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THE NEWER PHYSIOLOGY IN SURGICAL AND GENERAL PRACTICE

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PREFACE TO THIRD EDITION

READERS of the first edition of this book will find that approximately half of the present volume is new, hence the change in title. Large sections have been omitted to make room for these additions without greatly increasing the size of the book.

In the third edition, new chapters are introduced on vitamines and the genital glands; the articles on surgical shock, the digestive apparatus, the pituitary and pineal glands, and on chloroform poisoning are largely rewritten. There are also important additions to the chapters on the thyroid gland and the physiology of the spinal cord, besides minor changes elsewhere.

A. R. S.

June, 1914.

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 principally concern 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.

BRISTOL,
September, 1911.

The Newer Physiology in Surgical and General Practice

CHAPTER I.

VITAMINES.

Beri-beri—Growth—Scurvy—Rickets.

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 year or two, 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 is still a terrible scourge amongst the inhabitants of the Malay States; is often seen in coolies at English seaports; and has broken out in an asylum in Dublin. Improving the allowance of food in the prisons of the Straits Settlements has failed to limit the disease.

The outstanding feature of the incidence of beri-beri in the Straits is, that while the Tamils are exempt, the Chinese suffer 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 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 usually given has been that the bare rice grain becomes contaminated in some way; but recent experiments by Casimir Funk and others bring 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. Milk, yeast, and ox-brain all contain this mysterious substance, as well as rice-husk, and will cure the neuritis. From 100 kilos of yeast 2·5 grams of the crystals were obtained.

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.

The principle having been once 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 " vitamines."

Hopkins has lately 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 only a teaspoonful of milk is supplied daily, growth becomes normal. Even sarcoma-cells require vitamines, 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.

It has been known for centuries that scurvy is a deficiency disease ; but exactly where the deficiency lies has always been uncertain. In days gone by, sailing ships on long voyages were full of scurvy, the crews being thoroughly incapacitated by it, and many expeditions failing in consequence. When it became compulsory by law to carry fresh vegetables and lime or lemon juice, the disease became a thing of the past. It broke out during the siege of Paris. 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. Arctic and Antarctic explorers still suffer, and both Captain Scott's expeditions have given rise to cases ; but Nansen found that fresh meat, even without vegetables, is sufficient to prevent it ; and members of Scott's and Shackleton's parties proved the truth of this. Monkeys can be given scurvy by feeding on stale meat.

Much more commonly the disease is seen in young infants fed upon boiled, stale, or artificially-prepared milk. It is said that if the milk is bottled first and only just raised to boiling point, so that no precipitate is lost, scurvy does not occur. It is quite easy to prevent or cure it by giving grape or orange juice frequently.

Many suggestions have been made as to the exact nature of the deficiency in scurvy, the citrates, malates, and other alkaline salts being specially blamed ;

but these will not cure or prevent the disease. It was said that calcium citrate was precipitated from milk by boiling, but evidently this cannot be the explanation when citrates fail to control scurvy. Holst and Fröhlich have imitated the symptoms in guinea-pigs by confining them to a grain diet; they are rapidly cured by fresh vegetables or fresh milk. Milk heated to 70° is still efficient; if kept at 98° for ten minutes the antiscorbutic power is lost. No doubt a vitamine is destroyed. Probably this vitamine may fail at the end of a long lactation, even in fresh human milk, thus accounting for a few authentic cases of scurvy in breast-fed babies.

The bodies in milk which protect against scurvy and against beri-beri are not identical. They differ in their reaction to heat. All vitamines appear to be delicate substances which are lost in the process of keeping.

Rickets is, no doubt, another 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. We must wait for further observations before deciding whether the pathology of the disease is simply fat starvation, or whether the patients have been deprived of a necessary vitamine.

REFERENCES.*

FUNK.—*Brit. Med. Jour.*, 1913, i, p. 814; and articles in *Journal of Physiology*, 1911–1913.

HOPKINS.—*Proc. Royal Soc. Med.*, vol. vii, Nov., 1913; Therapeutical Section, p. 1.

* 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.

THE GENITAL GLANDS.

Functions of the ovary—Functions of the testis—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 has 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. We are as far as ever from understanding the real value of its occurrence. According to Blair Bell, a large quantity of calcium salts accumulate in the blood, which menstruation removes, menstrual blood being very rich in calcium.

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 bloodstained discharge followed by a brief period of fertility.

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 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. 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 a 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, aged 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.

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.

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 traveller's tale.

The symptoms of the artificial menopause following double oöphorectomy may be much relieved by grafting a piece 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.*

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

The Corpus Luteum. — 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 or in the human subject in the later months of pregnancy does not usually lead to abortion; one patient went on to full term in spite of double oöphorectomy as early as the sixth week.

Whether the internal secretions of the ovary are due to the corpus luteum or to the interstitial glandular cells is quite uncertain. There is some evidence of other obscure internal secretory functions besides those mentioned. A rare disease called osteomalacia, characterized by softening and bending due to decalcification of the bones, makes great progress during pregnancy, and in some cases at least is cured by a double oöphorectomy.

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. 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.

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 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 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.

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 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. The mere fact of infertility does not abolish sex, which is dependent upon the combined working of a number of internal secretions.

The Ductless 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, leads to sexual infantilism.

On the other hand, great enlargement, and therefore presumably, hypersecretion of the cortex of the suprarenal (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 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 aged seven showed precocious development and menstruation; an ovarian swelling was removed, and the signs of puberty subsided.

It is found in gynæcological practice that thyroid and pituitary feeding may hasten puberty in cases where it is unduly delayed. 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 Ductless 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.

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 recently 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, and we have not yet found a way to utilize this in the human subject.

The physiological stimulus which starts the lactation is an internal secretion derived from the fœtus. 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.

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 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

* Some English text-books incorrectly say the first.

chemical factor, at any rate in sea-urchins and star-fish, because in these animals the purely female ovum can be induced to develop into a larva by concentrated seawater, tannin, or even violent shaking. Perhaps, however, these animals are not far removed from parthenogenesis, and the part played by the male in vertebrates is probably more important.

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 fertilization 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.

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 clinical value.

REFERENCES.

MARSHALL.—" The Physiology of Reproduction."
BIEDL.—" The Internal Secretory Organs," 1913.
BLAIR BELL.—*Proc. Royal Soc. Med.*, 1913, Dec., vol. vii, Obstetric section, p. 47.

CHAPTER III.

SURGICAL SHOCK.

The exhausted vasomotor centre theory of Crile and Mummery—The acapnia theory of Yandell Henderson—The oligæmia theory of Cobbett and Vale—The adrenalin exhaustion theory—The nature of surgical shock; its diagnosis, treatment, and prevention—Intravenous saline transfusion.

THERE were four great barriers which stood across the path of the first pioneers of surgery, and even to this very day make the quack and the bonesetter hesitate to resort to the knife. The first of these was hæmorrhage. The second was pain. This barrier fell down when anæsthetics were introduced. The third was sepsis, a danger which Lord Lister showed us how to triumph over. The last great barrier to be conquered is shock. But three victories make us very confident of final success, and we believe that one day surgery will have lost its main terrors and will be able to bring benefit to patients who are now doomed to die unrelieved; for instance, cases of intracranial or intrathoracic disease, and what we now call inoperable carcinoma. We may not hope to prevent or treat surgical shock until we have an accurate conception of its nature and causation, and we shall proceed to pass in review some of the suggestions which have been made, and to see how they fare under the criticism of exact experiment.

