuscles.

Cannon and others have made red cell-counts of the blood of patients with the shock-hæmorrhage complex, and find that there may be a higher count of corpuscles in the capillaries than in the veins.

The same has been reported in the capillaries of the intestinal villi of shocked animals. That this disparity may occur is undoubted; it suggests either that the force of the circulation is not enough to move on the corpuscles from the narrow capillaries, or else that the plasma exudes out through their walls, leaving the corpuscles behind. That this is the main cause of the fall in blood-pressure seems very improbable. In four out of five shock cases at a casualty clearing station in France, my colleagues and I failed to find any difference in the vein and capillary count. If the capillaries were markedly dilated, one would expect the mucous membranes to be flushed and to bleed easily, but as a matter of fact they are pale and scarcely bleed at all.

It is widely believed that the total blood volume in shock is reduced, and that here lies the explanation of the fall in blood-pressure. It may be that this view is correct, but it appears to have been too readily accepted. The older experimental work on the subject was far from satisfactory, though it is repeatedly quoted. My own observations on the specific gravity of the blood during the onset of pure shock, even in fatal cases, show no concentration, except in extensive burns, where there may be loss of fluid from the damaged surface, and scorching of the plasma. Only once did I meet with an abnormally high blood-count in a shock case in France. According to Guthrie, in experiments on shocked animals there is an *increase* of the blood volume, up to 20 per cent. Observations by the vital-red method are urgently required; several American workers

(Keith, Robertson, and others) have shown that there is a fall in the total blood volume in cases of the shock-hæmorrhage complex, which of course is only to be expected, but I have not yet seen any satisfactory reports of estimations in pure shock cases in the human subject.

Keith showed that if the blood volume is 75 per cent of the normal or over, the blood-pressure is usually above 95 mm. of Hg, and recovery is probable ; a blood volume between 65 and 75 per cent of the normal, with a blood-pressure below 90, means that the condition is grave, and if the blood volume falls below 65 per cent, blood-pressure below 60, recovery is very improbable. I found the total blood volume in a fatal case of shock-hæmorrhage as low as three pints. Erlanger and Gasser, in cases of pure shock in experimental animals, find that the blood volume is reduced to 80 per cent, but there is no rise in percentage of blood-proteins or blood-corpuscles.

It is quite clear, therefore, that the vital-red method does not give the whole blood volume, but only the volume of the actively circulating blood ; a good deal is evidently lying in a stagnant back-water in some capillary areas, probably the muscles, intestinal villi, and other viscera. There is little, if any, loss of water to the circulating blood, so the blood-count and specific gravity do not rise. The vital-red evidently does not reach the stagnant area.

This capillary stagnation may or may not give rise to a high blood-count in the skin capillaries ; in my experience of war and civilian cases it usually does not.

As Keith has shown, the virtual loss of circulating blood volume due to stagnation cannot be due to hæmorrhage alone. A blood-donor may give as much as 800 c.c., and yet his blood volume may be made up to normal within an hour.

The stagnation in the visceral and muscle capillaries has not yet been conclusively demonstrated by histology in man, though Turck gives some pictures of it. Certainly it does not occur in the brain capillaries.

Metabolism in Shock.—Evidence has accumulated that important chemical changes take place when the blood-pressure falls. Both in experimental animals and in wounded soldiers there is quite constantly a considerable degree of acidosis. This has been demonstrated by Cannon and others, using the van Slyke apparatus and technique, which shows a fall in the alkali reserve of the blood. These observations were verified by O. H. Robertson at the casualty clearing station where I was posted. Dukes and I also made analyses of the ammonia nitrogen in the urine, which is a well-recognized indicator of acidosis, and found a very marked rise, which only comes on after the blood-pressure falls, and increases as the shock deepens. We found that the acid is neither lactic nor diacetic. There is some evidence that amino-acids are being excreted in excess (Lovell).

It does not appear that the acidosis is the primary cause of the symptoms in shock. In point of time it follows rather than precedes the circulatory depression. Higher degrees of acidosis may be obtained experimentally without causing the animal

any inconvenience. Alkaline transfusion is little if any more successful than saline transfusion in the treatment of shock.

The late Professor B. Moore maintained, not very convincingly, that there is really an alkalosis, not an acidosis.

Changes in Nerve-cells.—Crile and Dolley have described loss of the Nissl granules and other signs of exhaustion in the cells of Purkinje in the cerebellum in human and animal cases of shock, and similar changes have been observed by Mott in other nerve centres. I have worked over the central nervous system in detail in four cases of shock, and some controls. The first was a patient with multiple simple fractures after a heavy fall, the second a crushed chest, the third a gunshot injury of the spine and abdomen with hæmorrhage as well as shock. They all died within twenty-four hours. In each case the findings were concordant ; the nerve-cells of the spinal cord, the posterior root ganglia, and the motor areas and nuclei of the brain showed no abnormality, but the sensory cells of the brain showed a profound loss of Nissl granules (gracile and cuneate nuclei, optic thalamus). The suggested explanation is that they were exhausted by a bombardment of painful sensory messages. Other cells showed less marked changes—the Purkinje cells of the cerebellum, Deiters' nucleus, etc. In one case the vagus nucleus had suffered.

In a fourth case, a labourer with a smashed sacrum, compound fracture of the femur, and considerable retroperitoneal and external hæmorrhage, death was

delayed till the second day, and the Betz cells were more severely affected, but the motor nerve nuclei escaped.

EXPERIMENTAL MEANS OF INDUCING SHOCK-LIKE CONDITIONS.

It is not easy to induce typical shock in experimental animals by procedures analogous to those which give rise to it in man. According to Guthrie, even crushing the brachial or sciatic plexuses often fails to lead to a fall of blood-pressure, and multiple amputations of limbs high up are also unreliable. The most constant experimental method of causing a marked fall of blood-pressure that will go on to a fatal termination if the stimulus is persisted in, is pulling and twisting of the intestines, but it needs to be prolonged.

Several workers show that ligature of a limb followed by crushing of the muscles, and then release of the ligature, with massage, so as to flood the circulation with crush-products, is productive of a shock-like condition (Turck, Bayliss, Cannon). There is a fall of blood-pressure, lowered temperature, and sometimes even death. If the ligature is kept on, and the limb amputated, no such symptoms are observed. Grafting in, or injecting extracts of, the crushed muscle produces the symptoms, and they are not prevented by previous section of the spinal cord (to check ascending nervous impulses). It seems clear, then, that there is a chemical poison at work, probably some product of autolysis. A comparatively small loss of blood, that would not

incommode a normal animal, brings on severe collapse under these circumstances.

It is well known that extensive muscle injuries often gave rise to shock in the war, and that early amputation might save the patient's life. Too much importance must not be attached to this, because it has slowly become recognized that gas-gangrene infection was common and early, produced shock-like symptoms, and specially affected damaged muscle.

Whilst it is admitted that absorption of products of autolysis after crushing may be a contributory cause of the clinical picture we know as shock, it does not seem possible that this can be the main factor. Patients may exhibit the most typical symptoms, leading to fall of blood-pressure and death, after a gunshot wound of the abdomen, a Wertheim hysterectomy, or an amputation at the hip-joint, but in none of these is there much opportunity for absorption of crush-products. Crile some years ago crossed the circulation of two dogs by leading the carotid arteries and jugular veins of one to the other, and found that signs of shock were only induced in the traumatized animal. Lindsay and I injected 10 c.c. of the blood of a wounded man, just dead of shock, into a rabbit, which was none the worse for it, though 10 c.c. is a large dose for an animal of that weight.

Dale and Laidlaw show that a condition resembling shock may be induced in animals by poisoning with histamine. There is a fall of blood-pressure and a concentration of the total blood-volume. The

reduced pressure is not due to any failure of the heart or relaxation of the arteries—indeed, the arteries are contracted—but to a paralytic dilatation of the capillaries, so that much of the blood is withdrawn from the functioning circulation and pooled, as it were, in a backwater. The limbs swell in a plethysmograph, and the intestines are reddened. The red cell-count may rise to 13 million, and hæmoglobin 140 per cent. The total blood volume by the 'vital-red' method is greatly reduced. Local application of histamine to the cat's pancreas shows flushing and œdema, but the arteries do not stand out.

There is a double effect—a stagnation of the corpuscles in the capillaries, and an exudation of plasma from the capillaries into the tissues. In fact, the phenomena closely resemble those seen in inflammation.

THEORIES OF SHOCK.

Most of the older theories combated in previous editions of this book are now practically abandoned.

The view that the underlying cause of all the manifestations is an exhaustion paralysis of the overstimulated vasomotor centre is out of the running, because there is plenty of animal evidence that this centre can still give good reflexes; also, if this view were correct, there ought to be vasodilatation of the arteries, which is not true.

The acapnia theory, that shock is due to loss of carbon dioxide, fails because there is no evidence that such loss occurs in human cases. My analyses

showed a normal blood-content of carbon dioxide even in fatal shock. Also, shock can develop when the patient is being given ether from Clover's inhaler. Further, re-breathing, or inhalation of CO_2, does not relieve the condition.

Exhaustion of the suprarenal glands will not explain the fall of blood-pressure, because, as I have shown, in patients dead of shock the glands still contain plenty of adrenalin. Stewart and Rogoff find that during the onset of shock in animals there is no change in the adrenalin output in the suprarenal veins. Bedford, on the other hand, believes that there is a slight increase in the output, but of slow development.

During the war several observers expressed the opinion that a main factor in shock is fat-embolism. They declared that a similar clinical picture can be produced by injecting fat globules into the circulation ; and also, that in patients dead of shock, fatty droplets may be found in the capillary blood of the lungs and brain. The theory cannot be accepted. It is unreasonable to suppose that fat-embolism will occur after a gunshot injury of the abdomen, or during such a dangerous operation as Wertheim's hysterectomy or amputation at the hip-joint. Blood normally contains visible fat in animals (McKibben). My own blood, drawn for purposes of group serum testing in France, was full of fat.

As already mentioned, some believe that intoxication with crush-products from the muscles is the cause of shock. Reasons were given for allowing

that this may be an element in some cases, but that it is not the main factor.

According to Roger, it is to an inhibition or fatigue of the nerve-cells, first in the bulbar centres and later throughout the brain and spinal cord, and involving at length all the cells of the body, that we must look as the basis for the phenomena of shock. Guthrie, and also Crile, have put forward similar theories. Crile demonstrates changes in the cells of the liver and adrenals as well as in the brain. He believes that the cause of the breakdown of the cells is an intracellular acidosis.

The conception is somewhat vague. By the study of the Nissl granules we have a fairly delicate method of estimating the functional activity of various groups of nerve-cells. Although the sensory nuclei of the brain are gravely affected, and some other important nuclei and cell groups, such as the Purkinje cells of the cerebellum, Deiters' nucleus, and the vagus nucleus, may show less extensive changes, yet the bulk of the nerve-cells in the brain and cord are unaltered, unless the patient survives more than a day, or when there has been much loss of blood, when all the brain-cells suffer. The direct evidence for the theory is therefore very shadowy.

It may prove that our problems will be solved for us by the more recent conception that in shock a great deal of the circulating blood is pooled in a backwater in the dilated capillaries, and that much of the plasma escapes into the tissues; but here again there are grave difficulties. If we accept this

view, how shall we explain the pallor of the skin and lips, the inconstancy of the raised red cell-count in the capillaries, and the rarity of supranormal red cell-counts and hæmoglobin estimations? Dale's picture of the animal dead of histamine poisoning, with all its organs in a state resembling inflammation, is quite unlike the pallid appearance of a man dead of shock. These difficulties may largely be met if the evidence is confirmed that much of the blood is stagnant in the visceral and muscle capillaries, on account of failure of the *vis a tergo*, or an active dilatation of the capillaries themselves.

I do not believe that we possess sufficient information just at present to justify us in theorizing. As Sherlock Holmes used to repeat, it is wrong to draw conclusions before you have collected all your facts. One suggestion may, however, be ventured. The fall in blood-pressure may be due in part to loss of muscular tone in the voluntary muscles; this loss of tone in its turn may be accounted for by the exhaustion of the sensory nerve-cells in the brain-stem.

There is a condition well known to experimental physiologists called *spinal shock*. In monkeys, and to a much less extent in cats and dogs, a high transection of the spinal cord is followed by grave interference with the functions of the cord distal to the section. For a period varying from hours to days, no reflexes can be obtained, muscular tone is abolished, and the blood-pressure falls. In human surgery we see the like condition in spinal concussion, in which, after a blow on the back, sensation,

voluntary power of movement, and reflexes may be abolished, but after a day or two are all restored to normal.

Sir Charles Sherrington has made some important investigations into the nature of spinal shock. In the first place, he shows that it only affects those segments of the cord distal to the lesion ; thus, after an upper dorsal transection the cervical segments are not in shock. Secondly, he shows that after recovery has taken place, a second transection—for instance, in the mid-dorsal region—will not reproduce the signs of spinal shock : proving it was due to the withdrawal of influences descending from the brain or brain-stem. Again, cutting across the mesencephalon, above the pons, does not induce spinal shock. Therefore the impulses preventing it must have come down from the region of the fourth ventricle. We also know that from this same region, and in particular from the central nuclei of the vestibular nerve, descend the impulses which give rise to excess of muscular tone. A transection of the mid-brain causes decerebrate rigidity of the limbs ; a second transection below the medulla abolishes the excess of tone. On this subject the writings of Sherrington and of Thiele may be consulted.

F. H. Pike, of Columbia University, has lately published a very important research on spinal shock, with particular reference to the blood-pressure. He shows that there is a certain residual blood-pressure, about 33 mm. of Hg, even after removal of the brain, provided that the cord is left intact, and that sen-

sory stimuli will raise this pressure reflexly. When the cord is totally removed there is a very great fall of pressure. Apart from removal of the cord, curare produces a considerable reduction of blood-pressure, both in normal and in spinal animals. This curare effect is not due to any action on the vessels, but to the abolition of tone of the voluntary muscles. This is in accord with the results of other workers.

Again, it is known that a high intraspinal anæsthesia induced in man by stovaine or some similar drug may give rise to a dangerous fall of blood-pressure by paralysing the lower part of the body. This risk led many surgeons, myself amongst the number, to abandon the use of intraspinal anæsthesia at casualty clearing stations.

Do we not here find another clue to our problem? The nuclei which are responsible for maintaining muscular tone are the very ones that have been shown to suffer the loss of their Nissl granules. The patient who is suffering from shock is usually found lying in a state of complete muscular relaxation. Loss of tone in the voluntary muscles will remove the support which they naturally give to the intramuscular veins and capillaries, and in a less degree to the intermuscular veins. Therefore the blood-pressure falls and the cardiac output is reduced, in spite of undiminished power of the heart muscle and contracted arteries.

It may be objected that muscular tone is reduced in various nervous diseases and under anæsthetics without a marked fall of blood-pressure; but it has

to be remembered that in the nervous affections the onset is very gradual and can be compensated, and under anæsthetics there is stimulation of the heart and vasomotor centre to counteract the loss of tone. Under ether, at any rate, the muscles may be very vigorous, as rigidity of the abdominal wall frequently reminds us. Chloroform, of course, does reduce the blood-pressure after a time.

Without venturing to formulate a cut-and-dried theory, then, one may suggest that the nociceptive impulses which bring about surgical shock do so by inhibiting or paralysing the important nuclei in the region of the fourth ventricle and perhaps in the cerebellum, which, as Sherrington and others have shown, are continually sending impulses down the spinal cord, maintaining its functional activity and increasing muscular tone. When such inhibition or paralysis takes place, the functions of the cord are greatly reduced, tone is abolished, and therefore, as a secondary result, the blood-pressure may fall. The respiratory centre, and perhaps even the vasomotor centre, share in this inhibition or paralysis; this is a very different conception from that which takes exhaustion of the vasomotor centre to be the prime cause of all the symptoms. Death is due to the reduced pressure failing to propel the blood through the capillaries and veins; so that the *vis a tergo* is no longer able to provide a proper filling for the heart, especially as the feeble respiratory movements fail to exert their important pumping action.

A very striking example of this sequence is met with in what is called 'the knock-out blow' in

pugilism, or rather, one of such blows. A vigorous drive on the point of the lower jaw in a line from the chin to the condyles is transmitted directly to the labyrinth of the internal ear, and, by way of the vestibular nerve, impulses reach the nuclei of which we have been speaking. As a result, a powerful athlete is immediately reduced to a mass of quivering, unstrung flesh, and may die outright. In a word, he is in a state of shock.

As a result of a moderate fall of blood-pressure, there is a much more marked reduction of blood-flow. Gesell showed that a fall of pressure from 124 to 84 mm. Hg in the cat reduces the blood-flow in the submaxillary gland to one-sixth. Therefore, before long all the tissue-cells of the body are suffering from an oxygen famine, and soon pass beyond recovery. The starved cells demand a local capillary dilatation, and this in its turn withdraws more of the circulating blood into a stagnant backwater.

PREVENTION AND TREATMENT OF SHOCK.

It is to be feared that in spite of all the research of workers, young and old and of all nations, we are still too often helpless in the presence of grave shock. Nevertheless, real progress has been made.

Fluids.—There is no doubt as to the value, slight but definite, of giving fluids. Probably potassium citrate is helpful, by keeping the acidosis within bounds. Saline per rectum or subcutaneously is also beneficial, but the administration should not be allowed to disturb the patient too much. Tea or coffee may help as nerve food.

Warmth.—All war experience agrees that, after a serious injury, cold much aggravates the risks to life. The patient ought therefore to be kept warm.

Sleep is of considerable value. It is well known that long wakefulness induces changes in the nerve-cells similar to those met with in shock, and that after sleep Nissl granules are restored to normal. Every effort should therefore be put forth to secure warmth, comfort, darkness, and quiet for the shocked patient. This is more important than 'fussing' him with long-continued saline injections. Whether morphia is indicated is a debatable point. Its use is strongly advocated by Crile, who advises repeated doses every hour until the respirations are reduced to twelve per minute. I have seen the method used with some success in casualty clearing stations. In one case suffering from compound fractured femur, under the care of Lieut.-Colonel Dun, the patient had been given over 2 grains of morphia in four hours; he was awake, free from pain, the pulse had improved, and the pupils were not contracted. He made a good recovery. On the other hand, it has been maintained that the reduced respirations will interfere with oxidation and so increase the acidosis. This seems too theoretical a reason to stand in the way. The moderate use of morphia in shock is certainly merciful and probably restorative, at any rate in cases where pain is extreme. It ought not to be used if the nails are blue.

Drugs.—Adrenalin is dangerous. Strychnine is certainly useless and possibly dangerous, as Crile and Lockhart-Mummery long ago pointed out.

Alcohol may give a little Dutch courage to patients with syncope, but in shock it does nothing but harm, especially after ether or chloroform has been administered, because in that case it does not even produce the brief rise of blood-pressure that precedes the longer fall. Pituitary extract was given on the theory that shock was due to arterial dilatation; the theory is erroneous, and the drug is probably useless unless there is an element of intestinal paralysis in the case; for that condition it is our best remedy. Camphor is well spoken of by some; I have little experience of it.

It will be replied to the above rather sweeping condemnation that in such-and-such a remembered incident a patient very bad on the operation-table was given strychnine, or brandy, or pituitary, and the pulse soon became better. To which the answer is, in the first place, that many remedies produce a brief stimulation of the circulation, followed by a prolonged depression; and next, that it is not universally known how common it is for patients' pulses to fail during the later stages of an operation, and then to improve greatly, apart from any drug treatment, during the stitching-up and application of dressings. It is this phenomenon which has given a fictitious reputation to strychnine and the rest in the treatment of shock during an operation.

One is almost compelled, however, to give some hypodermic remedy to pacify patients, friends, and nurses. I believe that digitalin is useful, both on theoretical grounds as a circulatory stimulant, and as a matter of experience.

Transfusion.—Intravenous saline transfusion, especially in large quantity, has a definite but very small and transient beneficial effect. It may tide the patient over a brief period, such as a critical operation. In a few hours its value is all gone.

In Bayliss's gum-saline tranfusion (6 per cent gum-acacia in normal saline) we have a remedy of proved value for cases of severe loss of blood and also for shock, but it must be given early, before the tissue-cells have suffered from the failure of the circulation. A normal quantity to introduce is about a pint, allowing fifteen minutes for it to run in. Both in animals and man it gives much more lasting results than salines, because the gum, being a colloid substance, does not readily diffuse out through the capillary endothelium into the tissues. Gum is not such an unphysiological substance as might be supposed; it consists of anhydrides of galactose and arabinose (a pentose sugar). It is certainly harmless in itself, but the sterilization must be reliable, and it is apt to grow moulds on keeping. It lasts longer than twenty-four hours, but less than three weeks, in the circulation.

Erlanger and Gasser, finding little or no benefit from Bayliss's gum in shocked animals, advise the use of a 25 per cent gum in 18 per cent dextrose; but it is very difficult to handle such a viscid solution, and the results in man are not very convincing.

Gum-transfusion, though convenient and valuable, has one defect: the fluid introduced acts merely as a passenger; it cannot give any active help to the oxygen-starved tissue-cells. Therefore it is

inferior both theoretically and in practice to blood-transfusion. The experience of the war has convinced everybody who saw it used to any extent that this is the best remedial measure in our armamentarium, certainly for the shock-hæmorrhage complex, and probably for pure shock. Admittedly it is difficult to get donors just when required; admittedly the technique is complicated; but if a method is the best, we ought to use it.

PREVENTION OF SHOCK DURING OPERATIONS.

It is difficult to produce shock in an over-transfused animal, and possibly a preliminary blood- or gum-transfusion may be of value. There is no doubt that warmth, gentleness in operating, clean-cutting instead of the pulling and tearing that Crile designates as 'carnivorous surgery', and attention to hæmostasis, are all important.

The nitrous-oxide-oxygen mixture is far superior to ether or chloroform in protecting the nerve-cells against the functional and histological changes induced by a bombardment of painful or potentially painful (nociceptive) impulses. Spinal anæsthesia did not come well through the ordeal of war; the abolition of muscular tone in the lower parts of the body allows a dangerous fall of blood-pressure. Crile's anoci-association methods are promising; the idea is to block all the nociceptive messages derived from the operated area by first exposing and injecting the main nerve-trunks with novocain. For peritoneal-covered surfaces the longer lasting

quinine-urea-hydrochloride is used. For some years I have mopped all suture-lines in gastro-intestinal surgery with this solution, and dipped the suture in it. This greatly reduces reflex gastro-intestinal paralysis above the part operated on, and in consequence the patient does not suffer to any extent from 'gas-pains', as the Americans expressively call them. The comfort after a big abdominal operation is often most remarkable.

After a big smash of a limb, it is probably wise to keep the tourniquet on until the limb is amputated, so as to avoid absorption of toxic crush-products.

INTRAVENOUS SALINE TRANSFUSION.

During the past few years, the scope for this proceeding has been enlarged considerably by the introduction of the intravenous methods of giving salvarsan for syphilis, or ether as a general anæsthetic; and the injection of hypertonic saline solutions for cholera, introduced by Sir Leonard Rogers, has proved life-saving in many cases. The success which has attended its use in the treatment of shock, and especially of collapse after hæmorrhage, has caused it to be used more and more extensively for these conditions. At the same time, some very serious drawbacks, in a degree avoidable, have come to light, and with these we must now deal.

We need barely mention the difficulty of finding and introducing the cannula into the vein, the danger of injecting air-bubbles, and the necessity, when the solution is made up in a private house, of using cooking salt, and not a table salt diluted with farinaceous

or other material. More care is necessary than is usually taken to see that the temperature at which the fluid *enters the vein* is correct ; that of the saline *in the funnel* may be many degrees higher, especially at first. It is easy to let the solution flow over the bulb of a thermometer before introducing the cannula. Then, again, the proper strength of sodium chloride (0·9 per cent ; a teaspoonful and a half to the pint) must be employed. It is far more physiological to use Ringer's fluid, containing calcium and potassium salts as well, with a little dextrose added to act as a foodstuff. Compressed tablets of the correct composition are upon the market. This fluid approximates more nearly to that of plasma, and is capable of maintaining the life and activity of the tissues much longer, than simple saline.

There are two dangers which may follow the transfusion. The first depends upon the water, and the second upon the salt. Wechselmann in Germany, and Hort and Penfold in England, have pointed out that water supposed to be sterile usually produces shivering and fever in animals, and frequently in man, after intravenous transfusion or subcutaneous injection. In Wechselmann's cases this was usually due to actual contamination with bacteria during the days or weeks that the water was left standing after distillation. The English observers found that although water just distilled and collected in a glass retort produced no fever, yet within a few days after standing in sealed sterile vessels it acquired the property of giving rise to fever, and that in spite of boiling or filtration through a Berkefeld filter

immediately before use. In some cases the temperature was high, but not fatal unless quite unsuitable injections were given.