It will be useful first to quote from an esteemed writer the symptoms of shock as they appeared before attempts had been made to fit them into any of the modern theories. Sir W. Watson Cheyne wrote in 1898 : " The patient who is suffering from shock is usually found lying in a state of complete muscular relaxation, or if he makes any movements they are very irregular and feeble. The face is pale and drawn, the pupils dilated, there is sweating about the head, the reflexes are very slight, there is diminished sensibility, but not absolute unconsciousness. The patient can answer questions when spoken to, but if not disturbed will generally lie in a semi-conscious condition. The respirations are feeble, irregular, and sighing. The pulse is small, frequent, and dicrotic. At first the pulse-rate is generally slowed, and increased frequency of the heart beat is regarded by some as a sign of the commencement of reaction. The skin is cold ; the temperature subnormal." With the possible exception of the statements concerning the pulse-frequency, this clinical picture will command universal assent. We shall have to refer to it again later.

THE THEORY OF CRILE AND MUMMERY.

The essence of the theory is that the vasomotor centre in the brain is first stimulated and then exhausted by painful, or as we should now say nociceptive, impulses coming to it from the afferent nerves. All the phenomena of shock are due to this primary exhaustion of the vasomotor centre. The most characteristic index of shock is the fall

of blood-pressure. It will not be necessary here to set forth the arguments by which this view was defended. Surgery undoubtedly owes a great debt to Crile's researches. He has established for us the importance of the sphygmomanometer in measuring shock, the value of nerve-blocking in preventing it, and the general principles of its avoidance and treatment. Nevertheless, it is scarcely going too far to say that the theory is beyond doubt erroneous. It has been maintained by a number of competent observers, both on clinical and experimental grounds, (*a*) That the peripheral arteries may be contracted, not dilated, during shock; and (*b*) That the vasomotor centre is not necessarily exhausted, even in extreme shock. If the failure of the vasomotor centre was the main factor in the genesis of shock, an examination of the pulse and blood-pressure would be a sure indication of the patient's condition. No doubt a bad pulse and a fall of tension are grave signs, but no surgeon, anæsthetist, or practitioner accustomed to judge of the prospects of a patient after a severe operation will dare to maintain that because the pulse is good and the blood-pressure normal there can be no fear of death from shock. Only too commonly, in spite of an apparently efficient vasomotor centre when the patient leaves the table, severe depression of all the vital functions comes on a few hours later, and death follows. There may be shock, then, with a normal blood-pressure.

Again, Mr. J. D. Malcolm has repeatedly pointed out that the condition of a patient in shock does not correspond with the clinical picture of vaso-

motor paralysis. Compare it, for instance, with belladonna poisoning, in which the small arterioles are undoubtedly released from nervous control, causing, as we know, a flushed skin. In shock, on the other hand, the skin is pale, the pulse is small, bleeding is scanty, and the anuria suggests that the renal vessels are contracted. The abdominal viscera are pale unless they have been long exposed. Seelig and Lyon point out that the retinal blood-vessels are contracted to one-half or one-third their normal calibre, and amaurosis may occur (it is possible, however, that the retinal vessels, like the cerebral, are not under the direct control of the vasomotor system). Warmth does the patient more good than cold, whereas if the cutaneous vessels were dilated the reverse should be the case. Mr. Malcolm's observations have not attracted the credence they deserve, because it is so difficult to understand how there can be a fall in blood-pressure with an efficient heart and contracted vessels.

Animal experimentation confirms the clinical findings. Even Professor Crile consistently records that the arteries in shock are empty. He also points out that crushing the testes causes a primary fall in blood-pressure without a previous rise ; the vaso-motor centre, therefore, cannot be in a condition of fatigue exhaustion. Seelig and Lyon measured the outflow from the cut femoral vein of an animal in five-second periods. The sciatic nerve was then cut, and the flow of course increased in consequence of the withdrawal of tonic vasoconstrictor impulses. They repeated the experiment on animals in a

condition of extreme shock. The outflow was naturally less than normal, but on cutting the sciatic nerve there was a prompt and considerable increase in the flow. Therefore the vasomotor centre must still have been sending out tonic impulses. Again, they found that in normal animals stimulation of the central end of the cut vagus causes a rise in blood-pressure. The rise is just as marked, in proportion, if the experiment is repeated in an animal in a state of extreme shock. Therefore, again, the centre cannot be exhausted. Porter found that the fall of blood-pressure due to stimulation of the depressor nerve also takes place, and is proportionally as marked, in shocked animals. Tyrrell Gray and Parsons found that when an animal is in a state of shock consequent on an operation on the hind limbs, so that stimulation of the sciatic nerve causes a fall instead of a rise of blood-pressure, yet stimulation of the brachial nerves will still produce a rise. The fatigue, therefore, was in the afferent pressor paths, not in the vasomotor centre.

We are left, then, with the conclusion that although shock commonly induces a fall of blood-pressure, the vasomotor centre is not primarily exhausted, and the vessels may be contracted. How can this paradox be explained? Boise believes that the cause of shock is spasm of the heart, but his view has met with little favour, and his experimental evidence is unsatisfactory. All observers agree that the heart has not seriously failed in shock. It responds excellently for a time to the extra work put upon it by a large saline transfusion. It is true

that the output of the ventricles in shock is small, but this is due to deficient filling, not to impaired contractile power. Once again, then, we must face the crucial paradox of shock, a fall in blood-pressure, in spite of normal heart and contracted peripheral arteries.

THE ACAPNIA THEORY OF YANDELL HENDERSON.

During the past few years a most important, if not revolutionary, series of papers has been appearing in an American journal of physiology, by Yandell Henderson and other workers in the Yale school, dealing with surgical shock in animals.

Because carbon dioxide is exhaled from the body by the lungs ; because, in conditions of asphyxia, the amount of the gas is greatly increased in the blood, it has perhaps been too readily assumed that it is nothing but a poison, and serves no useful purpose in the body and in the blood. Haldane and Priestley showed several years ago, that the activity of the respiratory centre depends, in ordinary circumstances, entirely on the CO_2 content of the blood. When this rises above a certain figure, constant for the individual, respiration is stimulated. This is the cause of each succeeding breath we draw. The gas is being furnished to the blood by the muscles, glands, and other tissues continuously ; each movement of expiration reduces the blood content. In violent exercise the breathing is excessive because more CO_2 is given off by the tissues ; after a swim under water it is excessive because the gas has been accumulating.

After several voluntary deep breaths, there is a quiescent interval, called *apnœa*, due to the reduction of the carbon dioxide to such a low figure that it is some time before it reaches an amount sufficient to stir the centre into activity again.

It will be noted that it is not lack of oxygen that excites the respiratory centre, but the rise of the CO_2 above a certain percentage. This has been shown not only by blood-gas analyses of the arterial and venous blood, but also and more especially by an estimation of the carbon dioxide in the air contained in the alveoli of the lungs. This percentage is a constant for the individual. In the open air or in a crowded room the ventilation by the lungs is so regulated as to maintain this constant. It does not vary in the alveoli, because it varies only within the narrowest limits in the blood. The amount of oxygen, on the other hand, is by no means constant.

Now, so far, there is no apparent application to surgical shock. But Henderson's thesis is that, not only does lack of carbon dioxide induce apnœa, that is, cessation of the activity of the respiratory centre, but it also reduces other important functions, so that the heart beats more quickly and the blood-pressure falls. This reduction of the CO_2 is called *acapnia*, and the suggestion is that acapnia is the prime cause of shock (*a* = lack of ; *capnos* = smoke).

According to Henderson, the deep and rapid breathing which, as we all know, is induced by pain, excitement, or exposure and handling of the intestines, reduces the CO_2 in the blood to a very low figure, whilst the oxygen, of course, is increased. This is

undeniable, and his blood-gas analyses bear it out in animals. Therefore, when the stimulus ceases, breathing becomes very shallow and occasional, and at the same time the blood-pressure falls and the heart beats quickly. This condition may lead to death, and indeed this is the usual consequence in animals. Henderson's theoretical conclusion as to the cause of death is that it is due to lack of oxygen, the store becoming exhausted before the CO_2 rises high enough to stimulate the centre into activity again; but this conflicts with the observation of Haldane and his coadjutors, that when the oxygen tension falls below 13 per cent of an atmosphere, lack of oxygen assumes the power of driving the respiratory centre whatever the CO_2 may be. Perhaps this effect is due to acid products thrown out by the oxygen-starved tissues.

Apart from the dubious explanation, however, the facts merit careful attention. It is possible in animals, merely by excessive artificial respiration, to reduce the CO_2 so much that respiration is shallow, the heart becomes rapid, blood-pressure falls, and death ensues in about three hours. On the other hand, when the pulmonary ventilation is reduced, and the carbon dioxide in the blood kept at or near its normal figure, very prolonged operations on dogs, extending over seven hours with the thorax opened, result in little or no shock. The rate of heart-beat and the blood-pressure can be varied exactly with the pulmonary ventilation. It is possible to make analyses of the blood-gases with about 3 c.c. of blood by Barcroft's method, from time to time. The means

by which carbon dioxide can be restored, and shock prevented or removed, are: the infusion into a vein of saline saturated with CO_2, and the increase of the dead space of the respiratory apparatus by making the animal breathe through a long glass tube, so that there is a good deal of to-and-fro breathing of expired air.

How then are the fall of blood-pressure and the quickening of the heart to be explained?

Crile and Henderson agree that there is no primary cardiac failure. After intravenous transfusion, for instance, the heart is perfectly capable of recovery. Henderson finds the primary cause of the failure in the *venous pressure*. When there is a reduction of CO_2 in the blood, the walls of the veins and the tissues supporting them relax, the pressure in the veins falls, blood accumulates in them, and only a small amount is transmitted to the heart. For a time, by constricting the arteries, a fair blood-pressure can be maintained; at last the supplies reaching the right auricle become so reduced that the arterial pressure falls, the heart-beat becomes quick, the output is small, and severe shock is now established. The quickened heart-rate may be due to some extent to escape from vagus control, the activity of the vagus centre suffering reduction, like that of the respiratory centre, on account of the low blood-content of carbon dioxide.

Some other factors of importance require mention. It is well known that operations involving exposure of the intestines, especially if they are handled and pulled about, are apt to induce shock. Henderson

shows that when the abdominal viscera are exposed to a current of air, they rapidly exhale CO_2. The rate of loss is about forty times as great as that from the skin. Consequently there is both a local and a general reduction of the carbon dioxide. The vessels of the peritoneum become dilated, peristalsis is reduced or inhibited altogether, and the systemic lack of CO_2 results in apnœa and, finally, the vascular phenomena of shock. It is well known that in partial asphyxia the intestinal movements are exaggerated. If the peritoneal cavity is filled with CO_2 gas, peristalsis is very active, like that seen with the x-rays in a normal animal, and quite unlike the quiescence which we are accustomed to observe even under light anæsthesia. Saline fluid saturated with CO_2 also produces peristalsis, avoids that paralytic condition of the bowel which is a bugbear of abdominal surgery, and prevents the redness and congestion of the vessels induced by the local acapnia.

Whilst the handling and pulling are actually going on, the painful stimuli are sufficient to avert fatal respiratory failure. It is well known that any pain increases the rate and depth of breathing. If death from shock occurs at this stage, it will be by failure of the circulation. But as soon as the painful impulses cease, neither pain nor CO_2 is present to stir the respiratory centre into activity, and death by failure of respiration soon ensues. It is a commonplace that patients usually survive the operation itself, but may die of shock a few hours afterwards. Henderson found that even a few minutes' cessation of the stimuli would allow the animals to lapse into

this fatal apnœa, while breathing could be restored on resuming the handling.

Deficiency of CO_2 in the blood has another remarkable effect. When the deviation from normal is considerable, there is a tendency for fluid to exude from the plasma into the tissues with great rapidity. This was first demonstrated by Sherrington and Copeman. The plasma therefore becomes concentrated, and the total volume of the blood is diminished. This further reduces the output of the heart. When this outpouring has become established, transfusion ceases to be of more than temporary benefit. Early in the course of shock, the introduction of saline into a vein will cure; later on it fails because the fluid merely escapes into the tissues.

Shock, or a condition exactly analogous to shock, may be induced not only by injury or pain, but also by toxæmia. Whilst Crile was investigating the former condition, Romberg and Pässler were making observations on the latter. They found that toxæmic shock was identical in its main features with traumatic shock, and, like Crile, they considered that it was due not to heart failure but to exhaustion of the vasomotor centre after prolonged activity. According to Henderson, however, in both these conditions it is the venous pressure and the venous return to the heart which are subnormal in the first place, and the final fall in the arterial pressure is due not to exhaustion of the vasomotor centre, but to the reduced output of the heart; this reduced output, in its turn, being due not to cardiac weakness but

to inadequate entry of blood along the venæ cavæ. Both Crile and the German observers laid great stress on the fact that stimulation of a sensory nerve fails to induce the usual rise of blood-pressure, by reflex arterial constriction, when advanced shock is present, and they interpreted this as due to exhaustion of the vasomotor centre; according to Henderson, the truth is that the centre is already sending out its maximum of impulses, but that the pressure is low notwithstanding, because there is so little blood actually circulating. He remarks that if the arteries were paralysed, an intravenous injection of saline would not raise, as it frequently does, the arterial blood-pressure to normal, "because the blood would run out through the capillaries too easily for any pressure to be developed."

There is experimental evidence that the venous pressure is not regulated by the nervous system, but rises and falls with the amount of CO_2 in the blood. Adrenalin has no influence on it. The carbon dioxide acts partly by influencing the tone of the muscle in the vein wall and in the supporting external tissues, and partly by controlling the escape of fluid by osmosis.

The measures which he used to *prevent* shock were to diminish the loss of carbon dioxide by keeping the artificial respiration very slow, and using a long tube attached to the trachea, so that a good deal of the expired air was in-breathed again. To *relieve* shock he adopted three measures:—

1. Pouring warm saline saturated and bubbling with CO_2 into the abdomen, and closing the cavity.

2. Transfusing warm saline saturated and bubbling with CO_2 into a vein.

3. Allowing the animal to breathe in and out of a bag containing air or, better, oxygen.

The saline is saturated by shaking it in a flask through which carbon dioxide has been bubbled from a cylinder or Kipp's apparatus; it is then warmed. The delivery tube from the CO_2 cylinder may be introduced into the abdominal cavity, and the gas bubbled through the fluid.