Another danger depends on the salt used. The total quantity injected may be very large—10 grm. or more. A condition of hydræmic plethora is likely to be induced, that is, a *dilution* and *increase in the total volume* of the blood. As Lazarus Barlow has shown, the specific gravity at once falls (e.g., from 1·064 to 1·054). The kidneys and lymph-channels promptly excrete the excess of fluid, and in many cases overshoot the mark, so that eventually the specific gravity may be 1·067, signifying of course that the blood is less in bulk and more concentrated than it was before. This does not occur if the supply of fluid is kept up by further injections, or saline given by the bowel.

If the kidneys are not capable of excreting the water and salt quickly enough, some degree of dropsy may occur, and, as the Grünbaums have pointed out, this may take the form of fatal œdema of the lungs, which has frequently been described as following saline transfusion, especially in patients with nephritis. The Grünbaums consider that the use of ether as an anæsthetic helps to determine the occurrence of such pulmonary œdema. If the salt solution injected is too concentrated, a greater degree of hydræmic plethora is induced, and the risks of pulmonary œdema are increased; naturally it is more likely to occur after a large injection than a small one.

To obtain the best results and the fewest fatalities, not more than thirty or forty ounces of freshly

distilled water, collected in a sterile glass vessel, should be injected. In this a powder having the composition of Ringer's fluid, with dextrose, should be dissolved. The powder must be sterilized or the solution boiled. The transfusion must be made slowly, and at a suitable temperature (100° F.), and it should be followed by saline injections per rectum to avoid the reversal of the effect. If Bright's disease is known to be present, the treatment should not be used.

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CHAPTER VIII.

RECENT WORK ON THE FUNCTIONS OF THE STOMACH AND INTESTINES.

MOVEMENTS OF THE STOMACH — MOVEMENTS OF THE INTESTINE—SENSATION IN THE ALIMENTARY CANAL—VARIATIONS IN THE GASTRIC JUICE—THE BILE—ABSORPTION IN THE COLON.

IT is true in a very special degree concerning the stomach and intestines, that we have learned much about the physiology of animals, but little of the functions of man. What is particularly needed at the present time for a better understanding of the processes that take place in the alimentary canal is more study of human material. Happily, during the past ten years a considerable amount of knowledge has been gained, but much still remains obscure; and especially we need information as to the relations between the functions of one part of the canal and another.

MOVEMENTS OF THE STOMACH.

There are several methods of studying these in man. One is by examining with the *x* rays after giving a barium (or bismuth) meal. Watching with the fluorescent screen is more informing than taking plates. Or, one may pass a stomach tube at intervals

and draw off the contents until the viscus is empty. Or, a rubber ball and tube (like that often used by photographers to release the shutter) may be swallowed, and the upper end of the tube attached to Marey's tambour. Many valuable observations have been made by this method by Carlson in America.

Studied by the *x*-ray method, the stomach is found to present a good deal of normal variation, and two types may be recognized, with various intermediate grades. There is the 'steerhorn' type, in strong, sthenic individuals, with a wide costal angle; the stomach is rather small, shaped like a cow's horn, and not dropped (Carman). In persons with a slack abdominal wall and narrow costal angle, the stomach is of the 'asthenic' type, shaped like a fish-hook, and often dropped down to the pelvis when the patient is standing. The old theory of a bilocular stomach, with a distinction between the cardiac end and the pyloric antrum, is now given up.

After an ordinary meal, movements of peristalsis start, usually about the middle of the cardiac reservoir, and advance in regular waves towards the pylorus, which remains tightly closed. The fundus does not show peristalsis, but exerts a steady pressure. In man, the waves are about three to the minute, and keep on so long as there is food present. Ordinarily one only sees indentations on the greater curvature; but if the stomach is contracting vigorously, there may be big waves on both curvatures almost meeting. If the pylorus is closed or obstructed,

an ebb can be seen receding from it after each wave. The consequence is that the gastric contents become thoroughly mixed with the digestive juices. After a while, when these contents are sufficiently acid, the pylorus begins to yield momentarily at intervals, and to let the food through into the duodenum. Whilst acid is present on the far side, the sphincter remains closed; when it is neutralized it opens again. Thus acid in the stomach opens the pylorus; acid in the duodenum closes it. This goes on until the stomach is empty. It is not certain that this observation of the physiologists holds good for man. McClure, Reynolds, and Schwartz found that the introduction of decinormal hydrochloric acid into the duodenum by means of a tube did not make any difference to the pyloric efflux as watched by the fluoroscope; nor did neutralization of the duodenal contents keep the pylorus closed. When the stomach has emptied itself, peristalsis may not cease (Hurst), but the pylorus lies open, and bile and duodenal contents pass in and out without causing any discomfort. The stomach normally empties in two to five hours: in the 'steerhorn' type rather earlier than in the 'asthenic' stomach. It is said that tickling the ribs may lead to a reflex emptying of the stomach, especially about three hours after a meal.

The effect of the principal foodstuffs on these movements must now be noticed. Water runs out at the pylorus almost as quickly as it enters by the cardiac orifice. The clotting of milk is probably designed to prevent the same thing happening;

otherwise it would run through the stomach and duodenum without giving the pepsin and trypsin time to act upon it. Carbohydrates do not stay long in the stomach; fats and proteins, however, may remain for several hours. In a normal human stomach, nothing should be present before breakfast in the morning; if there is, some stasis must be occurring.

A number of investigators at the Jefferson Medical College, Philadelphia, have made some interesting observations on the time taken to empty the stomach, and the total acidity developed, after partaking of various forms of meat. They find, like the radiographers, that there are two types of human stomach, the rapid and the slow, and that there may be as much as an hour's difference in the emptying time. The method employed was to pass a stomach tube to empty the stomach, then take the meal and leave the tube in place until the washings showed that everything had passed on into the duodenum. A great number of experiments were made on many subjects, and the meat was cooked in every conceivable way.

Beef takes $2\frac{1}{2}$ hours to leave the rapid type of stomach; $3\frac{1}{2}$ hours in the slow type. The acidity rises to equal 120 c.c. of decinormal alkali. Whether the meat is roast, boiled, or corned, the times and acidity are the same. Pork takes a little longer, and the acidity is rather less (on account of the fat mixed in with the meat fibre). Bacon and fried ham digest slowly—4 to $4\frac{1}{2}$ hours—and the acidity is low. Lamb is in all respects much the same as beef.

The rapid type of stomach deals with eggs, however cooked, in 2¼ hours, the slow type in 3 hours. The acidity only reaches 80. If the egg is cooked with fat, the time is a little longer. Raw egg-white is out of the stomach in 1½ hours.

Emotion hinders peristalsis. Excitable cats, especially males, often show no movements for a long time after being tied down; Cannon did most of his work with placid elderly female cats. Fever, such as distemper in dogs, also diminishes the movements; in fact food may lie all day without moving. There is great delay after abdominal operations. If the jejunum is cut across near the upper end and then sutured, the pylorus remains tightly closed for about six hours, even if food is given.

Solid pellets, such as bismuth pills or lead shot, are not allowed to escape readily, and a bread mixture, which usually began to pass out into the duodenum in fifteen minutes, was retained for forty minutes when the pills were given with it. This probably occurs when hard indigestible articles are taken as food, and the powerful peristalsis against a spasmodically contracted pylorus causes pain.

Hyperchlorhydria in animals induces prolonged spasm of the pylorus, lasting over many hours, because the acid in the duodenum takes so long being neutralized.

If the stomach, in man, empties in less than two hours, it must be regarded as definitely abnormal, and due either to a transient diarrhœa, or to achylia gastrica (i.e., absent HCl in the gastric juice), or to duodenal ulcer, or to a cancer holding the pylorus

open. In such a case, I have seen a full barium meal run out into the small intestine in fifteen minutes, without any peristalsis.

If, on the other hand, there is retention over six hours, some lesion must be present, but not necessarily in the stomach. A reflex from an abnormal appendix or gall-bladder, or chronic intestinal stasis, may give rise to considerable delay. In gastric ulcer or in cancer of the stomach, and in cases of stenosis of the pylorus, the meal may remain for twenty-four hours or longer, and one sees periods of violent peristalsis alternating with periods of exhaustion and quiescence. Flicking the upper abdomen will start a new assault on the pylorus.

In cases of gastric ulcer, there is often a persistent ring-contraction due to spasm, which is not abolished by atropine. In cases of reflex dyspepsia, the primary fault being in the duodenum, appendix, or elsewhere, any such spasm is less persistent, and is abolished by full doses of belladonna.

A very important function of the musculature of the stomach, both in health and disease, is the maintenance of a state of tonus. When the organ is partially filled, there are no empty spaces in it. The wall does not behave like an elastic bag, and yet it accommodates itself, when it is functioning normally, to the bulk of its contents. As we have seen, wide variations in this tone are compatible with health, and both the size and the position of the stomach in the abdomen depend upon it. The sensation of fullness so often complained of by patients, and the desire to bring up wind, probably

are due to some failure on the part of the muscles of the stomach to accommodate its size to its contents without undue pressure, and in many cases this failure is due to a nervous reflex having its original stimulus in the gall-bladder or the appendix.

MOVEMENTS OF THE INTESTINE.

We have always known that the small intestine is continually in movement, the main character of the movement being an onward sweeping wave called peristalsis, carrying the bowel contents from the stomach to the colon. Peristalsis consists of a wave of relaxation pursued by a wave of constriction. It is controlled by a purely local mechanism, and will go on after all nerves have been severed, or even after taking the intestines right out of the body. After cutting the bowel across, the wave is stopped at the point of division. Fortunately for the practice of end-to-end anastomosis of the intestines, any bowel contents which may be pushed through the junction will start a fresh wave of peristalsis on the distal side of the union. Though the movements are not dependent on nerves, they can be influenced by the central nervous system, as every one knows who has suffered from an attack of 'exam-funk diarrhœa'. The vagus stimulates peristaltic movements; the splanchnic nerves inhibit them. In the small intestine peristalsis is normally only from stomach to colon, and a barium meal makes the journey in about four hours. There is a sort of pendulum swing-swang of whole loops of bowel going on at the same time, and also a segmentation movement, breaking

up the alimentary contents into short lengths. In the jejunum, as seen with the *x* rays, the contents present a characteristic feathery appearance (the observer must be thoroughly 'dark-adapted' to see this); in the ileum this is not usually visible. In the large intestine the conditions are very different, and have an important bearing on certain operative procedures. The movements in man may be studied by skiagraphy after barium meals or barium enemata, and by observations on patients who have suffered various forms of colostomy, ileosigmoidostomy, and exclusion operations. When the abdomen is opened, intestinal peristalsis soon comes to an end on account of the rapid loss of CO_2 from its walls. Saline solution saturated with CO_2 restores the movements to normal.

The movements of the circular coat of muscle are controlled by the nerve-cells in the ganglia of Auerbach's and Meissner's plexuses. These ganglia are very interesting structures. They show large isolated polygonal nerve-cells closely packed round with small ovoid cells which appear to be of a primitive nature, neither nerve nor muscle, and showing the most beautiful myoneuronal junctions where the unstriped muscle-fibres pass in small bundles actually into direct continuity with these ovoid cells at some point or other in the ganglion, which elsewhere is enwrapped in fibrous tissue. The movements of the longitudinal coat are apparently myogenic, and may persist after the nerve-endings have been put out of action by atropine.

In the cæcum and the ascending, transverse,

descending, and pelvic portions of the colon, the motor functions are involuntary, as in the small intestine, but with some striking differences. The food residue does not travel at a slow regular rate of progress through the large intestine. It lingers in particular localities, such as the cæcum and ascending colon, the middle of the transverse colon, the pelvic colon, and the rectum, for hours at a time, and although it has been denied, it is certain that antiperistalsis occurs. In the small intestine antiperistalsis is rare and pathological. Three or four times a day, especially by a gastrocolic reflex after taking food, the intestinal contents are carried onwards for several feet by massive waves of peristalsis, of which the patient is normally quite unconscious. These waves have been witnessed by a number of *x*-ray workers. I have seen it myself once recently. Tyrrell Gray has observed the same phenomenon with the abdomen open and the patient under light anæsthesia; the contraction gives the impression of extraordinary power, and the long loop of the transverse colon becomes completely straightened out by the shortening of the longitudinal bands of muscle. Here we have the explanation of 'lienteric' diarrhœa immediately following a meal, and also the pain after food met with by some sufferers from chronic constipation. The bismuth meal normally reaches the pelvic colon in eighteen to twenty-four hours.

The existence of currents of antiperistalsis is very important surgically. Many patients on whom ileosigmoidostomy (turning the ileum into

the pelvic colon or sigmoid) has been performed for growth of the ascending colon have suffered great subsequent discomfort from the passage of gas and fæces into the blind loop of colon, from the opening into the sigmoid up into the descending colon, and so round towards the cæcum. In some cases a second operation has been necessary. In all anastomoses and excisions of the large intestine this physiological factor must be calculated upon and provided for. In some cases an appendicostomy has been performed to allow flatus to escape and to make lavage possible, but this is not very effectual. I have on several occasions, when performing an end-to-end anastomosis of the ileum to the pelvic colon to relieve obstructive conditions, exteriorized the distal stump of the ileum a few inches from the ileocæcal sphincter. More than once, especially after giving an aperient, the contents of the ileum having entered the pelvic colon have been carried by antiperistalsis round the descending, transverse, and ascending colons, forced the valve, and discharged on the surface through the stump of ileum. In most people antiperistalsis is not so strong as this, but it can be seen by barium skiagraphy sweeping the ileal efflux that has just entered the pelvic colon, up as far as the splenic flexure.

We are coming to look upon the stomach and intestines as resembling a canal system with lock-gates connected by telephone, so that the state of traffic at one lock has an influence upon the rate at which boats are allowed through the locks above and below. According to Keith, there are seven sphincters

guarding the stomach and intestines, besides one at the junction of the pharynx and œsophagus.

1. The *cardia*, at the junction of œsophagus and stomach, contains a special type of muscle called 'nodal tissue'.

2. The *pylorus*, with a node near the bile-duct.

3. The *duodenojejunal flexure*, with a special nerve-supply.

4 The *ileocæcal 'valve'* with a long tubular sphincter just above it, with a special nerve-supply from the vagus and splanchnics.

5. The *transverse colic sphincter*, just below the pylorus, with a special nerve-supply.

6. The *pelvirectal*, at the junction of the pelvic colon and rectum.

7. The *anus*.

The *clinical* evidence for some of these is at present slight or wanting, but concerning four or five there is no room for doubt.

Hurst has recently drawn attention to the functions of the ileocæcal sphincter, which guards the passage through the ileocæcal 'valve', and delays the entry of the contents of the small intestine until time has been allowed for proper absorption of foodstuffs. Skiagraphy after a barium meal shows that the vanguard of the meal reaches the cæcum in four to five hours, but that the rearguard is held up by the sphincter until about nine hours after the food was given. In cases of chronic appendicitis this sphincter may remain tightly contracted for as long as twenty-four hours—a highly significant observation, as we shall see. Whenever food is taken into the stomach,

the ileocæcal sphincter is reflexly inhibited, and some contents of the ileum pass through.

A patient was recently under my care who had had the cæcum opened more than a year before to cure chronic dysentery; the wall of the cæcum turned inside out and prolapsed through the wound, exposing the ileocæcal 'valve' on the surface so that its action could easily be watched (*see* Frontispiece). It was quite obvious that there was a raised ring of muscle constituting a sphincter guarding the orifice, and in ordinary this sphincter was closed. Within a few minutes of swallowing food the sphincter relaxed and lay quite patulous for half an hour or more after the meal had been finished, and jets and squirts of orange or brown liquid fæces were poured through the orifice, a teaspoonful or two at a time, every minute or so, by the peristalsis of the ileum. This peristalsis could be seen going on through the thin everted cæcal wall all the time; it never stopped even when the valve was not working. There were never any movements of the cæcum. This accords with what one sees on screening by the aid of *x* rays; the small intestine is never still, but the large intestine is usually quiescent. Applying acids or alkalis to the cæcal mucosa did not alter the efflux in any way. Pinching the cæcal wall would not start an efflux, but delayed it to some extent when it was already active. Similar cases have been described by Macewen and by Rutherford. In Rutherford's patient it was observed that rectal enemata caused great activity of the ileum with opening of the sphincter; this did not obtain in my case. Thus we see that the

ileocæcal sphincter is reflexly influenced by swallowing, and perhaps also by relaxation of the colon sphincters; indeed, it would appear that the passage of food into the stomach is the normal stimulus for emptying the contents of the distal coils of the ileum into the large intestine. The efflux did not entirely cease when no food was being taken, but one might watch for half an hour without anything occurring. Getting up and walking about led to greater activity. There was no great loss of flesh.

When for any reason, such as chronic intestinal stasis, bands or kinks, growths of the colon, or chronic appendicitis, the passage through from the ileum to the cæcum is delayed, there is also delay, up to twelve or twenty-four hours, in emptying of the stomach. When the cause of irritation or mechanical block in the ileocolic region is removed, proper emptying of the stomach in the normal time is soon restored. I have several times verified this by barium skiagraphy after operation.

The ileocæcal 'valve' is after all a valve, though its principal function is as a sphincter. In ordinary, enemata do not pass it, but they can often be made to do so. The incompetency can be demonstrated by watching a barium enema entering the ileum under the *x* rays.

Before turning from the motor functions of the intestines, another experimental observation merits attention. Pawlow found that strong stimulation of any sensory nerves might cause, in dogs, prolonged reflex arrest of peristalsis. Injury of abdominal viscera was particularly likely to do so. Cannon and

Murphy have shown that even gentle manipulation of the bowel causes cessation of all intestinal movements for three hours or more. The condition might be described as 'intestinal shock'. It is of great surgical importance. Arrest of peristalsis, quite apart from peritonitis, occasionally follows strangulated hernia, even after successful operation ; it may accompany gall-stone colic, and it may even occur as a neurosis or in association with organic nervous disease. Some interesting cases are reported by Walton in a discussion of the subject. The milder degrees of the condition will yield to turpentine enemata and to saline purges, but there are instances in which all drugs are vomited and the block seems to be too high for enemata to act. Here we may try the effect of physostigmine (eserine) salicylate in $\frac{1}{100}$-gr. doses, given hypodermically every four hours for six doses. Our personal experience of it is favourable. Walton shows by a chart that the evacuations when this drug is given after abdominal operations are much more frequent than without it. It is scarcely at all aperient in health, working best when the local nerve ganglia in the intestine are thrown out of action. It is of course an old and well-known remedy, acting like pilocarpine by stimulating the nerve-endings in unstriped muscle.

Pituitary extract often works well in these cases. It is better than physostigmine. When all else fails and drastic measures are needed to get the bowels to work, I use a sort of triple attack, giving two drops of croton oil by mouth, then four hours afterwards an alum enema, and immediately it has been

injected an intramuscular dose of pituitary. This has saved four or five cases that seemed certain to die of intestinal paralysis and toxæmia.

A few further points may be summarized briefly.

Intestinal colic is due to some interference with the normal relation between the wave of relaxation and the following wave of contraction, which make up normal peristalsis.

Ordinary constipation is rarely due to any prolongation of the normal four hours taken by the bismuth meal to pass from the stomach to the cæcum. Sometimes the delay is in the whole length of the colon ; sometimes the fæces reach the rectum and pelvic colon in good time, but are retained there.

There is a condition first described by Sir Arbuthnot Lane, and demonstrated by skiagraphy by Jordan, called chronic intestinal stasis. I used to regard it as a rare disease, but the experience of the past few years has led me to believe that it is very common, but often overlooked even at a laparotomy. The symptoms form an extraordinary and most perplexing mimicry of other and better defined ailments which give rise to abdominal pain, sometimes associated with extreme wasting or vomiting. Some of my cases presented the clinical picture of gastric ulcer or cancer, others of chronic appendicitis, others of cancer of the colon, and in some patients the symptoms were indefinite. Men, women, and children are all affected. At operation one finds great distention and dropping of all parts of the large intestine, especially the cæcum, with adhesion-bands holding it up. One of these bands

is called Jackson's pericolic membrane. The appendix is sometimes pressed into service to act as a sling-band. The ileum is kinked down near its termination by another band. The duodenum is greatly dilated. In this disease the whole lock-gate system is thoroughly disorganized, and food may lie for a day or longer in the stomach. It is uncertain how far all this is due to mechanical obstruction associated with dropping of all the viscera (the kidney often drops too), or whether the nervous reflexes that govern the sphincters—the telephone installation of the lock-gate system—have broken down. If medical treatment (corsets, belts, liquid paraffin) gives no relief, operation becomes necessary in the worst cases. I have no stereotyped procedure ; sometimes it is sufficient to remove the appendix and bands ; in other cases cæcoplication gives a good result. In bad cases, hemicolectomy may give great relief, the terminal portion of the ileum, the cæcum, ascending colon, and part of the transverse colon being removed. Sir Arbuthnot Lane removes the colon.

The movements of the intestines are to some extent excited by a hormone produced after meals in the gastric mucosa, extracts of which, during digestion but not during starvation, will excite peristalsis when given by intravenous injection. This hormone is also stored in the spleen. Under the name of 'hormonal' it has been introduced into medicine, and is of value both for cases of intestinal paralysis after operation, and also for chronic constipation. A single injection is said to cure an old-standing

constipation. Unfortunately it is not always active, and there have been a few fatalities, probably due to extraneous products in the splenic extract.

As we have seen, the small intestines are in a state of incessant peristalsis. If for any reason the contents of the ileum or jejunum are unable to pass along, dangerous toxins rapidly accumulate. If a six-inch length of a dog's small intestine is isolated and closed at each end, but the continuity of the bowel is restored by end-to-end union, in spite of the fact that there is no obstruction a fatal toxæmia develops. Within forty-eight hours the contents of the closed loop are highly poisonous to a normal dog, causing low blood-pressure, low temperature, diarrhœa, and vomiting. It is stated that the toxin is a proteose (Whipple, etc.), but it does not give rise to the formation of any antibodies if injected into another animal in repeated increasing doses. One sees this condition of toxæmia only too often when the small intestine is blocked by peritonitis or mechanical obstruction. It is the authentic cause of a good many deaths after wounds or operation that are wrongly attributed to shock.

SENSATION IN THE ALIMENTARY CANAL.

In his recent Goulstonian Lecture, Hurst shows that the sensory functions of the viscera are much more limited than those of the skin. The stomach and intestine do not possess any temperature sense or any tactile sense, nor is cutting painful, but pulling on the serous coat gives rise to severe pain. The feeling of heat or cold after swallowing liquids is

appreciated by the lower end of the œsophagus. Temperature and tactile sense are quite well developed in the œsophagus, and localization is very accurate—seldom more than an inch out.

Hydrochloric acid may be poured into the stomach, either through a stomach-tube or a gastrostomy wound, without producing any sensation at all, even if the percentage rises to 0·5 or even 2, and this is true also in cases of gastric ulcer. Alcohol does excite a burning feeling. Distention of the stomach causes a sensation of fullness; the amount of distention necessary depends on the tonicity of the gastric muscles. Gastralgia, whatever its cause, is due to colicky, irregular contractions of the muscle, the pylorus remaining closed. There is often a referred pain or tenderness in the cutaneous area also. The pain of peritonitis is probably quite a different thing. Sensation in the intestine corresponds closely in its physiology to sensation in the stomach. The anal canal, however, can detect thermal and tactile stimuli.

Carlson has recently shown, in a patient with a gastric fistula, that the sensation which we call hunger is due to waves of peristalsis in the empty stomach, of which he was able to obtain a graphic record.

Carlson and his fellow-workers have made some investigation as to the exact cause of pain in gastric and duodenal ulcer. In dogs with a duodenal or pyloric ulcer induced by injecting silver nitrate into the mucosa, the peristalsis of the stomach (recorded by the balloon method) is excessive, but is not

enough to account for the pain unless the nerves involved in the ulcer were hyperexcitable (Dundon). Carlson points out that the hyperchlorhydria, and the relief given by alkalis, are usually taken to mean that the pain is due to acid irritation of the exposed nerves in the ulcer; but the pain is discontinuous ('boring') in character, it may be present when the HCl is subnormal and may be absent when there is an ulcer present with hyperacidity, and alkalis may relieve pain when there is no ulcer or no hyperacidity. Putting in acid does not increase the pain. He finds that the pains synchronize with the contractions of the stomach as registered by the balloon method or watched with x rays. These contractions need not be excessive, but evidently the nerves involved in the ulcer are hypersensitive.