We may sum up the sequence, then, as follows :—

1. *Hyperpnœa*, that is, excessive breathing due to painful or nociceptive impulses.

2. Leading to *acapnia*, that is, reduction of carbon dioxide in the blood. In abdominal operations carbon dioxide is exhaled from the intestines, giving rise to a further reduction.

3. Acapnia causes *failure of the veno-pressor mechanism*, that is, loss of tone and consequent dilatation of the veins. According to the author, venous tone is controlled by the CO_2 in the blood.

4. *Venous anoxhæmia, tissue asphyxia, acidosis.*—Owing to the reduction of CO_2 in the blood, the respiratory centre is not roused to activity, and the oxygen in the blood is therefore not renewed, so that the tissues suffer from deprivation of oxygen, and acid products enter the blood.

5. *Acute oligæmia.*—Henderson considers that loss of carbon dioxide leads in some obscure way to rapid escape of the plasma from the circulatory blood out into the tissues.

6. *Death*, usually from tissue asphyxia, or from

failure of enough blood to get back to the heart to continue the circulation, on account of the oligæmia and the dilated toneless veins.

Whilst fully recognizing the great value of this research, the labour expended upon it, and the learning with which it has been supported, the present writer, although at first attracted by the theory, has felt compelled to abandon it as an explanation of routine surgical shock in man. No doubt it is possible to induce a condition resembling shock by acapnia in animals, and probably in man, and enthusiastic anæsthetists who are experimenting with the intratracheal administration of ether will do well to study Yandell Henderson's original papers.

The objections to acapnia as an explanation of human surgical shock following injury or operation are as follows. Some purely physiological criticisms are omitted. (1) Hyperpnœa from painful stimuli is not sufficiently severe or prolonged, one would have thought, to reduce the CO_2 from 40 to 50 per cent, the normal, down to 10 per cent, as in some of Henderson's analyses of the blood in shocked animals. Shock often comes on quite soon, in half an hour or less. (2) If the theory were true, shock would be impossible during an operation where a Clover's inhaler was used throughout. Some anæsthetists believe that the Clover is better than open ether in averting shock, but no one will suggest that any operation, however severe, can be performed with safety provided the patient is kept blue. (3) Even in animals in a condition of acapnia it was not found possible to save their lives by carbon

dioxide. (4) All Henderson's work was upon animals under experimental conditions. It is quite unsafe to apply the results to human surgery without study of the CO_2 content of the blood in man. The writer has therefore made analyses of the blood of patients and normal persons by means of Barcroft's apparatus. A hypodermic syringeful of blood was withdrawn from the median basilic or other vein, and the CO_2 content estimated immediately. It was found that in five patients showing shock, three of whom died, the quantity of carbon dioxide present was about 46·9 per cent, that is, a fraction higher than the normal. In Yandell Henderson's observations the CO_2 fell to 10 or 20 per cent. Two patients with cyanosis showed a rise to 59·5 and 74·2 per cent, proving that the method of estimation was capable of detecting the variations. Janeway and Ewing have recently published the results of some animal experiments showing that excessive artificial respiration will induce shock even if the CO_2 content of the blood is kept high.

We conclude, therefore, that acapnia is not the cause of ordinary surgical shock. We are still left face to face with the problem of a falling blood-pressure with normal heart and contracted arteries.

THE OLIGÆMIA THEORY OF COBBETT AND VALE.

There is one very tempting explanation of the phenomena of shock to which attention must next be directed. If the total blood volume were reduced

(*oligæmia* = scanty blood) the blood-pressure would fall and yet the heart and vasomotor centre might act well and the arteries be constricted. Sherrington and Copeman have shown that intraperitoneal operations and also scalds in animals do, as a matter of fact, raise the specific gravity of the blood. An intestinal anastomosis lasting a quarter of an hour raised the specific gravity in one animal from 1·054 to 1·062.

Roy and Cobbett opened the abdomen in dogs and cut, pulled, or ligatured the intestines for 12 to 18 hours continuously under an anæsthetic. At first the blood showed no change, then its specific gravity rose steadily, as much as by 0·014 at the end of the prolonged manipulations. The specific gravity of the intestines fell; that of the muscles rose. The blood-pressure began to drop some hours after the specific gravity of the blood rose. Cobbett has published these researches with the suggestion that a similar concentration of the blood is the causative factor in surgical shock, and Vale has attempted to establish the theory by blood examinations in man. On this view shock and collapse are identical. The suggestion is, of course, that the fluid lost has been poured out into the injured area. Grünbaum is quoted by Cobbett as having examined the blood after three laparotomies in man, and in each case there was a rise of from 5 to 7 points, but no details are given. Vale made observations on four patients, estimating the specific gravity by the Roy method. In the first case an abdominal fistula was closed by operation; the specific gravity before operation was

1·053, and afterwards 1·063; there is said to have been "mild shock," but the blood-pressure was 130. Three other cases were accidents each showing "mild shock." The results were as follows: Case 2, when seen, specific gravity 1·063, next day 1·058. Case 3, when seen, specific gravity 1·066, next day 1·064. Case 4, when seen, specific gravity 1·063. next day 1·058. Although one is attracted by this theory at first sight, and it has been accepted by Malcolm and Yandell Henderson, it is difficult to understand where all the fluid has escaped to, or what drives it out. One does not see much exudate, for instance, in an amputation at the hip-joint, but shock may be severe. Vale's analyses were made by the difficult Roy method, and although his figures appear higher than usual, this is due to the fact that those ordinarily quoted are obtained by Hammerschlag's method, which gives results decidedly lower. Moreover, it does not appear that any of Vale's cases were suffering from a marked degree of shock. However, it was not difficult to obtain definite evidence as to the correctness of the theory, and I have therefore estimated the specific gravity of the blood in a number of cases of surgical shock.

Method.—Hammerschlag's method, slightly modified, was employed. A mixture of chloroform and xylol was prepared having a specific gravity approximately that of blood. A few drops of blood were obtained from the patient's ear, without squeezing, and immediately transferred by a capillary tube to the mixture, to which chloroform or xylol were

added until the blood neither rose nor sank. The whole estimation needs to be carried out quickly. Then the specific gravity of the mixture was taken with a hydrometer. It is easy to obtain readings correct to the third decimal. As Levy has pointed out, the method gives results which are rather too low, because the hydrometer is graduated for watery solutions, and surface tension in the chloroform-xylol mixture is different. One has therefore to use the same hydrometer and correct its readings by a special estimation. With the hydrometer used in these experiments one has to add 0·003 to the reading obtained. The normal specific gravity of human blood is about 1·057 in women and 1·060 in man. These results are rather higher than those quoted by the older text-books, because these did not correct the hydrometer readings. All the figures given here are corrected readings. Out of a large number of analyses made on patients under the care of various surgeons at the Bristol Royal Infirmary, it was found that there was never a marked rise of specific gravity in ordinary surgical shock. In all but one case, there was practically no rise, and several times there was a fall. Therefore oligæmia cannot be an important factor in shock. Three typical analyses are given here as illustrations.

1. Female, aged 43. Wertheim's hysterectomy for cancer of cervix. Full anoci-association. Bladder wounded and sewn up. Bad shock at end (two hours), pulse quick and feeble, blood-pressure 70. At beginning, specific gravity, 1·046 ; at end, specific gravity, 1·047. *Sequel*, died fifteen hours after.

2. Male, aged 40. Arthroplasty of hip; patient feeble, with ankylosed spine. Took one and a half hours. Pulse soft and feeble, disappeared at intervals. Blood-pressure near end, 85; temperature after operation, 96·6°. Specific gravity at beginning, 1·062. Specific gravity at end, 1·063. *Sequel*, recovered. Blood-pressure three days later, 115.

3. Female, aged 18. Extensive burns seven hours before, involving abdomen, buttocks, thighs, hands, and arms. Pulse good, but looked ill; vomiting; thirsty. Specific gravity, 1·072. Next day, specific gravity, 1·072. Twelve days later specific gravity, 1·059. *Sequel*, recovered.

It will be observed that Cases 1 and 2 showed every sign of grave shock, but there was no considerable alteration of specific gravity; nothing but a rise of 0·010 would influence blood-pressure.

In Case 3 and in other burn cases, however, there was a very remarkable rise, corresponding to a loss of fluid of about one quart, and lasting over twenty-four hours. Probably this is the cause of some of the symptoms of a severe burn, and obviously the administration of saline is urgently indicated.

A third point of interest is with reference to two cases of Wertheim's hysterectomy. It was observed that the specific gravity before operation was very low—1·048 and 1·046, instead of 1·057. This was probably the result of prolonged loss of blood. Both cases died from shock. It has been found by Douglas that a fall in the specific gravity of the blood is common in cancerous cachexia. We may have here an easy means of detecting cases whose general

condition is already too grave to permit of major surgery. The estimation of the specific gravity is simple, only takes three minutes, and can be done with a drop or two of blood. It remains to be determined just where the limits of safety lie. In the two fatal cases there was a fall of 0·010.

THE SUPRARENAL EXHAUSTION THEORY.

Perhaps no one has definitely formulated any such theory as yet, but it is certainly deserving of examination. Recent physiological research has shown that painful stimuli lead to a reflex outpouring of adrenalin from the suprarenal glands into the circulating blood. If this took place to a considerable extent there would be a preliminary rise of blood-pressure, followed, perhaps, by suprarenal exhaustion and a profound fall of pressure in spite of a normal heart and vasomotor centre. Bainbridge and Parkinson found absence of the chromaffin substance in the medulla of the suprarenals in two patients who died from shock. Priestley found the same absence in 84 per cent of cases dying with a low blood-pressure. Here, at least, is a *primâ facie* case for the suprarenal exhaustion theory.

Examination of the chromaffin substance is not a very convincing means of settling the problem. It is quite probable that the chromaffin substance and the adrenalin content run parallel, and there are observations in support of this view, but it would be much more satisfactory to make direct estimations of the quantity of adrenalin in the blood and in the suprarenal glands in cases of shock. For this purpose

I have devised an *adrenalinoscope*, which is a further advance on a method already used by Douglas Cow and also by O. B. Meyer.

THE AUTHOR'S ADRENALINOSCOPE.

A rabbit is killed by a blow on the head, and the thoracic aorta rapidly dissected out. With fine sharp scissors a spiral strip of aorta is cut about a quarter of an inch wide from the whole length of the aorta. We thus obtain a strip about three inches long, in which the circular muscle of the aorta is running longitudinally, so that a vasoconstrictor drug will induce shortening. One end of the spiral is transfixed on a hook secured in a cork at the bottom of a vertical glass cylinder, and the upper end is connected by a thread with a long lever recording its movements on a smoked drum. The spiral is, of course, stretched straight by the weight of the lever. The glass cylinder contains warm normal saline, which can be drawn off through a tube with stopcock in the cork at the bottom, and replaced by running in the test fluid gently down the side of the cylinder containing the strip of aorta. If any appreciable quantity of adrenalin is present, the distant point of the writing lever will rise within a minute or two, and then fall again a few minutes later. It is difficult to avoid a very steady fall of the point of the lever from stretching of the aorta, but this does not interfere with the reaction.

This adrenalinoscope is extraordinarily delicate, and will show an appreciable contraction with as little as 1 in 500 million of Parke, Davis & Co.'s

adrenalin (i.e., 1 in 500,000 of their solution, which is 1 in 1000). I have used this method, first, to find whether there is any evidence that the blood is flooded with adrenalin during a surgical operation ; and second, to estimate the relative quantity of adrenalin left in the suprarenal glands after death from shock. In two cases a hypodermic syringeful of oxalated blood was withdrawn from a vein towards the end of the operation, and diluted with sufficient saline to fill the glass cylinder containing the spiral strip. In neither case was any adrenalin contraction recorded.

It may be objected that there would not be sufficient adrenalin in the circulating blood of the patient to react even to so delicate an adrenalinoscope as one detecting 1 in 500 million, but calculating from the supposed quantity in the human suprarenals, 5 mgrams according to Battelli, it is difficult to believe that the glands could be exhausted in an hour or two and yet the amount in the blood escape recognition.

More convincing, perhaps, are observations on the suprarenal glands of patients dying from shock. These were removed as soon as possible after death (from six to twenty-four hours), packed and transported in ice, cut open in 15 c.c. of normal saline, and the medullas thoroughly scraped out. Various dilutions in normal saline were then tested in the adrenalinoscope to determine the highest dilution giving a definite rise of the lever. In four cases of shock, tested against controls, there was no reduction of adrenalin in the suprarenals. In fact, the patient

showing the largest quantity of adrenalin was a woman who died as the result of a street accident producing multiple fractures and leading to a fatal issue in four and a half hours. Adrenalin exhaustion, therefore, is not the cause of surgical shock.

WHAT, THEN, IS THE NATURE OF SURGICAL SHOCK?

We have failed to discover any evidence that changes in the blood are the essential factor in the production of surgical shock, and are left face to face again with the crucial problem, how to find an explanation for a falling blood-pressure with a normal heart and vasomotor centre and contracted peripheral arteries. Since the examination of the blood has not helped us, we must return to the central nervous system.

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 peripheral blood-vessels dilate. 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.

Professor 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 that 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 mercury, even after removal of the brain, provided that the cord is left intact, and that sensory 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.

Do we not here find a clue to our problem ? We turn back to the very first sentence of Sir Watson Cheyne's classical description of shock, and read, "The patient who is suffering from shock is usually found lying in a state of complete muscular relaxation." And, later, "the reflexes are very slight." Loss of tone in the voluntary muscles, in the abdominal wall especially, allows great dilatation of the veins, and here, as Crile observed in his experimental animals, the blood accumulates. Therefore the blood-pressure falls and the cardiac output is reduced in spite of undiminished power of the heart muscle and contracted arteries.

We must draw attention to the very significant fact that although the intramuscular and abdominal veins are dilated in shock, this cannot be due to some universal venodilator effect, because, as anyone who has had to perform intravenous transfusion on these cases will bear witness, the subcutaneous veins are smaller than normal. 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 with 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 paralyzing 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 accumulation of blood in the great 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.