The sensory nerves of the stomach are the vagi, and the splanchnic nerves, particularly those fibres which enter by the sixth to the ninth dorsal roots. This subject is referred to again in Chapter XIII (*see* p. 266).

The small and large intestines (except the rectum) are not sensitive to tactile or thermal stimuli, but are exceedingly sensitive to any dragging on their mesentery. It is a debatable point whether intestinal colic, and the pain of appendicitis or of intestinal obstruction, are derived from the stimulation of the nerves in the bowel wall, or, as Tyrrell Gray thinks from clinical evidence, from dragging on the mesentery or stretching of the visceral peritoneum.

VARIATIONS IN THE GASTRIC JUICE.

We do not know much about variations in the amount of pepsin in the gastric juice. According to Edie, in newly-born rabbits only rennin is present; in adult rabbits, only pepsin.

The amount of acid normally present as free HCl is given differently by different physiologists, some following Töpfer and relying on amido-azo-benzol as the indicator, others using the more accurate but somewhat tedious method of Willcox.*

It has been customary to take the normal quantity of free HCl as 0·2 per cent, but Panton and Tidy and other workers show that 0·1 is more accurate, after a standard test-meal. The total gastric acidity is about 50 c.c. of decinormal acid, using 100 c.c. of the gastric juice to make the test. The same quantity of juice contains enough free HCl to neutralize about 30 c.c. of decinormal alkali. The indicator for the total acidity test is phenol-phthalein, and for the free HCl either Töpfer's reagent, or phloroglucin and vanillin, which is more accurate.

The *total acidity* of course includes lactic acid and any other fermentation acids, also acid phosphates, and is of no great importance.

An interesting self-regulating mechanism of the acidity of the gastric juice has recently been described. As secreted, in animals and man, the hydrochloric acid is as much as 0·5 per cent; but it is neutralized, partly by food and partly by the

* *Lancet*, 1905, i, 1566.

regurgitation of pancreatic and intestinal juices, down to 0·2 or 0·1 per cent, which is the optimum, and in health it is maintained at this standard. In hyperchlorhydria this regulation breaks down, and the acidity approximates to 0·5 per cent.

By whichever method the estimation is made, it would appear that diet exercises little or no effect on the percentage of active hydrochloric acid, although it so markedly affects the pepsin. Nevertheless, the percentage of acid is liable to change, and the changes are of great value for both diagnosis and treatment.

Increased relative amount of HCl is particularly common in duodenal ulcer, so much so that an analysis of a test meal is of diagnostic importance. It is less constantly seen in gastric ulcer, and, as has recently been pointed out, in many other affections of the alimentary canal, such as appendicitis. It is probable that the cases which have been diagnosed as simple hyperchlorhydria have usually some latent disease, if not in the stomach or duodenum, then in the gall-bladder, kidney, or appendix, and removal of the offending organ will cure the hyperchlorhydria. The symptom characteristic of such a condition is 'hunger-pain', that is, a feeling of gnawing of the stomach, which may be only a discomfort or may amount to positive pain; it occurs two or three hours after a meal, and is relieved by food or alkalis. It is probably due to the spasmodic contraction of the pylorus set up by the long persistence of the acidity on the duodenal side. Another view is that it is caused by incipient self-digestion of the stomach.

This is normally guarded against by an antipepsin in the mucous membrane reversing the activity of the gastric juice; but the continual presence of an abnormally powerful combination of acid and pepsin breaks down the resistance, just as is seen in an exaggerated degree when a healthy man dies suddenly during the process of digestion; the supply of antipepsin fails with the circulation, and a big hole is dissolved through the stomach wall post mortem. It is highly probable that hyperchlorhydria is a cause as well as a consequence of gastric ulcer; certainly it determines the peculiar punched-out character which the typical round ulcer assumes. It is significant that more than one such lesion is occasionally present, as though the excessively acid juice resulting from the irritation of some initial abrasion not only had deepened that lesion into an ulcer, but had determined the formation of others also. It is again significant that the typical punched-out ulcer occurs just where the acid has access, and nowhere else—at the lower orifice of the œsophagus, in the stomach, and in the first two inches of the duodenum, while in the jejunum it is unknown except at the site of a previous gastrojejunostomy opening, and not even then unless this operation has failed to cure the hyperchlorhydria, which usually means that the orifice was too small or badly placed. A curious and suggestive symptom of hyperchlorhydria is pyrosis, a periodical copious secretion of saliva, probably designed to neutralize the acidity when swallowed.

When the hyperchlorhydria is not associated with,

or precedes, ulceration of the stomach or duodenum, the appendix or gall-bladder is probably at fault. The appendix, for instance, may show adhesions or stenosis.

Sherren found the appendix normal in only 4 out of 65 cases of duodenal ulcer, and 5 out of 41 cases of gastric ulcer. Moynihan, Paterson, the Mayos, and others have shown that the majority of the gastric and duodenal ulcers met with on the operation table are associated with appendicitis. The sequence is, first appendicitis, then hyperchlorhydria and stasis, and thirdly ulceration.

In many cases, however, of reflex stomach symptoms due to the appendix, the hydrochloric acid of the gastric juice is deficient. Chronic dyspepsia is often the only complaint in persons who have no hyperchlorhydria, show no local symptoms of trouble in the appendix, but are cured by removal of that organ. The majority of the patients diagnosed as gastric ulcer in the medical wards of a hospital, and recovering without operation, in all probability have no ulcer at all, but only reflex gastric symptoms following on gall-stones, movable kidney, or appendicitis. In 20 per cent of the patients with symptoms of gastric ulcer operated on at the Bristol Royal Infirmary before modern *x*-ray methods enabled us to make a more precise diagnosis, no ulcer was found. Why disease of the appendix, or gall-bladder, should cause these symptoms it is difficult to decide. It can scarcely be due to toxic absorption, as the appendix may be quite fibrotic. Perhaps the simplest explanation is that the ileocæcal sphinc-

ter remains tightly closed and produces reflex delay in emptying the stomach, with occasional mid-gastric spasm. In other cases there may be hyperchlorhydria as a nervous reflex. In chronic intestinal stasis the hydrochloric acid in the gastric juice is usually deficient. There may be all the symptoms of gastric ulcer, but the pain usually comes on sooner after food, or persists all the time. Reflex closure of the pylorus and delayed or irregular emptying appears to be the cause of the symptoms in this type of case.

At the present time the tendency is to pay less attention to variations in the gastric juice, either in the causation or the diagnosis of diseases of the stomach, and to attribute more importance to changes in motility, concerning which we may learn so much by *x*-ray examination. At the same time, however, the method of fractional gastric analysis has been introduced. The patient swallows a Reyfuss tube, and retains it during the period of digestion, so that samples can be withdrawn for analysis every fifteen minutes. There are two types of normal human stomach, more or less corresponding apparently to the 'steerhorn' and the 'asthenic' varieties as defined by *x* rays. In the first, the acidity rules higher, and reaches a maximum in one and a half hours; in the other and less acid type, the maximum is reached in one hour. Hydrochloric acid may be entirely absent, without any evidence of any disease, during the first hour. Bennett and Venables have shown that making hypnotic suggestions of nausea, or of anxiety (e.g., to a flying officer, that he was going

to 'crash' in enemy territory), may lead to considerable delay in the secretion of acid juice.

THE BILE.

A few points of interest may be mentioned in connection with the functions of the gall-bladder and the bile-passages, bearing on some questions connected with gall-stones and their complications.

It is obvious that the main purpose of the gall-bladder can scarcely be to store the bile. Thirty ounces may escape from a biliary fistula in the human subject, yet the supposed reservoir will only hold about an ounce. A much more probable theory is that it acts as a pressure-bulb, to regulate the flow into the duodenum. Animal experimentation shows that after it has been removed the ducts dilate, and the pressure, normally about 100 mm. of water, falls nearly to zero. Those species which have no gall-bladder have a very low pressure in the ducts. Fats or soaps in the duodenum evoke a reflex contraction of the gall-bladder, and lead to expulsion of bile down the ducts. This may account for the discomfort suffered by patients with gall-stones after a fatty meal.

The origin of gall-stones has been much debated, and even now the question cannot be regarded as settled. There is no doubt that in the great majority of cases, where multiple calculi composed of bile-stained cholesterin are present, the formation of stones has been preceded and determined by an infection of the mucosa, which normally contributes water, inorganic salts, and mucus to the bile.

Cholesterin deposits are by no means confined to the gall-bladder; many infected and enclosed epithelial surfaces can form them (for instance, the maxillary antrum, the middle ear, dental and ovarian cysts, hydroceles). The source of the infection is probably the bowel by way of the portal vein, the liver-cells, and the bile; in cases of splenomegalic jaundice, the spleen may be the offender. There is, however, a single pure white cholesterin stone which appears to be sterile, and in a sterile gall-bladder; it may be that this is deposited as a result of increased cholesterin in the blood. Observers differ very much as to whether there is any constant association between cholesterinæmia and gall-stones; probably there is not.

It is well known that re-absorption of bile pigment from the liver cells, by way of the lymphatics, into the blood-stream, may occur from various causes and give rise to jaundice. This may be due to organic obstruction, or to a transient catarrh, or to blood-destruction; this last may be induced experimentally by giving toluylene-diamine. Van den Bergh shows that in the presence of obstructive jaundice there is so much bilirubin in the plasma that it will immediately give the diazo-reaction; in catarrhal or hæmolytic jaundice the reaction is delayed. This appears to be a test of considerable clinical value (McNee).

ABSORPTION IN THE COLON.

We may sum up the ordinary functions of the various parts of the bowel with regard to absorption thus :—

Drugs, salts, and sugars are absorbed in the stomach.

Proteins (as amino-acids), carbohydrates (as sugar), and fats (as soap and glycerin) are absorbed in the small intestine.

Water is absorbed in the large intestine.

The practical physician or surgeon is concerned with the physiologist's answer to two questions. First, Is the colon a necessary organ, or may it be eliminated with safety? Second, Can the large intestine absorb useful foodstuffs in case of need?

With regard to the first point, we are at once confronted with the fact that in some bats the colon is exceedingly short. Again, it is well known that patients with an artificial anus in the cæcum are able to keep up their nutrition. The same is true after the ileum has been cut across and turned into the sigmoid. Careful analyses made by Groves and Walker Hall under these conditions show that the normal amount of water can still be absorbed by the short piece of rectum and sigmoid traversed by the food; the fæces are not too fluid. By comparing the amount of water in the intestinal contents at the ileocæcal valve and as passed naturally in man, they conclude that the colon absorbs about 10 to 20 per cent of water from the fæces. Bacteria make up nearly half the weight of the fæces as passed normally. Treves, Lane, and others have excised almost the whole colon without the patient's nutrition suffering.

We conclude then that the colon is not a necessary organ. If, however, a permanent artificial anus is

made in the ileum more than 12 to 18 inches away from the ileocæcal valve, absorption is inadequate, and the patient dies of starvation. He will, however, live for a long time if plenty of fluid is given by the rectum. It is sometimes good treatment in a case of acute intestinal obstruction, with extensive paralysis of the coils of the small intestine, to make a temporary opening into the jejunum, to allow time for the paralysis to recover.

Turning to the second question, it is scarcely necessary to call attention to its very great importance. If the colon cannot absorb a reasonable quantity of foodstuffs, the whole theory of feeding by nutrient enemata would collapse.

In the experiments described above, Groves and Walker Hall found that the absorption of nitrogen and fat by the colon was so small as to be negligible. Laidlaw and Ryffel, analysing the urine during rectal feeding, found that the nitrogen output corresponded pretty closely to the published figures for professional fasting men at the same date of starvation; the enemata used were, however, not particularly suitable, consisting of the whites of nine eggs, six ounces of raw starch, and twenty-four ounces of peptonized milk. The albumin and starch were probably not touched. Langdon Brown found no difference in the urea of the urine, whether the patients were given peptonized milk or normal saline. Careful analysis of the figures given by Boyd and Robertson, and also a number of observations made by the present writer, furnish convincing evidence that, as measured by the standard of the nitrogen

output in the urine, the absorption of nitrogenous foodstuffs from the rectum is practically nil.

Sharkey and others claim that a good deal of nitrogen can be absorbed by the rectum, basing their findings on the analysis of rectal washings ; but this method is open to criticism, as sometimes, in spite of washing out, the patient may pass an enormous putrid evacuation, showing that lavage was not effectual.

Now this failure to absorb might be due to one of two causes. First, it may be that the large intestine has no power of absorbing nitrogenous foodstuffs in any form. Second, it may be that no erepsin is present in its secretion, so that there are no amino-acids formed from the peptone of the enema. The crucial experiment is, Can amino-acids be absorbed ?

To determine this the writer, with Dr. Bywaters, has made by the Kjeldahl method daily analyses of nitrogen in the urine in patients to whom enemata were given, either of milk pancreatized for twenty-four hours so as to convert most of the protein into amino-acids, or, in other cases, of synthetic amino-acids (Merck). Usually ordinary ward nutrients, peptonized for twenty minutes, were given for a few days first, and then the amino-acid preparations used instead. In each of five patients the nitrogen output in the urine was greatly increased by the use of amino-acids in the nutrients. Figures of two such cases are given in the Appendix.

We conclude, therefore, that amino-acids can be absorbed, and that we may hope to give nourishment

to patients by rectal injections of milk pancreatized for twenty-four hours, although ordinary peptonized milk is a failure.

It is quite certain that dextrose can be absorbed from the rectum, because it will cure acidosis when given in this way, and also it will raise the respiratory quotient by increasing the amount of CO_2 expired. Tallerman, very recently, has demonstrated that the blood-sugar content, estimated by Maclean's method, may be increased by giving glucose enemata. Taken by the mouth, the maximum increase in the blood was 0·06 per cent, which was reached in half an hour; given by the rectum, the rise was 0·03, and was attained more slowly, after eighty minutes. Boyd and Robertson showed that practically no sugar can be recovered from the rectal washings of a patient given peptone and sugar enemata, although peptone is always returned. Lactose appears not to be absorbed; it fails to control acidosis.

It is very difficult to obtain evidence as to whether fats are absorbed. In a patient who had a fistula of the thoracic duct, only from 3·7 to 5·5 per cent of the fat given per rectum was recovered from the fistula.

In another patient the thoracic duct was blocked and a lymphatic vessel had ruptured into the urinary passages, so that most of the fat absorbed by the lacteals escaped into the urine, which became milky after a fatty meal (chyluria). There was no chyluria when all fats were stopped by mouth and nutrient enemata containing milk administered.

It must not be supposed that rectal feeding supplies absolute rest to the stomach. It may be observed in patients with a gastrostomy wound that each nutrient enema excites a reflex flow of gastric juice.

Those who believe in the possibility of feeding patients satisfactorily by nutrient enemata usually rely upon some incorrect published analyses by Ewald, an observation by Leube that a dog can be kept alive for many months by injections of chopped meat and pancreas (this method causes toxic symptoms in man), and the remarkable fact that the weight may be fairly well sustained at first. This happens even if nothing but water is given, and is due to the fact that the patients, usually sufferers from hæmatemesis, are exsanguinated to start with and greedily absorb water. Patients have been kept alive on nutrients for several weeks, but it is well known that there are sometimes sudden and unaccountable deaths. It must not be forgotten that if water is supplied life will usually be prolonged for a month with no food at all, and in one instance a man was alive after sixty-four days of complete starvation. If water also is withheld, death takes place in about a week ; but a girl buried in an Italian earthquake lived eleven days without either food or drink. The remarkable survival of Alderman MacSwiney for over two months is fresh in our memories.

We conclude, therefore, that feeding with nutrients composed of peptonized milk is sheer starvation, but that better results may be obtained with

enemata composed of dextrose and long-pancreatized milk.

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CHAPTER IX.

THE GENITAL GLANDS.

FUNCTIONS OF THE OVARY—FUNCTIONS OF THE TESTIS—HERMAPHRODITISM—CONTROL OF THE GENITAL GLANDS BY INTERNAL SECRETIONS—THE SECRETION OF MILK—THE OVUM—CHEMICAL DIAGNOSIS OF PREGNANCY.

STUDENTS of physiology do not usually devote as much attention to the functions of the reproductive apparatus as the clinical importance of the subject demands, and writers of text-books have been in the habit of relegating it to a very brief chapter at the end of the book.

FUNCTIONS OF THE OVARY.

The functions of the ovary may be classed under three headings: the production of ova, the control of menstruation, and the internal secretion. The corpus luteum may have other functions, to be considered separately.

The ovary shows on microscopical examination ripe and unripe ova, the former enclosed in the Graafian follicles, corpora lutea of varying age, and certain glandular interstitial cells which probably furnish the internal secretions, and are supposed to be the starting-point of multilocular cystic disease of the ovary. We shall consider menstruation first.

Menstruation.—We shall not discuss the histology of this process, except to say that the mucous mem-

brane of the uterus becomes greatly thickened and engorged every month, and hæmorrhages take place into it which carry away parts of the superficial layers. According to Blair Bell, a large quantity of calcium salts accumulates in the blood, which menstruation removes, menstrual blood being very rich in calcium, up to thirty times the amount present in circulating blood. In the male, the amount of calcium in circulating blood is very stable; in the female, during the years of sexual activity, it rises before a period, and then falls, rising again during the next month.

There is no doubt that menstruation is determined by an internal secretion from the ovaries, and when these are both removed it almost invariably ceases.

Marshall and Heape have shown that the process is by no means peculiar to the human subject. In a great variety of animals, such as deer, dogs, sheep, and monkeys, there is a regular cycle of changes leading up to the œstrum or rut, and after great overgrowth of the mucous membrane of the uterus there is a mucous and often blood-stained discharge, followed by a brief period of fertility.

Apparently the reason for the occurrence of menstruation is connected with the great demands that pregnancy makes on the mother. She has to make perfect by practice a mechanism for supplying at short notice all the chemical substances which might be required for building up a baby; calcium for the bones, for instance. It may be compared with an arsenal preparing for war in times of precarious peace. But all the materials cannot be stored

indefinitely, so they are discharged—sold off, as it were—every month.

There is some relation between the calcium metabolism and the functions of the ovaries. When these are removed, in cats, the total excretion of calcium by the body (urine, etc.) is halved. In the disease called osteomalacia, rather rare in this country, the available calcium is not sufficient for the mother and child, due more probably to some ovarian fault than to an actual lack in the diet, and the bones of the mother during pregnancy become soft, deformed, and decalcified. Removal of both ovaries has a remarkable curative effect. An English example has recently been published by Hellier, of Leeds. These patients usually have many children.

Each menstrual period is apparently the result of two factors at least, the calcium value of the blood, and the internal secretion of the ovary. There is some evidence that pressure on the ovary will determine a 'period'. Amenorrhœa is the rule when calcium is deficient, and in this type of case calcium therapy will cure it (Beckwith Whitehouse). Much of the material lost, of course, is secretion from the uterine glands; in fact, there may be little or no blood, but merely a flow of this secretion by itself. Ordinarily there is blood, which has been clotted, and then redissolved (fibrinolysis) by the contents of the uterine secretion.

Profuse menstruation is usually attributed to 'endometritis'; but this is seldom true. An infection of the uterine mucosa commonly causes a flow of pus, not blood, though acute gonorrhœa may give rise to

both. Sometimes, of course, hæmorrhage is due to actual disease, such as retained products of conception, polypi, growths, and the like. There are, however, many cases in which this does not obtain, and there is a physiological menorrhagia due to impaired co-ordination of the ovary, the uterine mucosa, and the ductless glands. This is especially seen at puberty, and near the menopause. Whitehouse distinguishes three types. The first is associated with *hypertrophy of the endometrium*, readily determined by the curette; it may be $\frac{1}{3}$ inch thick. As the uterine secretion is copious, clots are rarely passed. If curetting does not cure, it will be necessary to try radium or x rays, to abate the functional activity both of the uterus and of the ovary. If this fails, hysterectomy may be needed.

In the second type, there is *atrophy of the endometrium*, and the curette brings almost nothing away. The patient is usually near the menopause, and the ovaries are still active, but the endometrium is already senile, and does not furnish enough material to lead to immediate clotting and fibrinolysis of the blood, so that hæmorrhage is severe, and the blood clots only after it leaves the endometrium. Therefore clots *are* passed. The same may occur in young girls. Curettage does no good; radium may be used cautiously, taking care not to overdo it in the young. Mammary or thymus extract, being antagonistic to the ovary, are worth a trial. Blair Bell advises pituitary extract or adrenalin for the same reason. Hysterectomy remains as a last resource.

In the third type, there is *hyperactivity of the*

endometrium, part of which is in the pre-menstrual and part in the post-menstrual stage of the cycle. It usually dates from a pregnancy, and the hæmorrhage, though prolonged, is not generally severe. If treatment is necessary, thyroid extract or curettage may help.

Ovulation.—The rupture of the Graafian follicle and shedding out of the ovum is called ovulation. It has been much debated whether the time of ovulation coincides with that of menstruation in the human subject. In the animals above described no doubt this is true, and in the human subject the age-limits of fertility and of menstruation are approximately the same. Nevertheless the relationship cannot be exact, because pregnancy has occurred before the first menstruation, and observations on the ovaries during abdominal operations at various times in the menstrual cycle show that although ovulation commonly takes place at about the same time as menstruation, this is by no means invariable (Lawson Tait, Blair Bell). If it were so, the Jewish race would probably have become extinct, because, in obedience to the Levitical law, amongst strict Jews husband and wife live apart during and for some days after menstruation.

There is some evidence that in primitive man there was only one annual period of special fertility. There is a Javan tribe amongst which all the births are said to take place in February. Many animals that in the wild state only go into œstrum once or twice a year become fertile all the time in captivity.

After bilateral removal of the ovaries the patient is of course sterile and menstruation ceases, but in a few rare cases, apparently owing to abnormal outlying fragments of ovary remaining behind, pregnancy has occurred and menstruation continued.

By some mysterious chemical attraction, the shed ovum finds its way into the Fallopian tube. If one tube is blocked, the other may receive the ovum, because cases are not very infrequent of a tubal pregnancy on one side with the corpus luteum in the opposite ovary.

There appears to be in some families an hereditary tendency at each ovulation to rupture several Graafian follicles and shed out more than one ovum at a time. A case was recently reported of a woman, age 35, who had two sets of quadruplets, three sets of triplets, and five sets of twins. Her mother had twenty-eight children, and her grandmother twenty-nine, including quadruplets and triplets. In another case a woman had four twin pregnancies, her mother and aunt one each, and her grandmother two.

Internal Secretions of the Ovary.—One internal secretion controls menstruation. Another, or the same, appears to act upon the vasomotor system; when it is withdrawn by artificial removal of the ovaries or by the cessation of their function at the menopause, the patient often suffers from flushings, headaches, and other neuroses. The severity of the upset depends on the previous activity of the ovaries. In women of a pronounced feminine type, with strong sex feelings and well-developed breasts,

the symptoms may be marked. In women of a masculine type and flat breasts, they are apt to be but little in evidence.

Under these same circumstances the breasts, uterus, and vagina atrophy, and obesity may develop. The influence over breast tissue extends even to cancerous tumours growing in it; double oöphorectomy in a considerable number of cases of inoperable cancer has caused retrogression of the growth, and once or twice, apparently, a cure has resulted. On the other hand, pregnancy shortly after removal of cancerous breast usually leads to recurrence, and during pregnancy a cancer of the breast grows with frightful rapidity. Removal of the ovaries in cats leads to atrophy of the uterus; ovarian grafting checks this.

We do not possess much information as to the consequences of removal of both ovaries in little girls. A statement appears in some books that the operation is performed in Persia, and that women of a masculine type result; but this is a travellers' tale.

The symptoms of the artificial menopause following double oöphorectomy may be much relieved by grafting a piece either of the patient's ovary, or less satisfactorily that from another person, into the abdominal wall. In some cases menstruation has remained unaffected, and when the graft has been into the peritoneum, it is said that pregnancy has occurred.*

One of the most experienced advocates of ovarian

* See *Archiv. gén. chirurg.*, 1911, p. 550.

grafting is Professor Tuffier, who has used it on 250 occasions. In 20 cases in which he grafted from one woman to another, the procedure was ineffective; menopause symptoms were not abated, and menstruation was not established if the uterus had been left. Auto-transplantation was much more successful; in one woman of 18, menstruation persisted for twelve years. In one case, he had to remove the graft, and the periods ceased.