Perhaps it may be found possible to localize with accuracy the nuclei which are principally affected in surgical shock by histological examination for chromatolysis. Dolley and Crile have published very remarkable observations on changes in the nerve-cells in shocked or hunted animals, showing dissipation of the Nissl granules. These changes were best marked, not in the vasomotor centre as Crile's theory would demand, but in the Purkinje cells of the cerebellum. Tyrrell Gray and Parsons found changes in the cuneate and gracile nuclei of the medulla.

I have so far had the opportunity of examining the brain of only one case by this laborious method, and therefore must express conclusions with all reserve. The patient was a healthy man who died two and a half hours after a fall from a ladder which caused a fractured pelvis, fractured humerus, and retroperitoneal hæmatoma. The brain-stem and cerebellum were removed, hardened in formalin, sectioned with the freezing microtome, and stained by Nissl's method. The examination of a number of sections showed the following changes. Purkinje cells of cerebellum : all full of Nissl granules ; no abnormal cells found in some hundreds examined. Cells of dentate nucleus of cerebellum : practically all normal. Cells of various motor nuclei in medulla : all normal. Cells of inferior olive : the majority normal ; a few

showed reduction of Nissl granules. Cells of Deiters' nucleus (lateral vestibular): some normal cells; majority showed considerable reduction of the granules, and many cells had practically none left. Cells of gracile and cuneate nuclei: very remarkable absence of Nissl granules: scarcely a granule to be found in the whole nucleus. We know that reduction of the Nissl granules is usually an evidence of exhaustion of nerve-cells, but it must distinctly be understood that we have no evidence that if a nerve cell is paralyzed it must necessarily show histological changes, and absence of chromatolysis would not therefore prove that certain nuclei were able to function properly.

THE DIAGNOSIS, TREATMENT, AND PREVENTION OF SHOCK.

It must regretfully be admitted that such a conception of shock makes diagnosis and treatment much more difficult. And first, *diagnosis* is difficult because we may no longer place implicit reliance upon the blood-pressure. No doubt a fall of pressure is our best sign of shock, but it ceases to be infallible. For instance, crushing the testis may induce a reflex depression through the vasomotor centre, which is perfectly recoverable without any other symptom of shock. Again, and surely we have all learned only too well the truth of this, a patient may be far worse than the pulse and pressure would lead one to think. A diagnosis of shock nowadays must take into account the whole clinical picture described by Sir Watson Cheyne, as well as the readings of the sphygmomanometer.

In the *treatment* of shock, the failure of the simpler theories leaves us sadly bereft of our weapons for meeting it. It was so easy to give pituitary extract for paralyzed vasomotors, carbon dioxide for acapnia, intravenous or subcutaneous saline for oligæmia, and adrenalin injections for exhaustion of the suprarenals, and so hard to understand why they might one and all fail. But what can one do for paralysis of the nerve-cells of all the vital centres? Evidently it is not enough merely to raise the blood-pressure, although that may help a little by driving more blood to the brain, and so give the damaged nerve-cells the most favourable conditions for recovery. Saline transfusion or infusion has its value in maintaining the output of the heart. Recently the use of sodium bicarbonate instead of chloride has been advocated by several American writers on experimental grounds, though they find it hard to give a satisfactory explanation of its action.

It is doubtful if pituitary extract or adrenalin do any good, and Crile's teaching as to the futility of strychnine and alcohol is probably correct. Happily it is possible, to some extent, to exert pressure on the dilated veins and so replace the deficient muscular tone by means of elastic bandages for the limbs and abdomen, taking care not to impede the action of the diaphragm. Intraperitoneal saline fluid in large quantity would help in the same way. In cases of shock from burns, the indications for introducing plenty of saline are clear.

It is to the *prevention* of shock that we must look

with some degree of confidence for the future. And here lies the abiding value of Professor Crile's work. His conception is that general anæsthetics, whilst they protect the cerebral cortex from painful impulses, do not afford much protection to the lower level centres in the brain-stem. Inasmuch as the cutting, crushing, dragging, burning, or other injuries inflicted on the limbs or viscera cannot be spoken of as painful when owing to the ether or chloroform no pain is felt, these are described as " nociceptive " impulses (Sherrington). Crile's method is to prevent the origin or block the path of the nociceptive impulses by means of local anæsthetics, principally novocain for the skin, nerve-trunks, and subcutaneous tissues, and quinine-urea-hydrochloride for the peritoneum. Although the patient is under a general anæsthetic, the line of skin incision is injected with novocain. In an amputation, the main nerves are blocked with the same drug. All suture lines and cut edges of the peritoneum are mopped with the quinine-urea-HCl solution (0·5 per cent of each) before and afterwards. Intraspinal anæsthesia is of course an extension of the method.

Further, all manipulations must be conducted with the most extreme gentleness. Crile protests very strongly against what he calls " carnivorous " surgery. And, thirdly, he finds that nitrous-oxide-oxygen produces much less chromatolysis of nerve-cells than ether or chloroform, and therefore uses it for nearly all operations.

The results, though not yet perfect, are most promising. Shock is greatly diminished, painful

post-operative flatulence, due to intestinal paralysis reflexly induced by the injury to the peritoneum, is more or less completely abolished, and the death-rate is reduced. The writer can testify by personal experience to the truth of these claims ; the comfort after a big abdominal operation is sometimes most remarkable.

Nevertheless, something remains to be desired. The local anæsthetics are not yet perfect in their action. Case 1, recorded above, died of shock in spite of very thorough use of these methods (called by Crile " anoci-association "). Quinine-urea-hydrochloride, which is used for the peritoneum instead of novocain because the anæsthesia is more long-lasting, has the great drawback of being destructive to the tissues, and may cause trouble with the wound or even impair the security of an intestinal anastomosis. However, it ought not to be an insoluble problem for the chemist to produce a more powerful, long-lasting, non-destructive local anæsthetic, and when this is in our hands the prevention of surgical shock will be as feasible as the triumph over those three conquered foes, hæmorrhage, pain, and sepsis.

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 Rogers reports great benefit from the injection of hypertonic saline solutions for cholera. 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 food-stuff. 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 will.

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 Berkefeldt 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—ten grams 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 was 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.

These unfavourable possibilities are not mentioned to proscribe the use of saline transfusion, but to call attention to the best methods of avoiding complications. Of the last eight cases in which it has been used at the Bristol Royal Infirmary, only one (a case of mesenteric thrombosis) died, although the treatment is reserved for the most desperate conditions, especially hæmorrhage, and most of the patients were pulseless. In these cases it does not appear to have produced either fever or lung complications, although a solution which had been standing was used. Several of the patients, however, had fever before the injection began, and this continued. Not more than one or two pints were used, and this was followed up by saline per rectum in most instances.

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 be used only when the need is desperate.

Unfortunately, saline transfusion is usually wanted at a moment's notice, and a freshly distilled water may not be obtainable. It is fortunate therefore that the effects are not likely to be very serious even if a stale but sterile sample has to be used.

What has been said with regard to intravenous transfusion applies also to subcutaneous injection.

It is becoming increasingly common to replace some of the sodium chloride in saline solutions given by the bowel by glucose, which acts as a food. Two drachms of glucose with one drachm of salt may be dissolved in a pint of water. Stronger solutions of glucose are apt to be irritating to the bowel.

REFERENCES.

RENDLE SHORT.—"Hunterian Lecture," *Lancet*, 1914, i, p. 371. (Includes full bibliography.)

HORT and PENFOLD.—*Brit. Med. Jour.*, 1911, ii, p. 1589.

GRÜNBAUM, A. S. and H.—*Brit. Med. Jour.*, 1911, ii, p. 1281.

CHAPTER IV.

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—Transplantation of bone—Application of modern researches to surgical practice—Relation of the ductless glands to 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. A very important research has recently been published which necessitates a radical change in some of our conceptions of this subject.

We may summarize the traditional teaching thus. 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 has been 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 look to the periosteum to produce ensheathing callus to bind the broken ends together again. 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.

Well entrenched as this view has been, it has recently been subjected to most damaging criticism by Sir William Macewen, who goes so far as to state 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. He supports his thesis by some most interesting experiments on animals, and observations on man.

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 loosens 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, finally more compact; the pituitary secretion causes it to undergo hypertrophy.

So much is known and admitted. The evidence which enables Macewen to go further and to deny any share to the periosteum as such, is as follows:—

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

absorbed completely; 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 subperiosteal 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.

Many surgeons besides Macewen have achieved success with bone transplantation. For instance, a piece of the fibula has been inserted to supply the defect in the humerus left by the removal of an intra-osseous cyst, and consolidation took place. The lower jaw and the tibia have several times been replaced in similar fashion by bone grafts from the same patient.

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 ensheathing 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 it is far better to trust to a single efficient movement once a week (to avoid adhesions) than to allow repeated small movements in the early stages.

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.

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.

Bone transplantation has now reached a thoroughly established position, and scores of successes have been reported. Parts of the tibia, humerus, skull, and lower jaw have repeatedly been replaced by slips from the fibula, rib, or other situations. Sometimes it is possible to maintain the blood-supply by preserving the periosteum and soft tissues over the graft with a pedicle, as when the fibula is put into a gap in the tibia. In other cases the strip of bone or the bone chips have to be detached entirely, or even transplanted from patient to patient, but they will frequently survive in part or in whole, acquire a new blood-supply, and unite up with the divided ends. Very small chips or bone dust are not successful, apparently because the osteoblasts are damaged; on the other hand, thick pieces of bone will die. If in any way possible, the graft should be taken from a young growing bone, especially that near the epiphyseal cartilage. Perhaps pieces of epiphyseal cartilage itself would be best of all, because it is content with a very small blood-supply.

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.

REFERENCE.

MACEWEN.—"The Growth of Bone," Glasgow, 1911.

CHAPTER V.

THE THYROID AND PARATHYROID GLANDS.

History—Removal of the thyroid and parathyroids—Removal of parathyroids alone—Removal of thyroid alone—Thyroid feeding—Chemistry of thyroid colloid—Parenchymatous goitre—Iodoform and thyroidism—Action of iodides on gummata and atheroma—Exophthalmic goitre—Practical deductions.

MUCH of the clinical and experimental work which has been done in connection with these glands can no longer be described as new, but it will be helpful to mention in passing some of the well-known results obtained by the first observers.

HISTORY.

As long ago as 1859, Schiff described the fatal result which inevitably supervenes after removal of the thyroid gland in dogs, but it was not until "cachexia strumipriva," or operative myxœdema, was found to follow so many of Kocher's early operations for goitre on patients coming from the goitrous Swiss valleys, that this fact attracted much attention. The relation of the thyroid to myxœdema was then established by Gull and Ord. The highly successful treatment of myxœdema and cretinism by thyroid feeding was introduced by Murray, following on the observation by Schiff and subsequent workers that transplantation of the gland beneath

the skin of the thyroidectomized animal relieved the symptoms.

REMOVAL OF THYROID AND PARATHYROIDS.

We will consider first the consequences of removal of the thyroid gland in animals. The effect of total removal varies greatly with the species. Thus rodents are little if at all affected, sheep and cattle more so; in man and monkeys the symptoms are marked, and in carnivores, especially foxes, a rapidly fatal result ensues. To some extent this striking diversity depends, as we shall see, on the liability to simultaneous removal of the parathyroids; for a long time this was not recognized. Males are more severely affected than females, and castration is said to modify the symptoms. Thyroidectomized animals are very susceptible to cold, and keeping cats warm may save their lives; of course thyroid medication must be undertaken at the same time. It is well known that human patients with myxœdema feel the cold very much. The symptoms in dogs and monkeys are vomiting, muscular prostration, emaciation, and often death. Of great importance is the frequent occurrence of tetany. The spasms are at first slight, affecting the jaw muscles, then they spread over the whole body and may be fatal. This condition has several times followed a too extensive removal of the thyroid in man, and may also occur in myxœdema. Another symptom present frequently in monkeys is narrowing of the palpebral fissure, so-called enophthalmos; we shall see that administration of thyroid extract may

cause exophthalmos. True myxœdema is not often seen in the experimental animals. It has been induced in mild degree in monkeys by Horsley, Edmunds, and others, but not with any constancy, and in other animals it is not seen at all.

It is not usually possible to save the lives of dogs or monkeys whose thyroids have been removed, by feeding on sheep's thyroid, although a good deal of relief may be obtained for the symptoms in this way. Grafting a piece of the gland under the skin is successful for a while, but eventually it is absorbed.

The effects of removal of, or insufficient secretion by, the thyroid gland in man are *myxœdema*, and occasionally *tetany*.

In 408 cases in Kocher's clinic at Berne complete extirpation of the thyroid was followed by myxœdema in 69 cases, and a similar operation in 78 cases in Billroth's clinic was followed by tetany in 13 cases, of which 6 proved fatal. Feeding with sheep's thyroid is wonderfully successful in myxœdema, but is not usually effectual in tetany.

Partial removals of the thyroid in dogs produce symptoms of correspondingly lessened severity. Halstead found that in one case one-eighteenth of the gland sufficed to ward off symptoms of athyroidism, but the amount which could safely be left varied in different animals. One bitch which had lost two-thirds of her total thyroid became pregnant by a healthy male, and all her whelps had enormous goitres, a fact which has also been observed by Edmunds.

Histological examination of the portion remaining

shows a sequence of changes remarkably like those occurring in exophthalmic goitre, namely, distention and irregular shape of the vesicles, with watery fluid instead of colloid, and columnar epithelium instead of cubical.

REMOVAL OF PARATHYROIDS.

The variation in the symptom-complex following on thyroidectomy, and the variability of response to thyroid feeding, both depend on any coincident injury to the parathyroid glands. For many years these glands passed unrecognized, and most of the effects attributed above to removal of the thyroid are as a matter of fact due to loss of the parathyroids. These are two pairs of small glands, about one-third of an inch long and usually flattened in shape, lying behind the lateral lobes of the thyroid close to the trachea, not easily distinguishable from the thyroid except by the microscope, when they are seen to consist of columns of polygonal cells with no regular arrangement into acini, and secreting no colloid. One pair was discovered by Sandstrom in 1880, and the functions were investigated by Gley in 1892; but the second pair was not recognized till Kohn's monograph appeared in 1895. A number of physiologists have since described the effects of removal (Vassali and Generali, Edmunds, Moussu). If all four parathyroids are taken away, the animal succumbs rapidly, with symptoms just such as have been described under the heading of thyroidectomy, tetany being a marked feature. The signs are the same whether the thyroid gland is removed or left.