After ovulation has occurred, the Graafian follicle becomes converted into a gland containing a yellow fatty pigment, the corpus luteum. Ordinarily this is quite small; if pregnancy follows, it may reach a diameter of half to three-quarters of an inch. Apparently the internal secretion of this body determines the fixation of the ovum in the uterus, and perhaps also the subsequent overgrowth of that organ. If both ovaries are removed early in pregnancy, abortion always follows. In extra-uterine pregnancy the uterus enlarges although the fœtus is not inside it. Removal of both ovaries in animals in the later months of pregnancy does not usually lead to abortion. In the human subject it is very doubtful if this function applies; one patient went on to full term in spite of double oöphorectomy as early as the second week (Essen-Möller), and another at the sixth week.

Ovarian feeding has been tried to relieve the symptoms of the natural or artificial menopause, but the results are dubious. It is always difficult to foretell when an internal secretion will be capable of absorption through the intestinal wall unchanged.

According to Blair Bell, a combination of ovarian and thyroid extracts gives the best results. Bromides do more harm than good. Calcium salts have been used for the same troubles, and in some cases, at least, work remarkably well.

FUNCTIONS OF THE TESTIS.

The most obvious function of the testis, of course, is to produce spermatozoa, which it continues to do well on into old age.

The testis, however, contains other secretory cells between the tubules, sometimes called the cells of Leydig, and to these is attributed the production of an internal secretion. It is not uncommon for one or both testes to fail to descend (cryptorchism), and in bilateral cases the individual is nearly always sterile, but the secondary sexual characters are usually preserved. On microscopical examination the tubules are little developed, but the interstitial cells of Leydig appear to be normal. As we shall see, the evidence on this point is somewhat conflicting.

It has been much debated whether the failure to descend is the cause or the consequence of the failure to develop, and on the answer to this question depends the surgical treatment; if the first is true, it is highly desirable to find some operative procedure which will ensure the testis a permanent resting-place in the scrotum, but the evidence goes to show that this does not lead to proper growth of the gland, so we must conclude that descent fails because it is not worth while for the gubernaculum to bring down a defective organ.

When the testes on both sides are removed after puberty, the consequences are sterility, atrophy of the prostate gland, and in a few cases in old men mental impairment. The secondary sexual characters are not lost, and it is very doubtful if the dotage which has sometimes followed is really due to loss of any internal secretion or to nervous influence; most probably it is merely the consequence of a mutilating operation preying on the mind of a broken-down individual. In younger and healthier adults there is no mental change or loss of capacity.

The atrophy of the prostate is not constant, but the effects of castration have been taken advantage of to reduce the size of a prostatic enlargement causing obstruction. Ligature or excision of the vas deferens blocks the way for the external secretion of the testis, and leads to atrophy of the tubules and consequent sterility, but the internal secretion of the interstitial cells is not affected unless the main vessels of the cord are tied.

In boys, the results of castration are more far-reaching, causing not only sterility but also failure of the secondary sexual characters (eunuchism). As is well known, the operation has been practised for centuries upon the attendants and guards of the harem at Oriental courts. The beard and moustache do not usually appear, the voice is childish, the body fat, and the mental attitude to the world modified, although there is no loss of business capacity. The prostate and vesiculæ are atrophic, but there is not necessarily impotence. In cocks, testicular grafting partially obviated the effects of castration. Indeed,

it is even recorded that in a hen, after removal of the ovaries, testicular grafting caused the bird to grow a comb, wattles, and spurs, and start to crow; but this requires confirmation.

Following upon Brown-Séquard's famous contention that feeding on, or injection of, testicular extract had made him at 72 a young man again, attempts have been made, especially by vendors of expensive patent remedies, to convince the profession that the internal secretion of the testis can be taken as a rejuvenating drug, recalling the classical story of Medea's cauldron; but, as Biedl says, "exact and carefully controlled experiments with this substance have not been described". Auto-suggestion probably accounts for much of the alleged benefit.

HERMAPHRODITISM.

It is not proposed here to deal at all fully with the varieties of this interesting condition, but rather to look upon it from the physiological point of view. There are, of course, many cases with a cleft scrotum, small penis, hypospadias, and undescended testes, which present a superficial resemblance to the feminine type, and, though really boys, are apt to be brought up as girls; at puberty this gives rise to complications when the supposed girl grows hair on the face, and the voice breaks. More remarkable, but very much less common, are cases of true hermaphroditism, in which ovarian and testicular tissue are both present. In Blair Bell's case, the general appearance was feminine, and so were the external genitals; but there was a slight moustache, a mascu-

line arrangement of the pubic hair, a clitoris two inches long, and irregular menstruation. At operation, an ovary was found on one side, and a gland partly ovary and partly testis on the other; both were verified by the microscope, and photographs were published.

There is another type, and still stranger, in which the genital glands are of one sex (usually male) and the external sex organs and secondary sexual characters are of the opposite character. In Russell Andrews' patient, no one would have thought that he was not dealing with a normal woman, and a beautiful one at that, but both the genital glands removed by operation were testes, full of interstitial cells. Photographs may be seen in Blair Bell's book. This and other cases make it quite clear that the sex characters are not *simply* due to an internal secretion of the genital glands or their interstitial cells, but to hormones derived from the other endocrine organs as well. Most of these patients have an overgrowth of the suprarenal cortex.

It has been shown that what are called 'freemartins' in cattle, whose genital glands are ovaries, but the external sex organs and other characters partake more or less of the male type, are really females modified by male hormones derived from a male twin. A direct vascular connection can be traced between the two placentæ; if no such connection is present, a normal male and a normal female are born (Lillie).

CONTROL OF THE GENITAL GLANDS BY INTERNAL SECRETIONS.

Not only are the genital glands themselves the source of internal secretions, but there is a good deal of accumulating though ill-assorted evidence to show that their own activity is dependent upon chemical messengers (hormones), reaching them by the blood-stream, derived from what we call the ductless, or endocrine, glands.

What is it that makes a man masculine and a woman feminine? It used to be thought that the testis and the ovary were solely responsible. Now we know that masculinity and femininity may persist even after these glands are removed. Even more convincing is the evidence just related, that the secondary sex characters may be the opposite of those of the genital glands. The mere fact of infertility does not abolish sex, which is dependent upon the combined working of a number of internal secretions.

The Endocrine Glands before Puberty.—In young animals and in children the development of the ovary, testis, and other parts of the genital apparatus depends upon chemical stimuli received from the pituitary and thyroid glands. Experimental removal of these glands in young animals, or insufficiency diseases of either of them in man, may lead to sexual infantilism.

On the other hand, great enlargement, and therefore presumably hypersecretion, of the cortex of the suprarenal (which is nothing to do with the tumour

called hypernephroma) causes precocious sexual development of the male type. In boys this leads to overgrowth of the sexual organs, with early activity. In girls, there is enlargement of the clitoris, growth of hair on the face and the pubes, and sometimes a male type of external genitals (pseudo-hermaphroditism), but there is not premature menstruation or fertility.

Very few cases of overgrowth of the pineal gland are on record, but in some of these there has been sexual precocity in boys.

Sexual precocity in girls is not uncommon; it appears to be due to excessive ovarian secretion. In one case a girl seven years old showed precocious development and menstruation; an ovarian swelling was removed, and the signs of puberty subsided. Similar cases have since been recorded. These overgrowths of the ovary are usually malignant.

Delayed puberty in girls may be due to deficient ovarian secretion, in which case sex feeling and potency are also in abeyance, or to a mild degree of hypothyroidism or hypopituitism. It is found in gynæcological practice that thyroid and pituitary feeding may hasten puberty under such circumstances. After twenty, however, a small uterus cannot be stimulated to grow.

We have no sufficient evidence yet of the value or otherwise of feeding with the ductless glands in cases of cryptorchism with atrophic testes.

The Endocrine Glands after Puberty.—Here again deficient internal secretion of the thyroid

gland appears to be a cause of amenorrhœa, painful menstruation, and monthly pain in the breasts, and Blair Bell states that thyroid feeding cures many such cases. It is, of course, well known that myxœdema leads to amenorrhœa and sterility.

In cases of pituitary disorder also, amenorrhœa and sterility are the rule in women, and impotence in men. These are probably due to deficiency of the pituitary secretion, but this is not very clear. In acromegaly, menstruation is absent because the individual tends to conform to the male type, with big bones, coarse skin, a deep voice, and a large clitoris.

Not only do the secretions of the ductless glands influence the genital organs, but there is evidence of an effect in the reverse direction. During pregnancy the thyroid gland usually enlarges a little ; in Italy this has been taken for years as a sign of conception. The pituitary gland also shows enlargement (Erdheim and Stumme). Berry points out that adenomatous goitre nearly always occurs in single or nulliparous women.

It has already been stated that removal of the ovaries is a remedy for osteomalacia ; Bossi has advanced evidence that the same effect may be produced more conveniently by injections of adrenalin.

THE SECRETION OF MILK.

It is a very striking phenomenon that after twenty or thirty years of quiescence the mammary glands should suddenly spring into activity on the very day when the secretion is required. It cannot be due to

nervous influences, because there is no nervous mechanism controlling the flow of milk. For this reason pilocarpine does not increase, and belladonna preparations do not check, the secretion, in spite of their ancient reputation founded on analogy. It is true that when the child is put to one breast the other may pour out a little milk, but this is due to reflex contraction of the muscle about the ampullæ of the ducts. The only drug which increases the flow of milk is pituitary extract, but here again the action is probably on the muscle, not on the gland cells.

The physiological stimulus which starts the lactation is an internal secretion, but its exact origin and mode of working are not clear. Injection of extracts of fœtal animals into a non-pregnant female of the same species brings about hypertrophy and functional activity of the mammary glands (Starling and Lane-Claypon). The statement that this hormone is derived from the ovary can scarcely be true, because lactation is normal after double oöphorectomy. It is not uncommon for the rudimentary breasts, even of the fœtus, to be stimulated to a few days' activity ('witch's milk'). One of a pair of conjoined Siamese twins was recently delivered of a child, and both commenced lactating. It may be that the hormone derived from the fœtus makes the breasts develop, and its withdrawal starts the secretion ; the calcium and other nutriment prepared for the womb may be diverted to the mammary glands.

Once started, the secretion of milk is kept up by suction. When this ceases, the glands return to the quiescent state.

THE OVUM.

The epithelial and other cells of the adult are not immortal, and require frequent renewal to repair daily wear and tear. The cell-divisions bringing this about are initiated by the division of a body outside the nucleus, called the centrosome, which forms the *achromatic spindle*. A skein appears in the nucleus, which divides into V-shaped bodies called *chromosomes*, which in man are twenty-four in number. Each chromosome splits into two, forming forty-eight; of these, twenty-four pass to one daughter nucleus and twenty-four to the other. Finally, the cell protoplasm cleaves, and the nucleus returns to its resting condition. This process is called *homotype* (i.e. normal) *mitosis*.

Before it meets a spermatozoon, the nucleus of the ovum divides twice, extruding the two polar bodies. At the second of these divisions,* half the chromosomes—that is, in man, twelve—are thrown out, and the centrosome with them. This is to prevent parthenogenesis — the development of an ovum into a fœtus without a male element. In bees and wasps, where parthenogenesis occurs, this second or *heterotype mitosis* does not take place.

In the formation of the spermatozoon, also, a cell with twenty-four chromosomes divides into two spermatozoa with twelve each; the head is the nucleus, the neck the centrosome, and the tail is the cell body. Thus the fœtus starts life with twenty-four chromosomes, twelve from each parent. In

* Some English text-books incorrectly say the first,

these, according to Weissmann, is bound up its heredity, including the impulse to assume the general shape of mankind, the viscera with their proper anatomy and functions, and some resemblance to the facial appearance and even the tone of voice and character of the parents. How all this is crowded into such microscopical objects is the greatest marvel in biology.

The spermatozoon probably brings in some chemical factor, at any rate in sea-urchins and starfish, because in these animals the purely female ovum can be induced to develop into a larva by concentrated sea-water, tannin, or even violent shaking. Perhaps reproduction in these animals is not far removed from parthenogenesis, and the part played by the male in vertebrates is probably more important. Recently, however, it has been stated that stabbing an unfertilized frog's ovum will make it develop as far as the tadpole stage, but no further.

After fertilization, the ovum starts to divide into two, four, eight, and so on. Much light is thrown upon the process by the phenomenon of identical twins. Ordinary twins, due to the fertilization of two ova by two spermatozoa, are no more alike than any other pair of brothers or sisters. Identical twins probably result from the accidental separation of the two cells produced from the first division of a fertilized ovum, and the children have an identical heredity. They are exactly alike in sex, appearance, and even in deformities such as hernia. This shows that the sex and general conformation of the child

are probably fixed from the moment when a particular ovum and a particular spermatozoon meet.

The *causation of sex* is still a puzzle. It has been suggested that the left ovary gives rise to ova that will produce girls, and the right ovary generates boys, so that, as a critic remarked, it might be possible to prevent a national disappointment by removing a queen's left ovary. Differences in feeding a set of developing embryos are said to alter the proportion of males and females, but this is probably due to an excess in mortality of the one or the other. It is an ancient tradition that during a great war more boys than girls are born because the mothers are physically superior to the male weaklings who have not gone to the front; but Europe's recent ordeal lends very little support to the theory. Bearing on the view that the offspring is likely to belong to the same sex as the feebler parent, it may be mentioned that statistics have been published showing that when the man is older than the wife, male births are to female as 113 to 100 (the general average for all births is 106 boys to 100 girls); when the parents' ages are the same, there are 93·5 boys to 100 girls; and when the woman is older, 88·2 boys to 100 girls. These figures are corroborated by some, but contradicted by others. It is said that when old men marry young wives (a May and December wedding) the children are usually boys. A German writer, drawing his observations from the relation between the time of a soldier's leave, the time in the cycle of the wife's menstrual periods when he was at home, and the sex of the next child, concluded that concep-

tion just after menstruation leads to the birth of boys, and conception later to the birth of girls. None of these theories rests on any sufficient evidence. A more hopeful explanation may be based on the fact that in some invertebrates there is an additional *x* chromosome in all the female ova, but only in half the male spermatozoa; fertilization by a spermatozoon *with* the *x* chromosome gives rise to females, and without it to males. If this is true, sex is pure chance, unless variations in the health of the father affect the proportion of the two types of spermatozoa.

This has an interesting bearing on the mode of transmission of hæmophilia and pseudo-hypertrophic muscular dystrophy, which are handed on by the female, but affect only the boys in a family. Apparently the tendency resides in one of the chromosomes of the mother, and is passed on to her sons and daughters, but the *x* chromosome brings in an element which renders the tendency recessive or dormant.

Some bees are able to lay either a male or a female egg at will (Fabre).

Fertilization is supposed generally to take place in the Fallopian tubes, and it need not be immediately after sexual intercourse, as Nürnberger has twice found living spermatozoa in the tubes of patients a fortnight after the last opportunity therefor. In the rare cases of ovarian pregnancy it is evident that the spermatozoon had reached the Graafian follicle.

CHEMICAL DIAGNOSIS OF PREGNANCY.

When an unusual protein passes repeatedly into the circulation, antibodies of a ferment nature are produced to destroy it. Some protein from the placenta passes into the maternal blood-stream during pregnancy. Abderhalden has based upon this a method of serum diagnosis. Fresh placenta is treated with the patient's serum, and if she is pregnant, peptones are formed by digestion. These can be dialysed off through an animal membrane, and tested for by the biuret reaction. Though requiring extreme care in the technique, the method appears to be sufficiently accurate and reliable to be of some clinical value.

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CHAPTER X.

THE GROWTH OF BONE.

RECENT CHANGE IN OUR CONCEPTION OF THE GROWTH OF BONE—OSTEOBLASTS—INCREASE IN THE LENGTH OF BONE—INCREASE IN THE GIRTH OF BONE—FUNCTION OF THE PERIOSTEUM—THE REGENERATIVE POWERS OF BONE—APPLICATION OF MODERN RESEARCHES TO SURGICAL PRACTICE—BONE-GRAFTING—CHEMICAL FACTORS IN THE GROWTH OF BONE.

TWO closely allied problems, how bones increase in length and girth in the child, and how regeneration of new bone takes place after loss or injury, are of great interest and practical importance in surgery. Every case of separation of an epiphysis by accident, and every operation on the growing end of a bone in children, involves a consideration of the first problem; every case of fracture, necrosis, periostitis, or osteomyelitis depends for its proper understanding and rational treatment upon the second. The experimental work of Sir William Macewen, and the great interest taken in bone-grafting as a result of its use in the treatment of war injuries, and Albee's methods of dealing with tuberculous diseases of bone and joints, have necessitated a careful reconsideration of some of our conceptions of this subject.

Bone is laid down by certain cells called *osteoblasts*. In young animals, these are the direct descendants of cartilage cells. When the cartilage becomes

vascular, the cells undergo proliferation for a time; when they assume their individual maturity they cease to divide, and lay down calcareous salts all around themselves just as a coral polyp does; they are included in the midst of the bone thus formed as bone corpuscles.

Increase in the *length* of the bone takes place by the new additions at each end, where the layer of cartilage between the shaft and the epiphysis is constantly being transformed into bone; but inasmuch as its cells keep on dividing, the cartilage is not used up in the process until the age of eighteen to twenty-five is reached. It is usual for one epiphysis to unite later than the other, and in that case the increase of length is greater at this end than at the opposite, and the nutrient artery to the shaft will be directed away from the persistent epiphysis because the bone is, as it were, pushed down inside the periosteum.

So far, the results of recent investigation entirely support and amplify the older opinion. A classical experiment of John Hunter's may be quoted. He inserted two leaden shot into the tibia of a young pig, exactly two inches apart. When the animal had grown up, he found that although the bone was of course much longer, the shot were still exactly two inches apart. Evidently, then, the increase of length must have been at the ends, not by interstitial increase of the shaft.

More recently, Macewen has removed almost the whole shaft of the right radius in a young dog by the subperiosteal method, leaving the two ends. After six weeks, there was strong and vigorous growth

from each epiphysis, and, aided by a bending of the ulna, the two ends had come together, although no periosteal growth of bone had taken place. One of the epiphyses was damaged; from this end the new bony development was slenderer than from the uninjured end.

In another experiment, two and a half inches of bone with its periosteum were removed from the radius of a young dog, and metal caps fitted over the sawn extremities of the shaft remaining *in situ*. Seven weeks later, the gap was found completely bridged by bone, and the two metal caps had come together. Owing to bending of the ulna, they did not absolutely meet, but passed one another laterally.

In yet another case, the plate of cartilage between the shaft and epiphysis was removed from the radius of a young dog. The bone failed to grow at that end, and a lateral expansion of the epiphysis became attached to the ulna and stunted its growth also. This experiment is of course paralleled in man, when a separation of an epiphysis takes place, or when the growing end is removed in the excision of a joint.

Increase in the *girth* of bone used to be attributed to the periosteum. Between it and the bone, osteoblasts are to be found in young animals, and these lay down ring after ring of concentric lamellæ. If the developing animal is fed with pigment, such as madder, for a short period, there may be found months later a buried pigmented ring of bone which was laid down at that time. Another classical experiment we owe to Duhamel (1739), who buried a silver ring under the

periosteum of a young animal, and found some time after that the ring had become covered by subsequent bone formation.

It was the natural corollary from this belief, that when bone has been destroyed by inflammation or removed by operation, we must look to the periosteum to regenerate new bone ; and as a matter of fact it is well known that if the periosteum is stripped up from the shaft by a purulent collection beneath it, it does in most cases lay down a sheath of bone outside the space in which the pus lay. Again, after fractures we used to look to the periosteum to produce ensheathing callus to bind the broken ends together once more. Some regenerating power, however, must be allowed to osteoblasts derived from the bone itself, to explain the formation of callus between the actual fractured ends and in the medullary cavity.

It is now agreed that the function of the periosteum is not to produce bone, but to limit the production of bone, and that osseous regeneration takes place from the osteoblasts of the bone itself, not from the periosteum.

It has always been admitted that *some* power of laying down bone must be allowed to osteoblasts quite apart from the epiphyseal cartilages or the periosteum, because of course it is their province to fill in the Haversian canals with concentric rings of new bone, and also to cement the ends of a fracture as intermediary and intramedullary callus. The hardness and density of bone rather blind our eyes to the fact that, like every other living tissue, the processes of building up and breaking down, absorption and

new formation, are continually going on in its cells and molecules. When it is irritated, as for instance when a pin is driven into compact bone, absorption takes place, and the pin may loosen in the course of a day or two ; when it is withdrawn, osteoblasts wander into the track and fill it with new bone. Even so soft an organ as the tongue helps to maintain the shape of the jaw, and after a successful operation for cancer the lower teeth come in time to slope towards the buccal cavity. The interstitial changes in bone are affected by various toxins and internal secretions : during rickets the osseous tissue is at first softened, and finally becomes more compact ; the pituitary secretion causes it to undergo hypertrophy.

In a dog, a strip of periosteum a quarter of an inch broad and two inches long was peeled up from the radius, leaving the attachment to the epiphysis intact. It was buried between muscles. Eight weeks later, there was no trace of bone formation in the fibrous intermuscular band which represented the periosteum. On the other hand, there was a bony ridge outgrown from the area whence it had been stripped up. So far then from forming bone, the periosteum must have been preventing the outgrowth of bone.

In other experiments, a strip of periosteum was excised and immediately implanted in the neck of the same animal around the jugular vein. Usually it was entirely absorbed ; once a tiny osseous nodule was found, derived probably from an attached chip of bone. Macewen points out the great practical importance of this in such an operation as sub-

periosteal excision of the elbow. If care is not taken to inspect the periosteum, adherent bony flakes may be left which will grow, and lock the joint. If they are all removed, an excellent free joint results. This represents the experience of over two hundred cases. On the other hand, care must be taken not to encroach on the diaphysis of the humerus by removing too much, or it may sprout new bone.

In other experiments, Macewen removed portions or the whole length of a bone subperiosteally. No regeneration took place to fill the gap, except in a few cases where the animal was young, and the growing epiphyseal ends pushed the extremities together to diminish or obliterate the gap. No new periosteal bone was formed.

He then repeated Duhamel's silver-ring observation, and found that the burying beneath new osseous tissue occurred just as well if the bone in that neighbourhood, or indeed in its whole length, was first deprived of periosteum. The new bone could be seen overflowing the ring from the edges. In this case it is perfectly evident that the osteoblasts providing for growth must have come from the shaft, not from the periosteum.

A number of important observations are recorded demonstrating the regenerative powers of bone itself, apart from periosteum, and more particularly in young animals. These may be briefly summarized. Although grafts of periosteum into the neck will not grow osseous tissue, thin shavings of bone itself, similarly transplanted, will double in length and thickness in most cases. In a number of experiments,

pieces of bone an inch or more in length, or even comprising the whole shaft of a long bone, were successfully transplanted from one dog to another. In a classical case, Macewen built up a new humerus for a lad who had lost the shaft by acute necrosis, and although the wedges of bone, derived from excisions for deformed legs, were not covered with periosteum, they grew and consolidated, and now, more than thirty years after, aided by the great growth of the upper epiphysis, which has contributed the bulk of the humerus, the arm is strong and useful. In other cases, fragments of bone have been replaced to fill gaps in the skull, with excellent results.

Macewen has secured osseous growth by transplantation of bone chips into the omentum, and also, after burying glass tubes in the middle of a long bone, he has found the lumen of the tube invaded by osteoblasts, and osseous islands laid down. In one interesting case, a traumatic aneurysm formed from the brachial artery of a young patient in consequence of the penetration of the vessel by a spicule of the humerus, which was fractured. Osteoblasts washed out of the humerus were thus distributed throughout the clot lining the aneurysm, and it developed a regular bony wall. This would probably occur more frequently when the aorta erodes the vertebræ, but for the fact that in that case the patient's osteoblasts are usually senile.

In some experiments, after removing a length of the radius with its periosteum, the gap was filled with bone chips. Consolidation took place, but a

large tumour-like mass of callus formed, infiltrating the surrounding muscles. The osteoblasts from each chip had wandered out and proliferated, and when they became mature had surrounded themselves with calcareous deposit, which bound together not only the detached fragments and the broken ends, but also the muscles and tendons in the neighbourhood.

The experimental and clinical work of Hey Groves on fractures strongly supports the view that callus is derived from bone and not from periosteum.

The factors which induce bone-corpuscles to become active and proliferate are not perfectly understood. Macewen lays stress on relief from pressure, and no doubt this has great importance. Dissemination of osteoblasts by increased vascularity of the part is another factor. The periosteum, when intact, limits the osteoblasts to their own proper sphere, and prevents their encroaching on the muscles and fascial planes.

According to some German and French observations, blood-clot has an influence not only in providing a suitable medium in which bone may be formed, but, further, in exerting a direct chemical stimulus upon the osteoblasts.

We may now apply these researches to surgical practice, considering first the consequences and repair of fractures. In subperiosteal fractures, rapid and firm union takes place without any ensheathing callus, and the bone feels quite normal after a few months. When the periosteum is extensively torn, osteoblasts wander out beyond its limits, and en-

sheathing callus may be formed in quantity. Much will depend on the amount of movement to which the part is subjected. Vigorous movement, or, in those cases where the periosteum is stripped away, deep massage applied too early just over the site of the fracture, will disseminate the osteoblasts far and wide. Not only may the callus be excessive, and, perchance, lock the nearest joint, but muscles, nerves, or tendons may become ensheathed by new bone, and their functions be impaired.

Here belong those interesting and by no means infrequent cases in which, after a fracture, especially near the elbow-joint, an osseous mass develops in the muscles, as for instance in the brachialis anticus. This is called *traumatic myositis ossificans*. The mass can be moved apart from the bone, and casts a shadow with the *x* rays. What has happened is that massage or movements have scattered the osteoblasts far and wide, and they have, after a few weeks, performed their usual function, and regenerated bone in their new surroundings. It is significant that these cases have become common only since the modern treatment by massage and movements has been introduced, excellent as it is when suitably applied. If the periosteum had remained intact, this could never have occurred. The treatment, if such a lump forms, is not excision, which usually leads to recurrence, but strict limitation of movement by means of a splint.

The reason why so much more callus forms in animals than in man is because so much more movement of the broken ends takes place. In these

circumstances there is often a stage in which cartilage is to be found in the callus, on its way to form bone.

It is evident, therefore, that care should be exercised, after a fracture in which it is probable that the periosteum is torn, to avoid deep massage and movements close to the site of the fracture during the first fortnight, although they may well be applied to the neighbouring joints. When the fracture is very near a joint, as in the case of injuries of the elbow-joint, or a Colles's fracture, it is far better to allow no movements at all for the first three weeks.

It is well known that exostoses or spurs of bone usually form in the attachment of muscles or tendons. The probable explanation is that by the continual drag and, it may be, slight wrenches, some osteoblasts are detached from the bone and invade the tendon.

Universal myositis ossificans, such as occurs in a so-called 'brittle man', may be due to some such cause as this, or perhaps to embolism of osteoblasts.

The strongest evidence for the older view, that bone is laid down by the periosteum, is provided by cases of acute periostitis, where pus forming inside the bone finds its way out between the shaft and the periosteum, so that the latter is extensively stripped up. In many cases, new bone begins to form under the detached periosteum, outside the pus, and the shaft usually necroses.

Macewen explains this occurrence by declaring that if the inflammatory mischief is not very acute, vasodilatation takes place within the bone, and the

osteoblasts are carried out by the Haversian canals to the loose areolar space under the periosteum, to which fibrous membrane some of them adhere. When this is stripped up later, these osteoblasts lay down new bone, but those remaining on the shaft are deprived of their blood-supply and therefore die. If the inflammatory mischief in the centre of the bone is very acute, the whole shaft may die, especially if thrombosis occurs, and therefore no osteoblasts escape, so that no new bone at all can be laid down under the periosteum. This is by no means a rare occurrence.

In local periostitis, again, which should rather be described as an osteitis, the bone-forming cells are brought by the blood-stream to the loose areolar tissue underneath the periosteum, and finding there a line of least resistance, are able to lay down young bone, and so produce a localized swelling, marked out in a skiagram by a faint line of shadow close to, and parallel with, the shaft.

The truth of the matter probably is that the active osteoblasts beneath the periosteum in normal bone (the cambium layer) may adhere either to the surface of the bone, or to the under surface of the periosteum, under different circumstances; in Macewen's experiments they adhered to the bone, and this is probably the rule. When there is inflammation, and the periosteum is stripped up by pus, many of them prefer to stick to the periosteum.

During operations for the removal of bone, great efforts are often made to preserve the periosteum,

and sometimes, as for instance in excising the lower jaw, the membrane is preserved even at the risk of leaving septic material behind, in the vain hope that it will form new bone. The only possibility of its doing so is if osteoblasts have been driven out by inflammation and have become adherent to it. It is useless to expect healthy periosteum to regenerate bone, such as a piece of rib removed for empyema, though it may form a guide for the gap to be filled by growth from the epiphyseal end.

If after a fracture union fails to take place, as may occur when muscle or periosteum intervenes between the broken ends, the osteoblasts liberated from these do not maintain their power to lay down callus for an indefinite period of time. In a few weeks their activity wanes, and the ends of the shaft become smooth, rounded, dense, and somewhat avascular. The contained osteoblasts are senile, and it will avail nothing to bring the two surfaces together by an open operation. It is necessary at this stage to saw off the sclerosed bone, and to expose fresh normal surfaces with active osteoblasts. Often a step-cut operation gives the best prospect of union, affording as it does a larger area of raw bony surfaces to come into contact with each other.

Bone-grafting. — A great impetus has been given to the study of these problems by the numerous opportunities provided by war surgery for bone-grafting. Ununited fractures after wounds have been of common occurrence, and the surgeons have all been busy putting bone-grafts into the gaps. At

the same time, the Albee operation of introducing a bone-graft from the tibia into a furrow in the split spinous processes of the vertebræ for Pott's disease has become popular, and in my experience of a dozen or more cases this is one of the most satisfactory operations in surgery. A patient of mine who had been on his back for over four years was able to walk without pain in a few months, and has been able to re-open his shop. They are usually getting about in four months from the date of the operation. It must be granted that, whatever the technique, our experience has completely established the fact that a transplant of living bone from the same patient (autogenous graft) will usually live and grow and unite firmly with the ends of the bone into which it has been introduced.

There have been very many histological, skiagraphic, and other studies of the fate of the graft, and though controversy still rages between the two schools as to the part the periosteum plays in bone regeneration, one may begin to see a way of reconciling the facts on the one side and the other. It is quite clear that *young* osteoblasts can reproduce bone, and that old ones, shut up as bone-corpuscles in lacunæ, cannot. Also we know that bone deprived of periosteum can survive and form a useful graft, uniting with the ends of the shaft into which it is ingrafted. Nevertheless its periosteum should always be preserved if possible, because the little vessels passing from the periosteum to bone are important for the nutrition of the bone, and the

periosteum readily forms vascular connections with the surrounding tissues. Also, the most active young osteoblasts are found principally just beneath the periosteum, and on the surface of the bone-shaft. Other active osteoblasts line the Haversian canals and the lacunæ of cancellous bone, and are especially numerous in the endosteum, that is, the film of cells which lines the bony tube surrounding the marrow cavity. If a bone-graft is examined microscopically some months after the operation, the great bulk of it shows dead bone-corpuscles and some absorption going on, but beneath the periosteum and endosteum and around the lacunæ there is living, growing bone.

The success of a bone-grafting depends also on some other factors. Asepsis is, of course, essential, and so is secure fixation and freedom from movement during the first couple of months or so. The permanence and strength of the graft, however, depend on the use that is made of it. Function-less bone, buried in a muscle for instance, tends to absorb; useful bone, filling a gap in the jaw or radius, becomes stronger as the part is used. Bone-grafts into the femur and humerus have not so far been successful.

It is not yet decided whether rib-cartilage will survive well and function as a graft. I have used it for the lower jaw and also for closing skull gaps. It has two advantages, in that it is easy to work with and cut to shape, and that normally cartilage is accustomed to a scanty blood-supply. My cases did satisfactorily, but according to Leriche and

Policard the hyaline cartilage part of the graft is slowly absorbed.

Boiled human bone from another patient, or even boiled beef-bone, or ivory, is capable of healing in, and becoming incorporated with, the living bone, whose osteoclasts slowly erode it, and living osteoblasts grow in and to some extent replace the dead bone by living. Dead bone or ivory can therefore be used to bridge a gap in a long bone, but its survival and incorporation are not nearly so certain as when a living autogenous bone-graft is used.

CHEMICAL FACTORS IN THE GROWTH OF BONE.

There is some relationship, not well understood, between the internal secretions of the ductless glands and the growth of bone. Over-secretion of the pituitary gland, as we shall see, results in overgrowth of the bones, and may lead to gigantism. On the other hand, inadequate thyroid secretion will stunt the growth of the bones, as is seen in cretinism. Thyroid medication will occasionally lead to the consolidation of an ununited fracture, or, what comes to the same thing, the internal secretion of the thyroid gland may be increased by giving iodide of potassium.

It has been shown that in young animals particular amino-acids are necessary for proper growth to take place. The aromatic amino-acids, tyrosin and tryptophane, are of course necessary for life as well as for growth. Lysine is also necessary for growth. Certain vitamins also have a relation to growth,

but we need not repeat what has been said on this subject in Chapter III.

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CHAPTER XI.

THE PITUITARY AND PINEAL GLANDS.

STRUCTURE OF THE PITUITARY—THE EFFECTS OF REMOVAL IN ANIMALS—INJECTION OF EXTRACTS—PITUITARY FEEDING—ACROMEGALY AND GIGANTISM—FRÖHLICH'S TYPE—FUNCTIONS OF THE PITUITARY GLAND—THERAPEUTIC VALUE OF PITUITARY EXTRACT—THE PINEAL GLAND.

THE pituitary gland consists of three portions, the *pars anterior*, which is epithelial in structure, the *pars intermedia*, also consisting of epithelium and varying much in different animals, and the *pars nervosa*, made up of neuroglia cells and fibres.

The *pars anterior* is glandular, consisting of columns of epithelial cells which in young animals may line tubules; later, the lumen disappears. It shows three different types of cells, with eosinophile, basophile, or chromophobe protoplasm, whereof the last are ordinarily few and inconspicuous, and do not take the stains. There may also be masses of basophile colloid between the cells, especially near the *pars intermedia*. According to Blair Bell, the eosinophile cells are the normal active secretory cells, the basophile form a storage secretion, the small chromophobes are exhausted cells, and the large chromophobes, which are abundant in pregnancy and may take the eosin stain faintly, are only met with when there is an excessive demand for pituitary secretion.

The *pars intermedia* is poorly developed in man, extensive in the dog and cat. It consists of epithelial cells, faintly basophile, with a good deal of colloid, which may be eosinophile or basophile.

There is often a cleft separating the *pars anterior* and the *pars nervosa*. The whole gland, and especially the epithelial parts, is very vascular. In the cat the *pars nervosa* has a central cavity opening into the third ventricle.

The *pars anterior* and *pars intermedia* are derived from a pit in the dorsal wall of the pharynx; the *pars nervosa* is budded out from the brain, and the stalk persists.

Like the other endocrine glands, the pituitary may be studied by four methods. We have to find the effects, firstly, of removal in animals; and secondly, of the injection or ingestion of extracts. We have, thirdly, to make chemical analyses of the extracts, to isolate any active principle. Finally, a clinical study of symptoms in man associated with any abnormalities of the gland may be expected to throw a light on the problem, and the effect of treating these conditions will also need to be known.

These are here set forth in the rational, not in the historical, order. It may be said at once that the active principle or principles have not yet been isolated.

THE EFFECTS OF REMOVAL OF THE PITUITARY GLAND IN ANIMALS.

It is so difficult to remove the organ from its well-concealed nest that the earlier published results

inspired no confidence. It was said that the animals died, but the injury to vital structures was necessarily great, and it has been remarked that the result would probably have been equally fatal if the operator had removed the dorsum sellæ instead of the gland! But the careful and repeated observations of Paulesco on twenty-two animals, and of Cushing and his co-workers on about two hundred dogs, have completely established confidence in the statements now before us.

It is proved that removal of the anterior lobe alone, in dogs, produces just as much effect as removal of the whole gland, but that a removal limited to the posterior lobe causes no symptoms at all.

The animal, after a total removal, shows no deviation from the normal for a period varying from thirty-six hours to two weeks after the operation. Then it becomes unsteady, there is arching of the back, low temperature, shivering, and death in unconsciousness. Achsner, Handelsmann and Horsley, Morawski and others, find that death is by no means inevitable after enucleation either of the anterior lobe or the whole gland, and if we could be sure that they had not left part of the organ behind, the positive evidence of survivals must outweigh statements to the contrary. The carefully described experiments of Blair Bell confirm Cushing's observations that removal of the whole gland or *pars anterior* is fatal, and removal of the *pars nervosa* innocuous.

Cushing has found it possible to effect partial removals of the gland. In young animals, the result

is that an 'infantile' type is maintained, and the secondary sexual characters do not develop. In older animals, the genitals atrophy, and they get very fat. He gives convincing photographs showing that these changes are quite marked. Blair Bell found very little change except drowsiness and a variable degree of atrophy of the female genital organs after partial removals of the *pars anterior*, but in two cases he obtained adiposity and genital atrophy in marked degree by compression or separation of the stalk. One of his specimens is in the Museum of the Royal College of Surgeons. Probably the effect is due to interference with the blood-supply of the whole gland.

Another consequence is a remarkable influence upon the metabolism of sugar. It is well known that removal of the pancreas causes glycosuria. Partial removal of the pituitary, on the other hand, causes an increased power of warehousing sugar in the body. In man, if more than 150 grm. of glucose are taken at a dose, some will overflow in the urine. If the action of the pituitary is subnormal, judging by the results of animal experiments and a few observations on man, even a larger dose than this will not cause glycosuria.

Stimulation of the superior cervical sympathetic ganglion, or in fact of any sensory nerve, after the centre in the brain-stem controlling the amount of sugar in the blood has been upset by an anæsthetic (J. Mellanby), causes glycosuria in the rabbit, cat, or dog. This occurs if all down-running nerves, such as the vagi, are blocked, but is abolished by previous

removal of the posterior lobe of the pituitary. These experiments (Weed, Cushing, and Jacobson) support the view that the *pars nervosa* has an internal secretion that turns glycogen into glucose, and that this internal secretion is controlled by the sympathetic nervous system.

There is some obscure connection, not only between disease or removal of the pituitary and the genital glands, but also between the pituitary and the thyroid. Thyroidectomy leads to all the signs of excessive activity in the pituitary.

INJECTION OF EXTRACTS OF PITUITARY GLAND. PITUITARY FEEDING.

Injection of extracts of the anterior lobe causes no evident results. Injection of extracts of the posterior or nervous lobe causes quite constantly a prolonged rise of blood-pressure. Not only the blood-vessels, but all varieties of unstriped muscle, are stimulated to contract. Peristaltic movements are set up in the bowel, and the bladder and uterus, whether pregnant or not, also contract.

Prolonged pituitary feeding in animals leads to great emaciation. It was originally stated by Schäfer that young rats showed an exaggeration of growth when fed with this gland, but repetition of the experiment by himself and others does not confirm this.

Pituitary extract also stimulates the flow of milk in animals, but it is not yet proved that it does so in the human subject. It appears probable that the

effect is merely due to contraction of the unstriped muscle in the nipple ducts squeezing out secretion.

Extract of the *pars nervosa* is also a powerful diuretic.

CLINICAL RESULTS OF LESIONS OF THE PITUITARY GLAND.

It is well known that the somewhat rare diseases acromegaly and gigantism are generally, but not quite invariably, associated with an enlargement of the pituitary gland, which has usually been a simple overgrowth, although later adenoma or fibrosis may have developed. Whether acromegaly or gigantism will result appears to be principally a question of the age at which symptoms commence. If they have their onset before growth ceases, gigantism will result. The skulls of most of the classical cases of gigantism, including Patrick O'Byrne, Hunter's famous giant, and Patrick Cotter, the Bristol giant, have enormous sellæ turcicæ to accommodate the enlarged pituitary gland. It is probable that giants usually suffer from acromegaly as well. There are two authentic casts preserved in Bristol of Patrick Cotter's hand, one of which is much larger than the other; indeed, it is colossal, measuring 12 inches from wrist to finger-tips, whereas the earlier cast measures only 11 inches. His shoes, which are also preserved, are 15 inches long. It is therefore clear that although he was 7ft. 10 in. high, his hands and feet were large out of all proportion, and that the hand rapidly increased in size between the taking of the first and second casts. The lower jaw was enormous,

and out of all relation to the rest of the skull.* Cushing gives some striking photographs of a living giant, 8 ft. 3 in. high, showing enormous hands and feet.

Associated with the enlarged bones of the face, hands, and feet seen in acromegaly, there are in some cases other features; these are glycosuria, amenorrhœa, impotence, and, in the young, failure of the secondary sexual characters. The temperature is subnormal.

Not only the bones, but also the viscera, may be increased in size in acromegaly: the kidneys, liver, pancreas, and even the auriculoventricular bundle of the heart.

Fröhlich and others have shown that there is another group of cases, totally distinct from acromegaly, but again associated with tumours of the pituitary gland. These are characterized by excessive fatness, by infantile stature and development, by a childish type of the genital organs, and by absence of the secondary sexual characters. It may be that we shall yet find abnormalities of the pituitary gland in other varieties of infantilism or of adiposity.

Most cases of pituitary tumour which have been diagnosed during life have given additional evidence of their presence by involving the optic chiasma and causing blindness of the nasal half of each retina. The skiagram shows enlargement of the sella turcica. In many cases there are headache, vomiting, and other signs of intracranial pressure.

* E. Fawcett, *Jour. Royal Anthropological Institute*, 1909, xxxix, 196.

We must now attempt to classify our information, and endeavour to come to some clear conception of the functions of the pituitary gland, and the causation of these various types of disease.

Some years ago it was the prevalent opinion that the anterior and posterior lobes must be considered to be entirely unconnected glands, having a different development, histology, and function. The posterior lobe was connected with the production of an internal secretion, probably in the colloid furnished by the *pars intermedia*, which was poured into the ventricular system of the brain, and extracts of this lobe raised the blood-pressure. There is some evidence that in acromegaly the anterior lobe is specially at fault; it may be disproportionately enlarged, and may show a superabundance of secretion granules.

Now, however, there is a tendency to unify the functions of the hypophysis and to regard it as one gland, although the distribution of the colloid is unequal in the various parts.

Whether the gland is necessary to life is unsettled.

The diseases fall into two groups: those in which the internal secretion is excessive (hyperpituitism), and those in which it is diminished or absent (hypopituitism).

Hyperpituitism is characterized by signs of acromegaly in adults, or gigantism if it begins before growth has ceased. The gland is usually enlarged, showing microscopically a simple overgrowth. There may be glycosuria. The cases run a chronic course for years unless symptoms of cerebral compression come on.

Hypopituitism produces the Fröhlich type, with atrophy of the genitals, infantilism, and excessive fatness. There is often a drowsy mental state; indeed, one is tempted to believe that that very accurate observer, Charles Dickens, must have had such a case in mind when he invented the immortal Fat Boy in Pickwick. All these symptoms can be mimicked by partial excisions of the pituitary gland in animals. Cushing's results as to which lobe is at fault are discordant. Probably, as Blair Bell suggests, it is the whole gland that is at fault.

It is true that cases of acromegaly may eventually develop impotence, sterility, and amenorrhœa; this is at first sight difficult to fit into the picture. Apparently in the female sufferer from acromegaly there is an approximation to the male type, with coarse skin, deep voice, big bones, and enlargement of the clitoris; hence the amenorrhœa. In the male there is often increased sexuality at first, followed by impotence; this is explained as hypopituitism succeeding an excess. The same sequence is seen in diseases of the thyroid gland. Dr. E. C. Williams at a medical meeting in Bristol recently showed a boy, age six, with hyperpituitism, as evidenced by marked overgrowth, and an enlargement of the pituitary fossa in the skiagram. The ossification of the bones had reached the stage characteristic of a lad of fourteen. The external genital organs were also those of a boy of fourteen. He was mentally normal, but rather slow.

A very valuable measure of the function of the pituitary gland may be obtained by observations on

the power of warehousing sugar. If the internal secretion is deficient, huge quantities of glucose will not cause glycosuria. This is the cause of the adiposity. Hypopituitism is usually due to malignant growths encroaching on the gland, and is frequently followed by death.

We are now in possession of some indications for treatment. For acromegaly and gigantism little can be done. Pituitary feeding does more harm than good. If there are symptoms of cerebral compression or gradually increasing blindness from involvement of the optic chiasma, an operation may be performed to relieve pressure and remove part of the gland. Scores of cases have now been treated in this way (Cushing reports 43 operated on by himself), and the mortality is not high. Several observers record a definite shrinkage of the bones afterwards.

THE USES OF PITUITARY EXTRACT.

Patients suffering from the Fröhlich type may be treated by pituitary feeding, the whole gland of cattle being used. The dose is about 12 gr. a day, but Cushing sometimes prescribes as much as 100 gr. three times daily. This may be worked out by its influence on the sugar tolerance. Remarkable results have been obtained in a few cases. If mouth-feeding is not successful, a dose of whole-gland extract may be given hypodermically every twenty-four hours; this has proved very effectual sometimes. If there are signs of intracranial pressure a decompression operation is indicated.

The hope that pituitary feeding would prove to be a remedy for increasing the stature of small children is not likely to be realized in view of the fact that Schäfer has failed to verify his earlier observations on young rats.

Feeding with the whole gland is also advised for certain cases of amenorrhœa attributed to hypopituitism. Unfortunately it is apt to cause severe headache.

On the other hand, there is said to be a type of headache which is due to disorders of the pituitary and is often cured by administering the whole gland. This headache is frontal, deep behind the eyes, gives rise to great prostration, and there may be vomiting. It is commoner in women than men, and may coincide with menstruation. The pain lasts half an hour to two days. There may be a craving for sweets. There may be coarse hair with male distribution in the female (Pardee).

Pituitary extract, containing the principle found in the posterior lobe which acts on unstriped muscle, is now an ordinary article of commerce for many therapeutic purposes. It is a favourite remedy for surgical and toxæmic shock, and many observers are convinced that it does good by raising the blood-pressure. For reasons discussed in the chapter on surgical shock, I am not sure that pituitary extract is really of any value in this condition. A very valuable effect is that it promotes peristalsis even when purgatives fail or are vomited, as in intestinal paralysis after abdominal operations. A third indication is to increase labour pains; sometimes

in cases of weak pains the child is expelled very rapidly after an injection. It must not be used in obstructed labour, or the uterus may rupture. It is also given—is invaluable according to some—in daily intramuscular doses for menorrhagia of puberty or the menopause. It is a powerful diuretic. As a galactagogue its success so far has been doubtful.

It was originally stated that pituitary extract must not be given frequently at short intervals, or its effect may be reversed, but there is some doubt about this.

The dried extract of posterior lobe may be given orally in 5-grain doses, combined with calcium lactate, for menopausal flushings, and with great benefit (Blair Bell).

The dose of the 20 per cent extract used for intramuscular injection is 1 to 2 c.c. for shock or intestinal paralysis, and 0·5 c.c. for uterine inertia.

There is a considerable vogue just at present for mixed extracts of the endocrine glands as a therapeutic agent. They are given for debility, nervous exhaustion, and nocturnal incontinence of urine in children, also for some varieties of infantilism and backward development. The method is rather reminiscent of the fifty-ingredient prescriptions of pre-scientific medicine, used on the principle of a shot-gun in the hope that, even if most of the pellets missed, a few might hit; but in the present limited state of our knowledge we must be content to know that some observers have reported a certain number of good results.

THE PINEAL GLAND.

It has been customary to look upon the pineal gland as a developmental relic. The functionless unpaired eye of Hatteria, which appears to have been present, possibly in functional form, in some fossil reptiles, is supposed to be the substance of which the pineal gland is the useless shadow. It would be truly extraordinary if we had to believe that a superfluous relic had been handed down from the beginning of the Triassic period, throughout the whole family of the Mammalia, and still persisted in man.

Some evidence has lately come to light which would lead us to add the pineal to the list of glands with an internal secretion. It is true that excision, feeding, and injection of extracts throw no light on the problem; but histology shows that in children it contains glandular cells, which more or less atrophy in adults. Tumour of the pineal gland, in about a dozen recorded cases, has been associated with a remarkable precocity, including increased stature, premature development of the genital organs, growth of hair, and, in a few instances, an extraordinary mental vigour. One boy, at the age of five, discoursed learnedly concerning the immortality of the soul!

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CHAPTER XII.

OXALURIA.

IT has been found very difficult to obtain reliable estimates of oxalates in the urine. The method commonly employed, introduced by Dunlop, is open to serious objections from the chemical standpoint. Working with O. C. M. Davis, the writer has used a new and, theoretically, more reliable method, but it is not claimed that the results are more than approximate. There is still, therefore, some difference of opinion as to the metabolism of the oxalates, but the following conclusions are becoming generally accepted.

In ordinary circumstances, the whole of the oxalate in the urine is derived from articles of food. Milk, meat, and bread contain scarcely any oxalate ; most vegetables contain it, and rhubarb, strawberries, and sorrel contain a relatively large quantity. I have by taking much rhubarb induced an attack of oxaluria sufficiently marked to cause a good deal of smarting pain in the urethra from the sharpness of the oxalate crystals. On a milk diet, oxalates disappear from the urine. This may be demonstrated by adding methylated spirit and allowing to stand, when any oxalate present in solution is precipitated in characteristic octahedra. On a milk diet, no such crystals will be obtained.

None of the ordinary derangements of metabolism cause the appearance of oxalates in the urine if they are withheld from the food. Thus there is no oxaluria in fever, in leukæmia (illustrating the katabolism of nucleoproteins), or in diabetes. In a case of oxalic acid poisoning under my care, the excretion was enormous, and there was a heavy deposit of calcium oxalate crystals.

It is not, however, correct to say that oxaluria *never* occurs on an oxalate-free diet, though such a condition is rare. As is well known, the usual products of bacterial fermentation of carbohydrates in the bowel are various gases (CH_4, CO_2), lactic, acetic, and butyric acids, and alcohol. Miss Helen Baldwin has pointed out that in certain abnormal circumstances oxalic acid also may be formed in this way. Copious feeding on sugar will ruin a dog's digestion, and then oxalates may appear in the urine even on an oxalate-free diet. Occasionally she has met with such cases in a man. I have not chanced to observe such a case personally, and believe that they are not common.

Fermentation of carbohydrates in the stomach and intestines to an excessive degree is common enough, but it is only rarely that there is any formation of oxalates. I have never been able to obtain the crystals either from the gastric contents or from the urine of patients with obstruction of the pylorus and gastric dilatation, on an oxalate-free diet.

When ammoniacal fermentation of urine takes place, as on standing, any oxalate crystals present are rapidly dissolved and disappear.

The oxalate calculus is by far the most important variety occurring in the kidney. B. Moore has shown that a pure uric acid stone is found only in the bladder, and that all renal calculi are composed for the most part of calcium oxalate. This is fortunate for the *x*-ray diagnosis of the condition, and as it is comparatively easy to control the oxalate excretion, it makes it possible for us to advise the patient how to avoid a relapse after operation. To draw the practical lessons from our study, it is evident that any patient suffering from oxaluria should abjure the use of green vegetables, and fruits should be taken sparingly. If he is obeying directions, a fresh specimen of his urine, mixed with an equal amount of spirit and allowed to stand, will deposit only a few small crystals of oxalate, and a specimen without the addition of spirit will show no crystals even on centrifugalizing. Occasionally, however, one may find a case in which oxaluria persists even on a milk diet. We must then restrict the sugars and starches of the diet, and give remedies calculated to diminish fermentation in the stomach and intestines.

If patients object to dietetic restrictions, potassium citrate will often relieve, both by acting as a diuretic, and by making the urine alkaline, thus dissolving the crystals.

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A. RENDLE SHORT.—Von Noorden's *Metabolism and Practical Medicine*, i, 148.

CHAPTER XIII.

THE FUNCTIONS OF THE SPINAL CORD AND PERIPHERAL NERVES.

THE DOUBLE MOTOR PATH—THE DOUBLE SENSORY PATH—THE EXACT DIAGNOSIS OF SPINAL CORD INJURIES—LESIONS OF THE POSTERIOR NERVE-ROOTS—INJURIES AND REPAIR OF PERIPHERAL NERVES.

IN this chapter, as in so many others, we shall find that the injuries sustained by the wounded in the great war have shed a light on problems of function, though the investigations we have first to describe savour more of civilian than military practice.

THE DOUBLE MOTOR PATH.

We had become accustomed to think and speak of a single path for voluntary movements, consisting of an *upper motor neurone*, the pyramidal Betz cells of the precentral cortex and the pyramidal tract fibres, and a *lower motor neurone*, the anterior horn cells of the spinal cord (or motor nucleus in the brain-stem) and the medullated fibres of the peripheral nerves. There is now to be considered a good deal of evidence that the motor path is doubled throughout.

It has long been suspected that the pyramidal tracts could not be the only motor path. Babies can move their limbs before the pyramids myelinate.

After a hemiplegic stroke, certain stock movements such as standing and walking may persist, although the fibres of the pyramidal tracts may be almost entirely destroyed. In animals, as is well known, quite extensive lesions of these tracts or of the motor cortex do not produce lasting paralysis, even in the chimpanzee. Thromboses spoiling the arm centre, or the face centre, in man, give rise to paralysis, but there is often a remarkable degree of recovery of function later. In old hemiplegias, voluntary movement of the sound side may be accompanied by involuntary movements of the hemiplegic limbs. Similar movements may be obtained in the cat or chimpanzee by stimulating the red nucleus area. In the fœtal cat the movements resemble those of walking (Graham Brown).

The phenomena of spasticity point in the same direction. It is well known that after a hemiplegic stroke due to a lesion in the internal capsule there is marked rigidity of the paralysed side. Also in any animal a transection of the mesencephalon brings on a state of ' decerebrate rigidity,' the limbs becoming as stiff as if frozen. A second transection below the fourth ventricle abolishes this rigidity; a hemisection abolishes it on the side divided. Division of the posterior nerve-roots of a limb sets that limb free from the rigidity. Evidently, therefore, there is another innervation for the muscles besides that due to the pyramidal tract, and a reflex arc responsible for producing the spasticity. The researches of Sherrington, Thiele, Weed, and Bergmark seem to indicate that the path for the

reflex is as follows: posterior nerve root, tract of Gowers, cerebellum, superior cerebellar peduncle, red nucleus, rubrospinal tract. Section of any of these tracts will abolish decerebrate rigidity. Lesions of the inferior cerebellar peduncle do not influence the spasticity. The pyramidal and frontopontic and temporo-occipito-pontic tracts inhibit muscular tone. A pure cortical lesion frequently causes a *flaccid* paralysis, whereas a lesion of the internal capsule gives rise to spasticity, because in the latter case *all* the inhibitory tracts are likely to be involved, whereas a pure lesion of the precentral cortex spares the two corticopontic tracts.

We find, then, two motor paths in the brain-stem and spinal cord:—

1. The pyramidal tract, descending from the cerebral cortex, controlling finer and more skilled movements, inhibiting muscular tone.

2. The rubrospinal tract, descending from the red nucleus (probably influenced by the lenticular nucleus), controlling stock elementary movements, and exaggerating muscular tone. Perhaps the various anterolateral descending tracts (vestibulo-spinal, tectospinal, and the like) share in the function.

In diseases in which the cells of the lenticular ganglion degenerate, increased muscular tone and rigidity is a prominent symptom, and tremors may be present. This is seen in the condition called paralysis agitans. Chronic manganese poisoning may produce similar effects.

But it is not only in the central nervous system

that evidence has been found of a double motor path. Ramsay Hunt has some interesting observations to bring forward pointing to a double path in the motor nerves. There are, for instance, end-plates in striped muscle of non-medullated as well as of medullated nerve-fibres (Boeke), and Ranson has shown by his silver-pyridine method that the peripheral nerves contain a lot of non-medullated fibres. Striped muscle itself contains two elements; each fibre consists of a great number of cross-banded sarcostyles packed in sarcoplasm, as though a bundle of cross-striped pencils were put into a cylinder-glass containing treacle. In muscles designed for rapid action the sarcostyles predominate; in muscles where long, slow contraction is needed there is relatively more sarcoplasm. The sarcoplasm (corresponding to the treacle) is itself contractile.* The suggestion is that there is an older, simpler mechanism, consisting of rubrospinal tract, fine and non-medullated nerve-fibres, Boeke's end-plates, and sarcoplasm; and a newer mechanism capable of greater quickness and higher control—the pyramidal tract, coarse medullated nerve-fibres, ordinary motor end-plates, and sarcostyles. In the intercostal nerves, fine fibres are in excess; in the brachial plexus, coarse fibres.

Some curious phenomena in the healing of nerve lend support to the hypothesis. Ramsay Hunt describes cases in which after suture there was a period during which muscular tone and associated movements had returned, but voluntary power had

* This part of the theory is very uncertain.

not yet been recovered; indeed, in certain cases of musculospiral palsy it never did recover. The facial nerve shows this phenomenon best. There may be recovered tone, and even spasm, with restoration of such symmetrical movements as smiling, long before return of voluntary movement. The finer and non-medullated fibres presumably have regenerated before the coarser.

THE DOUBLE SENSORY PATH.

The researches of Head and his fellow-workers have shown that peripheral sensation may be grouped under three headings:—

1. *Epicritic sense*, including localization, light touch, and slighter variations of temperature.

2. *Protopathic sense*, a more elementary mechanism, preserved in the glans penis, and made evident after certain nerve-injuries, recognizing pain, and greater variations of temperature.

3. *Deep sensibility*, appreciating deep pressure.

Probably there are three different nerve-fibre paths subserving these functions.

In the spinal cord, however, a new grouping takes place; heat, cold, and pain sense travel by one route, and stereognosis, tactile discrimination, and kinæsthetic sense (sense of weight, and sense of position) by another.

An interesting investigation has been published by Ranson throwing some light on the way in which this re-grouping occurs. The bulk of the fibres in a spinal posterior nerve-root are non-medullated, only shown by special stains; they have the usual

cell-station in the posterior root ganglion, and the axon shows the T-shaped bifurcation. The centripetal branch of these non-medullated fibres enters the tract of Lissauer, and immediately plunges into the grey matter of the posterior horn. There are thus inner and outer divisions of the entering posterior nerve-roots; the inner medullated fibres enter the columns of Burdach, and the outer non-medullated enter the gelatinous substance of Rolando. Section of the outer division abolishes the evidences of pain such as struggling, the pressor vasomotor reflex, and quicker breathing, in the lightly anæsthetized animal, when the sensory nerves are stimulated. Section of the inner root has no such effect. It is suggested, therefore, that the outer non-medullated root is the path for pain and temperature sense, and that the inner medullated root is the path for muscular sense, stereognosis, and tactile sense. There is some doubt, however, as to the exact nature of these fibres, which stain with silver pyridin. Miss W. Parsons suggests that they are neuroglia, but they do not react with the ordinary neuroglia stains (Wilson).

As already remarked, there is a double sensory path up the spinal cord. Leaving out of consideration those tracts (the dorsal and ventral cerebellar, etc.) which do not carry up messages to the centres for consciousness, and also leaving out of account the possibility that sensory impulses may be transmitted up the grey matter of the cord with its short endogenous connecting fibres, there remain two main ascending tracts. These are :—

1. *The posterior columns of Goll and Burdach,* whose axons are derived from the entering posterior nerve-roots, which run uncrossed up to the gracile and cuneate nuclei.

2. *The spinothalamic tracts,* arising in the cells of the posterior horn, mostly of the opposite side, running up in the tract of Gowers, joining the mesial fillet in the brain-stem, and ending in the optic thalamus.

The messages conveyed by the columns of Goll and Burdach are also carried on to the optic thalamus, by way of the mesial fillet.

According to our present interpretation, which has to be based almost entirely on human evidence because animals cannot explain their feelings, pain and temperature sense are conveyed by the spinothalamic tract, whereas muscular sense, joint sense, and tactile discrimination—by which we distinguish whether two compass points are double or single—pass up the posterior columns ; the sense (stereognosis) by which we recognize unseen objects by the feel—as on putting a hand into a pocket containing coins, keys, a penknife, paper, etc.—also travels by this route.

Thus we find that whilst muscular sense, stereognosis, and tactile discrimination pass up the cord uncrossed, heat, cold, and pain senses cross, and there is a cell-station in the grey matter. Pain crosses at once ; temperature and tactile sense usually about five segments above. Hence syringomyelia and other lesions of the grey matter abolish temperature and pain sense. Sherrington has shown

that the pain impulses are not totally crossed ; a few pass up on the same side. Tactile sense, apparently, can follow either of these routes.

The diseases which throw most light on these problems are tumours of the spinal cord, and syringomyelia.

A tumour of the spinal cord :—

1. May affect the nerve-roots, in which case the symptoms may be confined to those roots.

2. May press on one side of the spinal cord. In this case there is usually pain radiating along the nerve-roots involved at the same time, which is important in the diagnosis.

Let us take the case of a tumour in the left lower cervical area. This will involve :—

(i). *The emerging roots of the lower cervical nerves* on the left side, causing pain, dulling of sensation, and flaccid paralysis with loss of reflexes, wasting, and reaction of degeneration, in the left arm.

TABLE TO ILLUSTRATE THE EFFECTS OF A TUMOUR OF THE LEFT LOWER CERVICAL REGION.

Right Arm.	*Left Arm.*
Normal.	Pain. Some anæsthesia. Flaccid paralysis, loss of reflexes, wasting.
Right Leg.	*Left Leg.*
Loss of sense of heat, cold, pain.	Loss of muscular sense, joint sense, tactile discrimination and recognition of objects. Spastic paralysis ; exaggerated reflexes.

(ii). *The pyramidal, rubrospinal, and vestibulo-spinal tracts* on the left side, causing paralysis of

the left leg. Inasmuch as the pyramidal tract is involved, muscular tone will be greatly increased. There will be, therefore, rigidity of the left leg and exaggerated reflexes.

(iii). *The cerebellar tracts and posterior columns* of the left side, causing loss of muscle and joint sense, and loss of tactile discrimination and recognition of objects on the left side.

(iv). *The spinothalamic tract*, by which heat, cold, and pain travel up from the right leg, will also be pressed upon.

Tactile sense may not be lost in either leg, as a double path, the one crossed and the other uncrossed, is open to it.

3. It may arise in the central grey matter. In this case there will be loss of the heat, cold, and pain senses on both sides, but tactile and muscular sense will remain. There may be some spastic paralysis of both legs. In the early stages the diagnosis from syringomyelia may be only a matter of opinion.

4. In some cases it may produce bilateral spastic paralysis with involvement of the sphincter functions and with anæsthesia without any dissociation phenomena. The diagnosis from transverse myelitis or vascular lesions is then very difficult.

Each of the thirty-one nerve-roots issuing from the spinal cord has a definite distribution, which may be motor, sensory, and visceral, and these have now been ascertained with some accuracy by a combination of anatomical, physiological, and clinical methods. As given in the various text-books and monographs, the information is a good deal more

than most of us can carry conveniently in our memories. It is hoped that the bare elements set down in the table may be found easier to remember, and adequate for most purposes. No two accounts agree exactly.

The main points may be emphasized first. With regard to the sensory distribution, there is a good deal of overlap, especially in the hand, where the seventh cervical supplies the radial half, the eighth cervical the inner half, and the first dorsal the one and a half fingers to which the ulnar nerve may be traced. The twelve dorsal nerves supply the chest and abdomen in bands like successive strips of plaster stretched round the body; the nipple lies between the fourth and fifth dorsal, and the umbilicus between the ninth and tenth. If we place the open hand on the thigh just below and parallel to Poupart's ligament, we cover the first lumbar area; the next handbreadth below is the second lumbar, and the next, including the region of the patella, is the third lumbar. The small sciatic nerve area corresponds to the second sacral, and the internal saphenous nerve area to the fourth lumbar segment.

With regard to motor distribution, the fifth cervical supplies the deltoid + biceps + supinator longus group, as well as the dorsal scapular muscles and rhomboids. In infantile palsy and other anterior horn or nerve-root affections, these muscles may be found paralysed and atrophied in company. On the other hand, a fracture of the spine irritating this segment brings about a characteristic position of the arms ⅄; the arms being raised beside the head. The seventh

cervical root supplies the abductor and opponens pollicis, but not the other muscles of the hand. This is of some importance in working out which roots are pressed on by a cervical rib. The first and second thoracic roots supply the sympathetic fibres to the pupil. I once had a case under my care with signs of ulnar nerve paralysis and a contracted pupil, following on a severe pull on the arm. The diagnosis was that the first thoracic root had been torn close to the spinal cord.

The anatomy of the lumbosacral plexus makes it easy to remember that the quadriceps and adductors must be supplied from the lumbar nerves, whereas the hamstrings and crural muscles are innervated from the sciatic roots. There is a general tendency for flexors to derive their nerve-supply from a level slightly below that for the extensors. It is easy to see why this should be the case if we glance at a quadruped, where the flexors are posterior to the extensors.

Flaccid paralysis and anæsthesia of the lower limbs, with sphincter trouble, may be due to a tumour growing either in the cauda equina or in the conus medullaris of the cord itself. The diagnosis is often difficult, but tumours of the cauda are usually characterized by a slower course, asymmetry, very violent pain, and Lasègue's sign—pain on flexing the thigh and thus pulling on the nerve-roots. Operative interference gives better results in these cases than in those where the cord itself is affected.

In a few cases recently recorded, where section of posterior nerve-roots had failed to relieve pain, a surgeon has divided the pain-path in the anterolateral

TABLE OF SPINAL SEGMENTAL DISTRIBUTION.

Segment	Muscle-Groups	Sensory Area	Viscera
I, II, III, C. ..	Neck muscles	Back of head ; neck	
IV, C. ..	Neck muscles ; diaphragm	Shoulder	Diaphragmatic pleura (central portion)
V, C. ..	Deltoid + biceps + supinator longus ; all muscles attached to scapula	Outer part of arm	
VI, C. ..	Muscles of shoulder, arm, and forearm	Radial part of forearm	
VII, C. ..	Ditto ditto ; abductor and opponens pollicis	Radial half of hand	
VIII, C. ..	Flexors of wrist ; hand muscles	Ulnar half of hand	
I, D. ..	Hand muscles	Ulnar border of forearm, one and a half fingers (= that of ulnar nerve)	Iris (pupillo-dilator fibres)
II, D. ..	Intercostals	Inner border of arm ..	Heart ; parietal pleura ; iris
III, IV, V, D.	Ditto	Bands round chest ..	Heart ; parietal pleura

Segment	Muscle-Groups	Sensory Area	Viscera
VI–IX, D. ..	Intercostals	Bands round chest and epigastrium	Stomach, parietal and diaphragmatic (peripheral) pleura
VII–X, D. ..	Intercostals; abdominal muscles	Bands round chest and abdomen	Liver, gall-bladder, lungs
X, D. ..	.. .. ..	.. .. ..	Ovary or testis
IX–XII, D. ..	Abdominal muscles ..	Bands round abdomen ..	Intestines, kidney, parietal and diaphragmatic (peripheral) pleura
I, L. ..	Abdominal muscles; ilio-psoas	Handbreadth below Poupart's ligament	
II, III, L. ..	Ilio-psoas; quadriceps; adductors	Front of thigh and knee	
IV, L. ..	Quadriceps; adductors ..	Inner side of leg (= that of internal saphenous nerve)	
V, L. ..	Glutei; hamstrings ..	Outer side of leg	
I, S. ..	Glutei; hamstrings; muscles of leg and foot	Foot	
II, S. ..	Muscles of foot ..	Back of thigh (= that of small sciatic nerve)	
III, IV, V, S. ..	Perineal muscles ..	Anus, perineum, genitals ..	Bladder, rectum, vulva, penis

region of the cord. To give success, this should be done on both sides, although by far the greater number of pain-fibres are crossed. Sherrington worked out the path by dividing the mesencephalon in dogs, after which injury they still turn and try to bite and growl if the foot is hurt, although they cannot, of course, psychically feel it. If then the spinal cord is hemisected on the right side, painful stimuli applied to the right foot produce much livelier snapping and growling than the same on the left side.

Souttar has recorded a case in which he divided the right anterolateral region of the cord in the upper dorsal region for unilateral left-sided gastric crises of tabes. The pain was completely abolished, but not the vomiting. No paralysis resulted. Pain sense in the left leg was abolished ; tactile, muscular, and joint sense remained. Strange to say, temperature sense also remained unimpaired. Although pain sense crosses almost at the level at which it enters, and temperature sense several segments further up, one would have expected all the messages entering in the lumbospinal region to have got across before reaching the upper dorsal level. Great heat was interpreted as pain.

A study of three patients with gastric crises of tabes treated by division of the posterior nerve-roots (5th to 8th thoracic), operated on by Sir William Thorburn, led to the conclusion that the *pain*, referred by the patient to the stomach, is conducted principally, but not entirely, by the splanchnic nerves, and the *impulses to vomit* by the vagi. There may

be a diffuse superficial pain left after posterior rhizotomy, associated with retention of muscular sense in the anæsthetic area ; possibly some sensory fibres enter by the anterior nerve-roots (Shawe).

THE EXACT DIAGNOSIS OF INJURIES OF THE SPINAL CORD.

The following lesions of the cord may be responsible for symptoms of paralysis or anæsthesia after an injury to the back.

1. Simple concussion, the injuries being microscopical or functional only, and the paralysis transient.
2. Complete division of all the nervous elements.
3. Pressure on the cord, due to bone, callus, or a foreign body, not causing a total transection.
4. Hæmorrhage into the spinal membranes.
5. Hæmorrhage into the cord itself.
6. Later complications such as myelitis, traumatic neurasthenia, etc.

This is not the place to consider all these in their surgical bearing. We want to look at them in relation to the physiology of the spinal cord.

Both in man and in animals, particularly monkeys, a transverse injury to the cord leads to the phenomenon known as *spinal shock*. All the reflex functions are severely depressed, and there is transient paralysis and anæsthesia. Sherrington has shown in animals that a transection, e.g., in the upper dorsal region, causes spinal shock only distal to the lesion ; the cervical cord is normal. If after recovery has occurred a second section is made in the mid-dorsal region, no spinal shock is produced.

Evidently it was due to the withdrawal of impulses running downwards from the brain-stem, probably from the region of Deiters' nucleus, because transection of the upper pons or mesencephalon does not cause spinal shock.

Concussion of the cord may be imitated in animals by removing the spinal laminæ and dropping weights from various heights on the exposed spinal cord. A light blow has no effect; a heavier blow causes a transient block of conduction, and a severe blow does permanent mischief.

Considerable difficulty may be experienced for a day or two in deciding whether a patient is suffering from a complete division of the cord due to the nip at the moment of fracturing the spine, or whether the symptoms are due merely to concussion. In the latter case a few days' rest will effect a cure. Sometimes one can get a hint earlier. If the distribution of the paralysis does not correspond to the distribution of the anæsthesia, and if the symptoms are asymmetrical, it is probable that they are due partly at least to concussion.

Spinal shock resulting from a complete transection in animals is very transient. In frogs it lasts a few minutes, in cats and dogs a day or less, in monkeys not much more. In a series of wounded men whose cords had been divided by gunshot injury, if the patient was carefully looked after, shock passed off in one to three weeks. In such cases there are three stages distinguishable:—

1. *Period of spinal shock*, with absent reflexes and paralysis of the bladder.

2. *Period of recovery*, reflexes returned, and bladder empties itself automatically when full.

3. *Period of terminal failure*, when the isolated segment of the spinal cord suffers from toxic degeneration or myelitis, and reflexes again fail, with paralysis of bladder, great wasting of the legs and reaction of degeneration, and trophic changes.

Sometimes the period of recovery is absent, especially if the patient becomes infected; this used to be described as the normal in man when the cord is completely divided, but it is now abundantly proved that there may be well-marked recovery of reflexes and spasticity even with an absolute transection.

It is frequently impossible from the symptoms and physical signs to decide whether the injury to the cord is complete or incomplete. Of course, if any sensation persists, or any true voluntary control, some tracts must still be left.

Even in the absence of any sensation or voluntary control in the parts below the injury, Riddoch has put us in possession of a sign that may sometimes be of value. It used to be taught that if the legs were rigid and showed reflexes, the transection was incomplete. This is not true.

The spasms that may be reflexly elicited in a case of complete transection are, however, always flexor, never extensor. If extensor reflexes or movements of progression can be obtained, as by pricking the thighs or drawing the prepuce over the erect penis, the lesion of the cord is not complete.

The practical point of course is that with an

incomplete injury it is well worth while to operate to remove pressure; if the conducting elements are totally divided, operation is useless.

The flexor spasms of the thighs elicited by stroking the inner side are often accompanied by reflex emptying of the bladder. This may aid in keeping the patient dry, by getting the urine evacuated regularly without needing a catheter.

Marked wasting of the legs generally means a complete transection and a hopeless prognosis.

Lesions of the cauda equina may wisely be explored, because suture of the roots or removal of pressure may lead to regeneration.

Hæmorrhage into the spinal membranes produces pain and spasm by involving the issuing nerve-roots. In addition, there will probably be some evidence of pressure on the cord, producing spastic paralysis and some anæsthesia below the lesion.

Hæmorrhage into the centre of the cord sometimes abolishes the pain and temperature senses, while tactile sense escapes. There will probably be spastic paraplegia as well.

It will not be necessary to refer here to the diagnosis of the later complications, such as myelitis and the various neuroses.

Unfortunately the central nervous system is so highly specialized that it has lost the power of regeneration after injury, not only in man, but also in nearly all animals. The newt, it is true, can form a new cord if its tail is lopped off, but the newt has marvellous powers of regeneration, and can even grow a new lens if the front of its eye is removed!

Histological evidence of partial regeneration has been obtained in mammals by Marinesco and others, but not functional restoration.

THE EFFECTS OF DIVISION OF THE POSTERIOR NERVE-ROOTS.

The effects may be classified as follows :—

1. Anæsthesia of the spinal area of skin supplied. The distribution of these in the human subject has been worked out thoroughly, and the charts of Head, Sherrington, and others are well known. Section of a single nerve-root scarcely ever causes any complete loss of sensation.

2. Ataxia of the corresponding limb, which may be severe.

3. Loss of tone, leading to marked flaccidity of the corresponding limb.

4. A variable degree of functional paralysis. Owing to the loss of sensory impulses, the ataxia and lack of tone, the patient, man or animal, prefers not to use the limb, although there is not a genuine paralysis.

5. Loss of reflexes.

6. Trophic lesions, such as ulcers, whitlows, etc.

It has recently been shown by Eloesser that bone and joint diseases similar to the Charcot joints of locomotor ataxia can be produced in cats by dividing all the posterior nerve-roots to a limb and then bruising or crushing the joints. Similar treatment of the joints on the side with sensory nerves intact caused no such changes. Extensive and grotesque departures from the normal were secured in some animals.

7. Usually not shock. This is rather surprising. I have taken the blood-pressure in two patients whilst four or five nerve-roots in the lumbar and sacral plexus were cut on each side, and there has been no sudden fall. There was a steady drop throughout the whole operation (under open ether anæsthesia) amounting to less than eight millimetres of mercury.

8. Certain degenerative changes. The posterior columns of the spinal cord show Wallerian degeneration running up to their termination in the gracile and cuneate nuclei of the medulla. As Warrington has pointed out, in animals the cells of the anterior horn on the same level as the severed roots show signs of chromatolysis, or dissipation of their Nissl granules. I have been able to demonstrate this in man. A patient who had been treated for gastric crises by resection of the posterior nerve-roots from the seventh to the tenth dorsal, died about two months afterwards. In the cervical region all the nerve-cells were normal, but in the region of the divided roots more than half the anterior horn cells, and all the cells of Clark's column, showed marked chromatolysis. This is interesting in the light of the various affections of the motor functions just mentioned.

The surgery of the posterior nerve-roots is yet in its infancy, but it promises to have a future. When it is resorted to earlier, it will most probably have a greater value.

There are two main indications for dividing the posterior nerve-roots. The one is pain, and the other

extreme rigidity in the course of spastic paraplegia or hemiplegia. The pain may be due to such a cause as the crises of locomotor ataxia, or the agonies of inoperable cancer. It is more successful for the latter than for the former.

When many roots are cut for spasticity, it is necessary to leave one or two intact, or a very decided amount of ataxy may be induced. The relief of adductor or other spasm is often very marked, if it has not become permanent in consequence of fibrous shortening of the muscles and tendons.

INJURIES AND REPAIR OF PERIPHERAL NERVE.

The terrible frequency of nerve injuries in the war has given a fresh impetus to the study of these problems, and a number of valuable researches have been published on the histology of regeneration and on other points.

One of our greatest difficulties has been to obtain reliable evidence, before operation, as to whether a nerve presenting all the signs and symptoms of complete division (paralysis, anæsthesia, and the like) was as a matter of fact cut across, or partly divided, or merely bruised or shocked. We found that a bullet passing near but not through a nerve frequently gave rise to a temporary paralysis of all its functions. If the electrical reactions remained normal (beyond the first ten days), a speedy recovery might be expected; but in very many cases there was reaction of degeneration just as in a case of

anatomical severance, yet the functional nature of the injury would be proved by spontaneous cure in a few weeks' time. Electrical testing has its limitations. Occasionally normal muscle shows A.C.C. greater than K.C.C.

In practice therefore, in such doubtful cases, it became customary to wait about three months to give nature every chance. Another advantage of waiting was that it gave time for the wound to become sterile. Only too often we had to wait not months but years to secure asepsis, without which nerve suturing is foredoomed to failure. It is an interesting question just when this waiting rule ought to be applied to nerve injuries in civilian practice. Even after three months, natural recovery is not hopeless. A musculospiral case of mine, with complete electrical reactions of degeneration, got well quite suddenly after nine months without operation. In some of these patients there probably was an anatomical division, but the two ends of the nerve, being in apposition, united spontaneously.

A new test has been introduced by Tinel, called 'distal tingling on percussion', or D.T.P., intended to help clear up the diagnosis in these cases. If, shall we say, the ulnar nerve is divided in the middle of the upper arm, and, after several months, tapping the ulnar trunk behind the internal condyle at the elbow sends a tingling sensation down the arm to the little finger, it certainly suggests that new nerve-fibres have grown down as far as the elbow. In practice, however, I have found the sign

gravely misleading more than once. The tapping may be transmitted by pulling on the end of the nerve above the injury; also, one has to be sure that the patient has not discovered that if he says he feels the tingling he may be let off operation!

The only reliable test is to explore the nerve and stimulate the trunk with the faradic current above and below the lesion. If it conducts, it will recover; if it does not, the scar should be excised and the two ends sutured. In an old-standing case with a small scar and the nerve apparently in continuity, it may be wiser to let it alone; regeneration may already have made some progress.

Pain and mottling of the skin are often more marked in cases of partial than complete division of a nerve.

The old controversy as to the method of nerve-regeneration is now definitely settled in favour of the view that the new nerve-fibres formed after suture are budded out from the cut central end. It will be found that new medullated fibres are present only in the proximal part of the regenerating nerve at first, whereas at a later date they reach the periphery. Only a few millimetres may have regenerated in a month. It has recently been shown, by Perroncito, that the fine fibrils which constitute the axis cylinders of the central end commence to grow, curl, bud, and branch within a few hours of the injury, apparently 'feeling for' the old track.

Mott and Halliburton have shown that if a nerve is cut and sutured, and time allowed for regeneration, after a second section at the same place the new

medullated fibres peripheral to the injury all degenerate. Had they been developed *in situ* by the activity of the sheath-cells, one would not expect degeneration after the second section, because they would not in that case have been cut off from their centre of origin. The deduction is that the new fibres were derived from the central end.

Convincing proof has been advanced by embryologists that the nerves in the embryo are not formed *in situ*, but are budded out from the nervous elements of the brain and spinal cord. By removing the medullary groove in frog embryos and planting it in lymph-clot, Ross Harrison has actually observed the developing nerve-cell grow out its axon at the rate of 20 in twenty-five minutes. The outgrowing axon is actively amœboid. He was able also, by destroying the ventral part of the developing spinal cord, to obtain tadpoles in which the muscles had no motor nerves. If it is allowed that in the embryo the nerves grow out from the central nervous system, the theory of central regeneration is placed upon a strong basis.

Two questions of great interest have recently received answers. First, Why does the medullary sheath of a nerve-fibre break up into fatty droplets when it is cut off from its trophic centre, that is, from its cell of origin in the central nervous system? Second, How does the budding axis cylinder of the central end of a divided nerve manage to find its way so accurately along the old path?

The questions are intimately related. Each furnishes the answer to the other. The medullary sheath

breaks up that it may liberate the chemical substance which attracts the sprouting axis cylinder. The new fibre follows the old path, because of the chemical attraction along that path.

Nature is full of analogies to this process of chemical attraction. Chemical particles, though infinitely diluted with air or soil, attract the vulture to the corpse in the desert, or the bloodhound to the hunted criminal. Smell is only a chemical analysis. Similarly, the leucocytes crowd out of the vessels to an inflamed area, in obedience to a law of chemical attraction.

If two celloidin tubes are presented to the central end of a divided nerve, the one containing emulsion of liver, and the other emulsion of brain, all the sprouting fibres pass into the brain emulsion, none into the tube containing liver (Forssman). The disintegration of the nervous matter lays down a line of bait to entice the regenerating fibres along paths of usefulness.

The phenomena of repair after suture next call for remark. It may be said at once that the sooner the operation is performed the better will be the results. If the muscles have ceased to contract to any form of electrical stimulus, operation is useless. It is very seldom that benefit will be obtained if two years have elapsed since the injury. When secondary suture fails to give a good result, the fault lies not with the degenerated nerve-fibres so much as with the nerve-cells in the spinal cord. If asepsis is secured, accurate primary suture seldom if ever fails.

Sherren, before the war, gave average time relations as follows :—

5–25 weeks : Commencing return of protopathic sense.
6–12 months : Complete return of protopathic sense.
12–18 months : Return of epicritic sense.
12–24 months : Motor recovery.

Taking the ulnar nerve as an example, recovery may be hoped for in twelve months when it has been divided at the wrist, or in twenty-four months when the injury was at the elbow.

These figures are rather on the slow side, judged by our experience during the war. According to Burrow and Carter, the average for the ulnar nerve (327 cases) was nine months ; sensation was never perfectly restored. The musculospiral began to improve in seven to eight months ; complete recovery was seen about the fifteenth month. In cases of median nerve injury (242 cases) the forearm flexors were restored in eight months, and the intrinsic muscles of the hand in fourteen to twenty months.

There is a good deal of variation, for some unknown reason, amongst the different nerves. The musculospiral recovers quickly and well after operation. The ulnar and the sciatic, especially the internal popliteal, are relatively slower and less perfect. It is apparently an advantage in healing that a nerve should contain principally motor fibres and not motor and sensory mixed, because there is so much the better chance of the down-growing motor fibres finding their way to muscle and not to skin.

In general, trophic and vasomotor recovery is the first to appear, then deep sensibility, then sensations of roughness and pressure pain. Radiating and ill-localized sensations referred to wide areas come next, then these give place to sensibility to light touch. By this time motor power is generally returning; it may come quite rapidly within a few days, and usually before the electric responses have returned to normal. Stereognosis returns late if it returns at all.

It sometimes happens that the recovery after a nerve injury, whether operated on or not, only extends to the proximal and not to the distal muscles. For instance, after section of the ulnar nerve, the forearm muscles may regain contractile power, but not those of the hand. This is especially likely to happen when there is a long gap of dense fibrous tissue, or fibrotic nerve, to be traversed by the young outgrowing fibres.

During recovery, a remarkable phenomenon has been described by Trotter, who had nerve sections performed upon himself. Any stimulus over the cutaneous area affected gives rise to a decidedly painful sensation, referred usually to the most distant part of that area.

Recovery after incomplete division of a nerve is more rapid, usually taking less than six months for sensory restoration; it is perhaps a year before motor power is normal. Protopathic sense does not return before epicritic, as it does when the nerve is completely divided; they are restored side by side at an equal rate.

The operation of *neurolysis*, or freeing a nerve from an adherent scar, is often followed at length by recovery, but it is probable that most of these cases, if not all, would have got well anyhow.

When a nerve-suture is being carried out, care should be taken not to rotate the ends, because there is evidence that the motor fibres destined for a particular muscle may run in a bundle in the nerve-trunk far above the point of origin of the twig given off to the muscle in question.

The last point we shall consider is how best to proceed when so much nerve has been lost that the ends cannot be got together. Many methods have been adopted, some of which are of little or no value and should be allowed to drop out of use. Amongst these may be mentioned the introduction of a bridge of silk or catgut, or of nerve derived from a cat, dog, or rabbit (which will undergo dissolution), and the device of splitting the nerve longitudinally and turning down one-half across the gap. It is quite evident why these fail. The silk, catgut, and probably the animal's nerve, cannot provide the necessary chemical attraction for the down-growing nerve-fibres. The splitting 'en-Y' does not lay down a continuous 'scent' along the tract; it is broken at the stem of the Y. Better results may be obtained by suturing into the interval a length of human nerve. This may be obtained from an amputated limb, but it is always possible to excise several inches of some unimportant nerve such as the internal cutaneous of the arm, and if this is too slender, two or more pieces may be used parallel to one another. The

nerve can be located before the anæsthetic is given by testing with an electric current; when the electrodes are applied over the nerve a tingling or pain is felt throughout its distribution. It is considered by some to be an advantage to protect the nerve junctions from invasion by fibrous tissue; this may be done by enclosing them in a ring or tube of superficial vein. Probably Cargile membrane does more harm than good.

There is yet another method, which is sometimes the only one available. Langley made some very interesting experiments on the effects of joining up the cut ends of different nerves, and found that their functions could be transposed. Thus he turned the cat's vagus into the cervical sympathetic, and allowed regeneration to take place. The vagus is of course the nerve of swallowing, and therefore, whenever the cat lapped milk, all the effects of stimulation of the cervical sympathetic were seen on the side operated on—dilatation of the pupil, starting of the eye, sweating, retraction of the nictitating membrane, pallor of the ear, bristling of the hair, and quickening of the heart-beat. When, however, the (purely sensory) lingual and the (purely motor) hypoglossal were crossed in like manner there was no result.

The method of nerve anastomosis was introduced into practical surgery by Ballance, who put part of the spinal accessory nerve into the peripheral end of the degenerated facial nerve to relieve intractable facial palsy. The result was excellent, but there was a tendency of course for the face and the trapezius to contract together, and smiling was accompanied

by jerking of the shoulder. The hypoglossal is now utilized instead of the spinal accessory to avoid this. It was hoped that there was a wide field of usefulness before this device of nerve anastomosis, especially in infantile palsy. For instance, if the anterior tibial muscles and peronei alone were affected, the external popliteal might be divided and the peripheral end put into a notch in the internal popliteal. Unhappily, published results are very disappointing, at any rate in the case of infantile paralysis; probably even the anterior horn cells supplying useful muscles have been damaged, and cannot take on more than ordinary work.

Our war experience has shown us that direct end-to-end suture of nerves is much superior to either nerve grafting or nerve transplantation. Some surgeons consider that both these devices are useless. We still await adequate lists of published end-results to enable us to decide the question. I have followed through eight cases in which I bridged a gap by transplanting two or three plies of the internal cutaneous nerve. Two were successful (a musculo-spiral and an external popliteal); six probably or certainly failed. Nerve anastomosis suffers from the drawback that notching the sound trunk may cause some paralysis of muscles that before the operation were intact; it is said that if no more than one-third of a trunk is divided, no paralysis follows, but only a very wide experience of notching every nerve in the body and in every part of their courses could justify such a statement.

Various devices of position may be made use of

to get the two ends of a nerve together across the gap, such as acutely flexing the knee for the sciatic ; such a nerve as the ulnar may with great advantage be displaced from behind the condyle. These procedures, whenever possible, are much to be preferred to nerve transplantation, and even more to nerve anastomosis. Some surgeons think it justifiable to resect the humerus and shorten it an inch, so as to get the ends of a nerve together. Sometimes, in the case of the musculospiral, a good result may be obtained by letting the nerve alone, and transplanting the tendons of the flexor carpi radialis, palmaris longus, and flexor carpi ulnaris into the extensors of the thumb and fingers.

Even after operation, a prolonged period of aftercare, with massage and electrical stimulation to prevent the muscles from becoming atrophic and functionless, is absolutely essential. A special point is that the paralysed muscle must be kept supported so that it cannot be stretched. Prolonged stretching is by itself sufficient to paralyse any muscle.

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CHAPTER XIV.

LOCALIZATION OF FUNCTION IN THE BRAIN.

LOCALIZATION OF SENSATION IN THE CEREBRAL CORTEX; VISION, HEARING, CUTANEOUS AND OTHER FORMS OF SENSATION—FUNCTIONS OF THE FRONTAL CORTEX—APRAXIA—APHASIA—INCREASED INTRACRANIAL PRESSURE.

THE large number of cases of localized injury to the brain occurring in the war has given a decided impetus to neurology. Painstaking investigations, of much larger groups of examples of a particular injury than civil practice could furnish, have been carried out by the most competent observers. Some of the results are given in this chapter.

LOCALIZATION OF SENSATION IN THE CEREBRAL CORTEX.

Vision.—It has long been known that visual sensations are received on the mesial surfaces of the occipital lobes, just above and below the calcarine fissure. Histologically, the area is mapped out by the white line of Gennari, which is a lamella of medullated fibres splitting the grey cortex, and by the occurrence in the pyramidal layers of certain stellate cells. This area slightly encroaches on the convexity of the hemisphere at the occipital pole.

This calcarine area is called the *visuosensory* cortex. For the interpretation of things seen we are dependent on the outer surface of the occipital cortex, the so-called *visuopsychic* area.

It is well known that the right half of each retina (that is, the nasal half of the left retina and the temporal half of the right) is represented in the right visuosensory area. Gordon Holmes and Lister have shown that a lesion of the upper lip of the calcarine fissure causes blindness of the upper half of each retina. This confirms previous work. Therefore a lesion of the left cortex above the calcarine fissure would render the upper left quadrant of each eye blind; the patient would not be able to see his right foot when sitting in a chair and looking straight forwards.

Further, they show that the macula, the point of most acute vision, with which we read, is represented in the little piece of visual cortex which overlaps the convexity of the hemisphere behind, and at the posterior end of the calcarine fissure. The representation is not bilateral, as used to be taught. If a bullet-track destroys the rest of the calcarine area but leaves the posterior poles intact, the patient's world looks as if seen through a telescope; the periphery is cut off.

Further, it is shown that each region of the visuosensory area corresponds to a region of the two retinæ, which always work together. That is to say, if the right calcarine fissure be taken as represented by the English Channel on the map, the North Sea standing for the occipital pole, then Dover

and Calais correspond to the region for the macula; Sussex and Hampshire, representing the sloping sides of the upper lip of the fissure, correspond to areas in each retina traversed by a line running from the macula horizontally to the right; and going up the Thames Valley, which represents the upper limits of the visuosensory area, corresponds to areas in the retinæ traversed by a line drawn vertically upwards from the macula—the higher on the cortex equals the higher on the retina, and the further forwards on the cortex equals the nearer the periphery of the retina.

Lesions of lateral surfaces of both hemispheres, the visuopsychic cortex, involving the angular, supramarginal, post-parietal, and occipital regions, give rise to loss of perception of size, depth, and distance, inability to recognize the nature of objects, and impairment of convergence and accommodation.

Hearing.—Although it is certain that monkeys which have suffered bilateral removal of the temporal cortex give every external evidence that they can hear, it is very difficult to be equally certain that sounds are still appreciated in consciousness by them, and recognized for what they signify. It is no more evidence of *conscious* hearing that a monkey looks round when a bell sounds, than it is of *conscious* pain that a man with a fractured spine withdraws a foot pricked by a pin. It might be a reflex from a lower-level centre, such as the posterior corpus quadrigeminum. Recently the whole cerebral cortex has been removed on both sides in monkeys (Macacus). One lived twenty-six days. They still responded

to noises by movements of the body and ears. Stimulation of the temporal cortex in monkeys causes pricking up of the ears.

At any rate, there is a fair amount of human evidence, both anatomical and clinical, to locate this function in the temporal convolutions and island of Reil, and none to locate it elsewhere. Fibres from the posterior corpus quadrigeminum, and some from the lateral fillet, which is well known to come from the cochlear nuclei, may be traced to this part of the cortex. Deafness and abnormal auditory sensations have been associated with disease of this region. Perhaps the most convincing observation on record was made by Harvey Cushing, who stimulated the exposed temporal cortex in a conscious man, and the patient said that he heard a buzzing noise.

There are cases on record of complete bilateral destruction of the temporal cortex with persistence of the island of Reil, and normal hearing. This may indicate that the island is more important as an auditory centre than the temporal convolutions.

Cutaneous and Other Forms of Sensation.—The great war has provided a wealth of clinical material for the study of those problems relating to the cerebral localization of the various forms of sensation derived from the limbs, which used to be so controversial. On this subject experiments on animals could give little or no information. Enormous lesions in monkeys were found to cause hemianæsthesia, but smaller removals gave rise to little if any defect of sensation. Sherrington has recently removed parts of the postcentral cortex

in a chimpanzee. The animal was not tame enough to allow detailed examination of its sensations afterwards, but there was no loss to the coarser methods of testing.

Cushing excited the postcentral convolution in two conscious patients who had previously been trephined, by unipolar faradic stimulation. He found that the brain itself was devoid of any sort of feeling, but that sensations of stroking, tingling, or warmth were produced, referred to the hand of the opposite side. The sensation was quite well defined and localized ; one area corresponded to the index finger, and another to the back of the hand. When the electrode was applied in front of the fissure of Rolando instead of behind, the fingers or hand moved, but there was no sensation. An incision in the postcentral convolution was quite painless, and caused some numbness of all forms of sensation in the hand.

Many years ago, before it was realized that the convolutions in front of and behind the fissure of Rolando differed in function, Ranson and also Laycock observed that a tingling sensation was elicited when they stimulated the exposed cortex in a conscious man, and apparently they both applied the electrodes in front of the fissure ; Cushing and others have failed to confirm this. Sir Victor Horsley published an account of the only case in which he had removed a cortical centre (part of the hand area) without encroaching upon the ascending parietal gyrus (for athetosis). Immediately after the operation there was complete flaccid paralysis of the arm

and some interference with sensation. The hand could detect cold, but not warmth; stroking with a wool pencil was not felt on the ungual phalanges; there was inaccuracy of location of pain and touch and loss of the sense of position; and objects placed in the hand were not recognized by touch (astereognosis). A year later, movement was recovered, except for some spastic paralysis in the two ulnar fingers; there were still astereognosis, inaccuracy of location, and slight dulling of sensation over the ulnar border of the hand. If the lesion had involved the postcentral cortex, the sensory disturbance, in his experience, would have been much more marked. The athetosis movements were cured.

It is quite certain that lesions in man involving the ascending parietal (postcentral) convolution almost always cause some interference with sensation, more so than defects of any other parts of the cortex would do. There is never complete anæsthesia, except just after an epileptic convulsion or injury, or in hysteria. Further, it is proved that the leg area is nearest the top, the arm area next, and that for the face lowest, corresponding to the distribution in the precentral (motor) convolution. Bergmark quotes thirty-three cases of lesions of the postcentral gyrus with sensory symptoms but no paralysis.

Sir H. Head has re-investigated the whole subject, using a large number of wounded officers and men as clinical material. The results are interesting and important. The more primitive sensations, those possessed by most vertebrates, such as tactile, heat,

and cold, are appreciated by the optic thalamus, which represents the primitive sensory cortex. It is the optic thalamus, also, that gives emotional colour to the sensations—that regards some as pleasurable, and others as painful. Obviously pleasure and pain are very primitive sensations. The degree of pleasure excited by, shall we say, gentle stroking or a spray of warm water, and the degree of pain excited by a pinprick, are partially damped down by impulses derived from the cortex. Fibres from all parts of the cortex converge on the lateral nucleus of the thalamus, and tend to control and inhibit excessive pain or pleasure arising from impulses received from the spinal cord. When this lateral nucleus is damaged, and only the mesial part of the thalamus is left intact, pinpricks are much more painful, and stroking or warmth more pleasant, than on the normal side. Sometimes music produces a remarkable emotional effect in the affected limbs, especially if it is solemn and majestic. A complete destruction, say of the right optic thalamus, produces hemianæsthesia of the left side of the body, with blindness of the right half of each retina, sometimes athetosis, and a curious form of facial paralysis. When the pyramidal tract is injured, causing hemiplegia, voluntary movements of the face are impaired, but emotional movements persist—a smile or an involuntary frown are still symmetrical. When the thalamus is damaged, voluntary movements are retained, but the emotional movements are no longer symmetrical. The explanation is that the emotional movements are of primitive origin, and therefore

controlled by the more primitive optic thalamus, not by the cortex.

A lesion of the postcentral cortex, therefore, does not cause complete anæsthesia, or abolish any of the senses of heat, cold, touch, or pain, because these are apprehended by the thalamus. The function of the sensory cortex is not merely to receive sensory messages, but to interpret them. If I hold a glass of hot water in my hand, the thalamus tells me that it is touching my hand, that it is hot, that it is unpleasantly hot; the middle part of the postcentral cortex, behind the motor area for the arm and hand, tells me that it is a smooth round glass, that it weighs so many ounces, and that it is of such and such a size.

Lesions of the postcentral cortex in the arm area produce the following disabilities. Certain fingers are affected, others are normal.

1. Sensations are very irregular and easily fatigued. A light touch or other means of testing is appreciated better at one time than another.

2. Recognition of space is very defective. The patient cannot recognize how much his fingers have been moved by the physician, he localizes badly, and two compass points are interpreted as one unless greatly spaced out on the skin tested.

3. He cannot judge weights, or compare shapes and sizes, or tell the difference between silk, velvet, cloth, and the like. When there is marked interference with sensation from a postcentral injury, muscular tone is deficient in the corresponding part.

We can go some way towards localization of these functions. A little loss of sensation may be produced by a lesion of the precentral gyrus, much more by injury of the postcentral, and some if the parietal convolutions just behind, and the angular gyrus, are involved. These constitute the sensory area of the cortex. The little finger is represented nearer the leg area, the thumb nearer the face area. Lesions of the precentral cortex particularly affect spatial sense; those of the postcentral gyrus have the greatest effect on judgements of weight and shape; marked disturbance of tactile sense indicates a lesion farther back or in the angular gyrus, which may also interfere with temperature sense. It will be remembered that Sir Victor Horsley's case of excision of the motor area for the hand had difficulty in localizing.

In reference to the views which have just been explained with regard to the emotional function of the optic thalamus, it is interesting to mention that Graham Brown has shown that stimulation of this nucleus in a chimpanzee gives rise to the movements which constitute laughter in apes.

FUNCTIONS OF THE FRONTAL CORTEX.

It is well known that the great motor centres are limited to the ascending frontal or precentral convolution. This has been abundantly proved by many methods: by the study of paralysis following localized lesions in man, or removals in man or apes; by electrical stimulation in man and apes; and histologically by the limitation to this region

of the giant pyramidal or Betz cells, which are the only cells to undergo chromatolysis when the pyramidal tracts are destroyed in the spinal cord.

The whole field of the observations on great apes has recently been gone over again by Sherrington and Leyton, using a truly generous amount of material—three gorillas, three orang-utans, and twenty-two chimpanzees. They give wonderful detailed diagrams of the exact spots that have to be stimulated to produce particular movements. They make a point that the cortex must not be allowed to cool, or the reactions no longer appear. After ablations of parts of the motor area, paralysis of course ensues, but there is a remarkable degree of recovery in a few days.

It often becomes of great importance to the surgeon to know whether a tumour causing hemiplegia is accessible, either in the cortex or close beneath it, or inaccessible, in the internal capsule or isthmus. The principal evidences of the former are the occurrence of monoplegias, the face, arm, or leg being affected alone without the others, whereas lesions of the internal capsule would paralyse all three;* secondly, persistent aphasia may be present; and thirdly, there may be recurring convulsions. The degree of sensory impairment is not of much assistance, but the considerations just advanced may sometimes be helpful.

* In monkeys the fibres to the head, arm, and leg are grouped in bundles in the internal capsule, but apparently this is not the case in man, and consequently small lesions cause mild hemiplegia, not monoplegia.

There is a good deal of evidence that if the paralysis is of a flaccid type the lesion is most probably cortical, though the converse is not necessarily true. In man, a cortical lesion is often (not always) accompanied by a flaccid paralysis with no Babinski sign and with normal or diminished reflexes (see cases quoted by Bergmark), but when the optic thalamus and internal capsule are involved, there is always marked rigidity. This subject has been referred to in the preceding chapter.

It is, however, true that *irritation* of the cortex, such as may be present just after a traumatic lesion, or during the growth of a tumour, may cause early contracture, so we should regard the *presence* of rigidity as an equivocal sign, but *absence* of rigidity as evidence of a cortical lesion.

The frontal cortex lying in front of the motor region is described as a 'silent area', and extensive tumours, degenerations, or injury may produce few or no symptoms. In a case under the writer's care, a wound one inch deep into the brain, from the vertex to the nose, caused by a chopper, made absolutely no difference to the woman's character, capacity, or intelligence, and indeed produced no symptoms at all beyond concussion, although she was under observation for many months. In the famous American crowbar case, where a large part of the frontal cortex on both sides was destroyed, there was no paralysis, but on returning to work the man, previously a capable foreman, had become weak, vacillating, inattentive, and profane. There are

quite commonly signs of mental dullness in patients with frontal lesions. In cats there are, after excisions of the frontal cortex, changes in the disposition, and recently acquired tricks may be lost.

Stimulation of this region, in Sherrington and Leyton's anthropoid apes, produced nothing but deviation of the eyes and opening of the lids. Similar results were got by stimulating the occipital cortex.

According to Sir Victor Horsley, abscesses of the brain involving the Rolandic area usually lead to a raised temperature on the opposite side of the body, whereas, if the location is in front of or behind this region, the temperature is subnormal.

APRAXIA.

More definite evidence, however, is now available. There are a number of carefully studied cases on record in which, with no actual paralysis, there has been a remarkable clumsiness in the performance of movements requiring any skill, and in which the patient has been quite unable to make some movement voluntarily or in response to command, although he may unconsciously do that very thing under the influence of emotion or by accident. This condition is called *apraxia*. It is most convincing when it is unilateral. Thus, a musician may lose the power of playing his instrument, or a clerk his power of writing. In Liepmann's classic case, one of the first to be described, there was apraxia of the right arm and leg. "Asked to put his right forefinger on his nose, he said, 'Yes', and with his stretched forefinger

executed wide circling movements in the air. He made the correct movement at once with his left hand. Asked to close his right hand into a fist, he performed various absurd movements of his arm and body, but attained the required goal at once with his left hand. When asked to give the examiner a certain object with his right hand, he frequently picked up the wrong thing, and, still holding it in his hand, used the left to take up the required object and present it to the physician." A patient of de Buck's, asked to lift her right arm, crossed it over her body, put it in her left axilla, and after making various other vigorous but futile efforts, said plaintively, " Je comprends bien ce que vous voulez, mais je ne parviens pas à le faire " : this just expresses the condition.

In some of the cases, there is imperfect recognition of objects or of their uses (agnosia), but these are complicated and cannot be described here.

It is an important fact that apraxia of the left arm is common in right hemiplegics, whereas apraxia of the right arm rarely occurs in left hemiplegics ; moreover, in the cases where there is apraxia of the left side with hemiplegia of the right, there is evidence that the lesion is cortical, not in the internal capsule. Thus Liepmann examined eighty-three hemiplegic patients, with these results :—

Forty-two had left hemiplegia ; they could nearly all obey directions with the right arm.

Forty-one had right hemiplegia ; of these, 20 had apraxia of the left arm, and 14 in this group also had aphasia (therefore the lesion was cortical) ;

21 had no apraxia, and of these only 4 had aphasia (in most of the other 17 cases the lesion was probably in the internal capsule).

Of course, as left-handed persons form one-twentieth of the community, it is possible to find a few cases of left hemiplegia with right apraxia.

There is good ground, then, for believing that the centres which *consciously initiate* voluntary movements for both sides of the body are limited to the left cortex in right-handed people, and that the precentral convolutions are merely the departure platforms for messages from the brain to the cord. Instructions are sent to the right precentral convolution by way of the corpus callosum. It is still in doubt whether the above-mentioned initiating centre is *in* the left precentral gyrus, or whether it lies *in front of* this, in the first and second frontal convolutions, as most neurologists maintain. It is quite certain that a lesion of the front part of the corpus callosum is characterized by apraxia of the left arm; this important discovery may well lead to successful surgical removal of tumours there situated. A lesion in the left frontal cortex may cause apraxia of both arms; there will probably be right hemiplegia also, which would mask the condition in the right arm.

To sum up, a lesion is cortical if there are present:

1. A monoplegia.

2. Hemiplegia with either (*a*) Aphasia which persists; (*b*) Recurring convulsions; (*c*) Flaccidity; (*d*) Apraxia of the opposite side.

Left-sided apraxia without hemiplegia indicates a lesion of the corpus callosum.

APHASIA.

The various types of aphasia have always presented problems of great complexity but of much interest. Recent studies of the subject have been very revolutionary in their tendency. We used to learn that there were three main centres for the appreciation and utterance of language, namely :—

1. *The motor centre*, controlling utterance, in Broca's convolution (the third left frontal).

2. *The auditory word centre*, appreciating spoken language, in the posterior part of the second left temporal convolution. This was also regarded as dominating and being necessary for the activity of the other two centres.

3. *The visual word centre*, appreciating written language, in the left angular gyrus, behind and above the auditory word centre.

Recently, however, the searching analyses of Marie and his pupils have raised very grave doubts about the first and third of the above, and many neurologists have agreed that Broca's convolution has no speech function at all ; very few now defend the existence of a separate visual word centre.

Briefly, the contention of Marie and Moutier may be put thus. Between 1861 and 1906, there have been published 304 cases of aphasia with autopsy. Of these, 201 were useless and 103 were relevant.

The majority even of the nineteen cases allowed by these writers they consider to be inconclusive for various reasons.

Useless	Lesion too extensive		175	
	Badly described		26	201
Relevant	Favourable to Broca's localization	Cortical lesions with aphasia	8	
		Subcortical lesions with aphasia	11	19
	Unfavourable to Broca's localization	Aphasia, but Broca's convolution normal	57	
		No aphasia, but Broca's convolution destroyed (in two cases, bilateral destruction)	27	84
				304

Two cases of Burckhart's are of sufficient surgical interest to be worth quoting. In the first, he removed 5 grm. of grey matter from the foot of the first and second left temporal gyri, but no word-deafness resulted. Eight months later he resected the cap and foot of the left third frontal gyrus (Broca's convolution), but no aphasia followed. In the second case he resected, in several operations, the left supramarginal, temporal, and third frontal gyri, but he failed to induce any speech defect. The patients were demented, with verbal delusions and logorrhœa, and the operations were done to stop their chatter. Needless to say, this was not a piece of British surgery.

Sherrington and Leyton removed Broca's area in a particularly vociferous chimpanzee, but the operation did not quiet it at all.

Marie maintains further that all patients with aphasia are mentally deficient; thus, the cook can no longer compound an omelette, and the pianist can no longer play the piano. He locates all the

speech functions diffusely in the left temporo-parietal region, maintaining that this is merely a region of intelligence specialized for language, and not a storehouse of sensory images; a mild lesion destroys the function last acquired, viz., reading, and a severer lesion produces loss of voluntary speech and of recognition of spoken language as well. What Marie calls 'anarthria'—a word previously used in another sense—meaning loss of power to utter speech, although the individual can say the words over to himself, is due to a lesion in 'the quadrilateral', bounded in front and behind by the anterior and posterior limiting sulci of the island of Reil, internally by the wall of the lateral ventricle, and externally by the surface of the island of Reil. In most cases of so-called Broca's aphasia, both the temporal cortex and the 'quadrilateral' are injured.

Defenders of the classical view, Dejerine in particular, have replied by advancing fresh cases with a lesion in Broca's gyrus with aphasia resulting; they contend that Marie's 'quadrilateral' contains the projection fibres of the third frontal convolution, which in their view explains the anarthria; and they maintain that most of the fifty-seven cases of aphasia in which Broca's convolution was intact were associated with much defect in understanding language spoken or written, and that the lesion was one of the dominant auditory word centre in the temporal lobe, without which Broca's convolution cannot work.

If it were proved that in cases of apraxia, previously

referred to, the lesion was in the first frontal convolution for the legs, and in the second frontal for the arms, the location of speech just in front of the motor centres for the face and mouth would receive strong support by analogy; but all this is still very uncertain.

Sir Henry Head classifies out aphasia on a functional basis as follows, and makes no attempt to relate the four types each to any particular localization of lesion.

1. *Verbal aphasia*, with defective word formation, but normal internal speech, and some ability to talk, but not perfectly.

2. *Nominal aphasia*, that is, defective use of nouns, in speaking and writing.

3. *Syntactical aphasia*, talking jargon.

4. *Semantic aphasia*, in which there is defective comprehension of the full meaning of words and phrases. Though the patient can speak and write, he cannot formulate a *general* conception, but only the details of which it is composed.

There are, however, cases to be met with of *pure alexia*, that is, loss of power to read though otherwise normal, and also of *pure agraphia*, in which comprehension of speech, talking, and reading are unaffected, but it is impossible to write. These two classes of patients show a subcortical lesion.

A patient who knows two languages, one native and one acquired, may recover the first, but not the second, after an attack of aphasia.

To sum up, we may express current opinion by accepting the existence of a large diffuse centre in

the left temporoparietal region in which recognition of spoken and written language and 'internal speech' take place; when it is seriously damaged these are all lost and the intelligence is impaired. Whether there is a special departure platform in Broca's convolution for uttering speech is uncertain, but probably there is. Lesions of the projection fibres from the cortex (? from Broca's convolution) will cause 'anarthria', that is, loss of external but not of internal speech.

Practical deductions are, not to trust aphasia as conclusive localizing evidence of a lesion in the left third frontal gyrus, but rather to look to the temporal region, especially if there is any defective appreciation of what is said or written; patients with left temporosphenoidal abscess, for instance, are usually unable to name correctly objects shown them. Moreover, we are encouraged to believe that there is no need to fear that small cortical injuries inflicted by the surgeon will cause aphasia; subcortical injuries are much more likely to do so, by cutting off projection fibres.

INCREASED INTRACRANIAL PRESSURE.

It is possible experimentally to produce optic neuritis, which is really an œdema of the optic disc and not a neuritis at all, by inserting bits of laminaria between the skull and the dura mater, which later swell up and encroach on the intracranial space.

There are two well-marked stages, as intracranial pressure, experimentally induced, increases. They

may be watched by putting in a glass window, and injecting water between the dura and the skull. At first, the pressure leads to a block of the venous outflow, and the brain is deeply congested. This stage is accompanied by excitement, spasms, and convulsions. Then, often quite suddenly, the dusky congested brain becomes white, when the pressure rises high enough to obliterate the veins, and paralytic symptoms ensue. Traumatic hæmorrhage on the surface of the brain is generally venous, not arterial, and the two stages are often quite well marked in clinical cases.

It is well known, of course, that the volume of the brain and cerebrospinal fluid within the skull can be altered scarcely at all, so long as the skull and spinal canal are intact. Any foreign body, such as a tumour, or a mass of blood-clot, or a piece of depressed bone, or a missile, can only be accommodated at the expense of the volume of circulating blood. To protect the vital medullary centres against fatal anæmia, the general blood-pressure is raised, and the blood races through the narrowed vessels of the brain at a much increased pace. The obvious treatment is to reduce the intracranial pressure by a lumbar puncture, or much more effectually by a large trephining. If the rise of pressure is of long duration, as in the case of a tumour, it is not necessary to open the dura (though usually advised) ; the steady pressure will cause the dura to yield. Sudden relief of tension in these cases, especially near the medulla, is very dangerous. Some surgeons remove a tumour of the cerebello-

pontine angle with a suction apparatus, so as to make the decompression as gradual as possible.

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CHAPTER XV.

THE ACTION OF CUTANEOUS ANÆSTHETICS.

DRUGS APPLIED TO THE UNBROKEN SKIN.

IT has been customary to relieve abdominal pain by the application of hot fomentations containing opium, to treat sprains and bruises with lead and opium, and to smear on glycerin of belladonna for the discomfort of white leg. What dyspeptic old lady has not worn a belladonna plaster over her heart, and what practitioner has not prescribed a belladonna liniment for vague aches and pains? The rationale of the treatment has been that belladonna, opium, and menthol are alleged local anæsthetics, and it is further supposed that they are absorbed by the unbroken skin. The truth is that they are *not* local anæsthetics, and that they are scarcely if at all absorbed through the unbroken skin. Neither aconite, cocaine, carbolic acid, belladonna, nor opium has any power to relieve pain when applied to normal, healthy skin.

It has been well said that " You have not proved a lie to be a lie, until you have shown how it came to be believed ". This is very true in science, and especially in medical science. The use of belladonna and opium to relieve local pain was an obvious deduction from their great power, when given by the

mouth, to relieve general pain by inducing sleep or allaying colicky contractions. In the case of belladonna and its alkaloid atropine, the fallacy was the more natural in that they have a genuine effect in paralysing nerve-endings; but, unfortunately, it is only the efferent nerve-endings in glands and unstriped muscle that are paralysed, not the sensory twigs in the skin.

The fallacy has been maintained by the practice of combining these drugs with other and more potent treatment; thus, belladonna is given with counter-irritants such as camphor or alcohol; warmth may be applied with the opium; friction helps the belladonna liniment to keep its reputation, and even the support of the strapping, with counter-irritants in it, assists the patient to believe in the value of a belladonna plaster.

We may go one step further, and say that the application of opium and belladonna to mucous membranes is equally futile. There is no evidence that opium suppositories after the operation for piles, or laudanum dropped into aching ears, have any direct local effect. Of course, morphia may be absorbed from the suppository, but in that case it presents no advantage over a dose given by mouth or hypodermically, and is less certain in its action.

To sum up, there is no drug in common use capable of acting as an anæsthetic on the unbroken skin, except ether and ethyl chloride, which freeze it, and the only drugs which relieve deep-seated pain when painted or rubbed into the skin are the counter-irritants.

Full details of the experimental data for these conclusions, which are accepted by the leading pharmacologists, will be found elsewhere. Briefly, the methods adopted were as follows.

Strong, even dangerously strong, solutions and ointments containing opium, atropine or belladonna, aconite, cocaine, carbolic acid, and menthol were rubbed into the skin of the finger, and on the tongue, and these were then examined to see if their sensibility was in any way altered. The methods of examining the skin of the finger were as follows. Each test was applied on more than one observer and after varying intervals of time.

1. *The Intolerable Temperature Test.*—For each observer there was a certain constant temperature which was just not intolerably hot when the finger was dipped into warm water for half a minute. This was determined before and after applying the drug under consideration.

2. *The Faradic Pain Test.*—The strength of current was determined, before and after the application of each drug, at which the damp finger first found electrical stimulation by means of electrodes led off from a faradic coil actually painful, the current used being small at first and gradually augmented.

3. *Thermal Discrimination Test.*—We found that we were able, by immersing the finger first in one beaker of warm water and then in another, to detect a difference in temperature of not less than one degree. This was tested before and after the application of each drug.

4. *General Testing* by means of a pin point, the

æsthesiometer, a wool pencil, etc., was also used. In testing the sensibility of the tongue, we used the faradic pain test as described above; we examined thermal discrimination by applying warm metal points at various temperatures; we used the æsthesiometer, and studied the effect of the drugs on taste.

Judged by these standards, the various drugs fared as follows:—

Opium.—A 5 per cent solution of morphine tartrate in water had no effect on skin or tongue.

Belladonna.—Very strong liniments had no anæsthetic effect. Indeed, if they had, the drug could be used instead of cocaine for eye surgery. The only sign we could obtain was diminution of sweating over the skin area treated. There was no flushing or blanching of the skin or mucous membrane.

Aconite.—Neither the B.P. liniment nor ointment had any effect on the skin. Solutions produced tingling of the tongue, but we were not quite confident whether there was or was not a little reduction in sensibility.

Cocaine.—Strong ointments and alcoholic solutions had no effect on the unbroken skin. Of course, if the skin is damaged, the effect is marked. A 10 per cent solution applied to the tongue produced considerable reduction of sensibility, by all our tests.

Menthol produces a curious stimulation of the nerve-endings which detect cold, as is well known. A discussion of its other actions would lead us too far, but any anæsthetic effect is purely that of a counter-irritant.

Carbolic Acid rather increases the sensitiveness of

the finger to painful stimuli. Its undoubted value in relieving toothache is due to its caustic action in destroying irritated nerve-endings. The numb feeling we get after prolonged soaking in 1–20 carbolic is due to the formation of a thin coating of killed epidermis over the hands.

The fact that even cocaine, which is thoroughly proved to paralyse sensory nerves, fails to produce the slightest effect when a 10 per cent solution in alcohol, or a 10 per cent ointment made with lanolin, is rubbed into the skin, is strong evidence that little if any of these alkaloids reaches the nerve-endings at all. Atropine finds its way into the sweat ducts sufficiently to reduce but not to abolish sweating by its action on the sweat glands. It is true that cases of poisoning from the application of belladonna to the skin are recorded, but only where there were abrasions or sores present, or perhaps in young children whose skin is very delicate.

It may be objected that there is sufficient clinical evidence of benefit from these drugs to defy negative results by experimental methods, but any who claim this must not confuse the issue by combining the belladonna or opium with camphor, heat, rest, or strapping. Again, it may be suggested that atropine, at least, has some vasomotor effect, but we failed to observe any, and indeed we doubt if it ever reaches the blood-vessels when rubbed into the unbroken skin.

It is a thankless task to pull down strongholds of belief, but it is necessary, if only to direct more attention to the true means of giving relief to pain, including general drug treatment, rest, massage,

counter-irritation, heat, and passive hyperæmia. Moreover, a recognition of the failure of drugs saves useless expense, and may banish from patients' houses some of the commonest of powerful poisons. Belladonna liniment, for instance, has been responsible for an immense number of alarms, illnesses, and even fatalities.

REFERENCE.

A. RENDLE SHORT AND WALTER SALISBURY, *Brit. Med. Jour.*, 1910, i, 560.

APPENDIX.

ABSORPTION OF NITROGEN FROM AMINO-ACIDS.

We have made several observations on patients 'fed' with nutrients of milk digested with pancreatic extract for twenty-four hours in an incubator, so as to convert most of the protein into amino-acids. Such nutrients are not irritating. An example of such a case is the following. (I am indebted to Mr. P. A. Opie and to Dr. Bywaters for some of the analyses.)

Case I.—A. H., age 25, female, suffering from vomiting and gastric pain, not relieved by a diet of peptonized milk, was put on nutrient enemata as follows :—

March 28–29.—By mouth : water.
By rectum : saline, 15 ounces three times a day.

March 29–*April* 1.—By mouth : water.
By rectum : 6 per cent glucose, 1 pint three times a day.

April 1–4.—By mouth : water.
By rectum : milk digested for twenty-four hours, 6 ounces every four hours.

April 4.—By mouth : peptonized milk.

	Urine in ounces	Ammonia N per cent	Daily output of N in urine in grams.	
March 28–29 ..	29		8·03	
,, 29–30 ..	22	3·2	6·28	Av.
,, 30–31 ..	26	0·8	4·36	6·04
,, 31–April 1*	26	12·3	5·56	
April 1–2 ..	16	12·7	7·66	
,, 2–3 ..	22	12·5	5·91	Av. 7·70
,, 3–4 ..	32	9·3	9·53	
,, 4–5 ..	31	0·5	9·02	

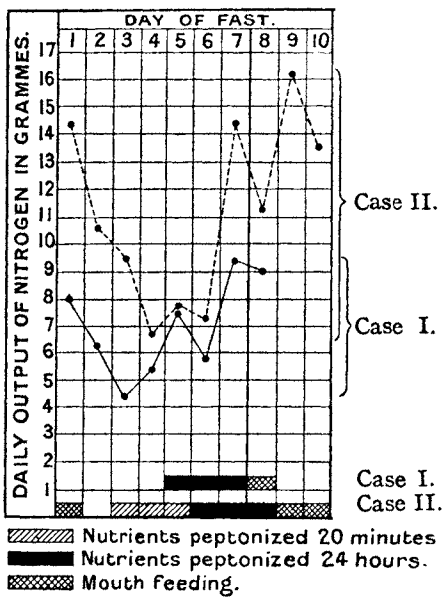
* Glucose not well retained.

It will be observed that instead of showing the usual steady fall, the nitrogen output is increased during the three days of feeding on amino-acids.

CASE II.—This patient, a man, was fed as follows, the daily output of nitrogen in the urine being also shown :—

	By mouth	By rectum	Urine in ounces	Ammonia N per cent	Daily output of N in urine in grams
April					
26–27	Milk	Nil	21	1·4	14·3
27–28	Water	Saline	19	2·9	10·7
28–29	,,	Milk peptonized 20 minutes; ℥v 6-hourly	21	3·5	9·6
29–30	,,	,,	20	4·8	6·8
30–May	,,	,,	16	2·9	7·9
May 1–2	,,	Milk peptonized 24 hours, ℥v 6-hourly, with ℥j of glucose	10	2·9	7·2
2–3	,,	,,	21	3·0	14·4
3–4	,,	,,	15	3·7	11·2
4–5	Pept. milk ℥v 2-hourly	Nil	23	2·8	16·1
5–6	Milk ℥vij 2-hourly	Nil	54	0·9	13·7

As the accompanying chart shows, the absorption and output of nitrogen are very considerably increased when the milk has been digested with pancreatic extract for twenty-four hours. The increased absorption, as usual, does not increase the output for about twenty-four hours.


DAY OF FAST.
1 2 3 4 5 6 7 8 9 10
DAILY OUTPUT OF NITROGEN IN GRAMMES.
17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1
Case II.
Case I.
Case I.
Case II.
Nutrients peptonized 20 minutes
Nutrients peptonized 24 hours.
Mouth Feeding.

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