Leaving one parathyroid is usually sufficient to prevent death, but tetany may still ensue.

Changes in the human parathyroids are said to be very frequent in cases of tetany in children or pregnant women, and also in osteomalacia, in which the inorganic matter of bone is largely removed. In fact it is probable that the tetany itself depends on some abnormality of the calcium metabolism of the body. The main function of the parathyroid glands is perhaps to control the calcium metabolism.

It would seem that in man, myxœdema is due to loss of the internal secretion of the thyroid itself, but that tetany and fatal symptoms in both man and animals are due to loss of the parathyroids. The convulsions of tetany in dogs may be arrested by feeding on a watery extract of twelve to twenty horses' parathyroids (Moussu).

REMOVAL OF THYROID ALONE.

Removal of the thyroid gland without the parathyroids is usually not fatal; myxœdema results in man; occasionally, perhaps, in animals also, but more commonly only cachexia. In young animals, however, the results are much more distinct, and Eiselsberg and others have induced very convincing cretinism, with a remarkable stunting of growth, in lambs, goats, rabbits, and asses. It is interesting and important to notice that the animals so treated developed exceedingly marked atheroma of the aorta, of which Eiselsberg gives good figures.

THYROID FEEDING.

We now turn to the effects of thyroid feeding in the normal man and animal. These are perfectly characteristic if large doses are given. The blood-pressure falls, the pulse becomes rapid (120–140 or more), there may be fever, headache is usual, and there is great mental depression or excitement in many cases. Exophthalmos has been recorded several times after an overdose in man (Béclere, Notthaft), and monkeys (Edmunds). The metabolic exchanges of the body are increased, consequently there are loss of weight and an increased output of urea, chlorides, and phosphates, and the gaseous exchanges in the lungs are above normal (Roos, Magnus Levy). It will be noticed that the parallelism with Graves' disease is very striking.

CHEMISTRY OF THYROID COLLOID.

Chemical investigation of the colloid has yielded some important results. The active principle, iodothyrin, has the characters of a globulin (Oswald) which contains a variable proportion of *iodine*. This element is usually abundant in the thyroid, but almost absent in the other tissues of the body. Its presence was first proved by Baumann of Freiburg, in 1896, and has been abundantly confirmed since. The amount present varies with the species and also with the individual; in some cases it falls below the limits of chemical recognition. Herbivores possess it in abundance, most vegetables containing iodine. In carnivores it is very scanty. In man it is nearly always present in recognizable quantities,

except in young children. Wells finds that the amount varies with the locality, and in general is inversely in proportion to the local prevalence of goitre. In parenchymatous goitre the iodine content is too low; in exophthalmic goitre it is too high. A principal function of the thyroid is to control the iodine metabolism of the body.

PARENCHYMATOUS GOITRE.

Directing our attention now to enlargements of the thyroid gland, we rule out those that are merely due to tumour formation, such as adenoma or cystic disease, and confine ourselves to the parenchymatous goitres. It has long been known that there is some connection between drinking-waters and the incidence of goitre. The disease is extraordinarily prevalent in certain districts, and especially where the water-supply is derived from particular geological formations, such as the molasse in Switzerland and the carboniferous limestone in Derbyshire. In Khokand, Turkestan, a very large proportion of the whole population suffers, and Russian soldiers stationed there rapidly acquire the disease. The introduction of a new water-supply has several times induced an epidemic of goitre in a town, or, on the other hand, reduced the number of cases in an endemic area. Thus at Rupperswyl, near Aarau, an endemic area in which 59 per cent of the children were goitrous, in 1884 the water-supply was changed for one from a non-goitrous district, and in ten years the percentage had fallen to eleven. There are on the Continent certain goitre wells called

Kropfbrunnen, at which young men anxious to escape conscription drink. They have been known for centuries, and the water will induce goitre in horses and dogs, as well as in man. Boiling the water destroys its remarkable effect on the thyroid gland. This has been taken to prove that some living organism is the effective cause, but another theory is more probable, as we shall see later.

During Captain Cook's voyage in 1772, it is related that the crew ran short of water, and had recourse to blocks of ice from the icebergs amongst which they were sailing, melting them in iron pots. Quite a number of those who partook of this water developed a goitre, other members of the crew escaping.

A large projecting swelling of the thyroid is not uncommon in trout kept in certain tanks or streams.

In the earlier stages, parenchymatous goitre can usually be cured, either by feeding on thyroid extract or by means of potassium iodide. Marine* has pointed out that in America there was formerly a serious commercial loss in some districts from cretin lambs, and that sheep and dogs with goitre were numerous; the substitution of an iodiferous salt for pure rock-salt has been completely successful in preventing all these manifestations.

Chalmers Watson, and more recently Edmunds, have obtained goitre in fowls by a meat diet. The low iodine-content of the meat makes it necessary for the thyroid to enlarge, so as to take the greatest advantage of what iodine it can get.

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* *Johns Hopkins Hosp. Bull.*, 1907, xviii, p. 359.

There is abundant evidence that iodides, and especially organic combinations of iodine such as iodoform, have great power in enhancing the activity of the thyroid gland. We have already seen that the gland normally secretes iodine into the blood-stream, combined with a globulin. Roos, and more recently Hunt and Seidel, have shown that the activity of the colloid varies directly with the amount of iodine contained in it. When iodides or iodoform are given by mouth, they are taken up by the thyroid and secreted in the blood-stream in the form of iodothyrin, the normal active principle of the gland. The amount of iodine in the gland in these circumstances rises considerably, as has been proved by Oswald in man, and by Hunt and Seidel in dogs.

What, then, is the relation between iodine metabolism and goitre?

In the first place, we may conclude that the thyroid enlarges in goitre because it is necessary for it to do increased work. A certain quantity of iodothyrin is needful for the general well-being of the individual; if the gland is scantily supplied with iodine, it must enlarge in order to take the fullest possible advantage of all that may be brought to it by the blood-stream. In the same way a kidney hypertrophies when its fellow is degenerated, in order to obtain more urea for excretion; and the red blood-corpuscles double in number when a man takes up his abode in the rarefied atmosphere of great altitudes, to make the best use of the diminished supply of oxygen. It has been shown by Oswald in a number

of observations that in goitre the thyroid colloid is exceedingly deficient in iodine, both in calves and man. Thus we get a clue to the successful treatment of the affection either by iodiferous compounds or by thyroid extract. It is well known that either of these remedies will cure early cases of goitre, before the enlargement becomes chronic. The success of the iodiferous rock-salt on the American farms may be accounted for in the same way. An explanation is also offered of the fact, noticed previously, that the whelps of bitches from whom a good part of the thyroid has been removed are all goitrous, the plasma supplied to the fœtal glands evidently containing a deficiency of iodine derived from the maternal thyroid. Of 2,333 cases of congenital goitre collected by Fabre and Thévenot,* the mother was almost invariably goitrous. The fœtal thyroid enlarges in order to obtain as much iodine as it can.

It was natural to suggest that the waters of the Kropfbrunnen were deficient in iodine, but this theory would overlook the fact that the bulk of our iodine is derived from vegetables, not from drinking-water, and as a matter of fact these wells show no constant deficiency or excess of iodine. It is more probable that they contain minute traces of some metal having a great affinity for iodine, and forming with it an insoluble compound. It is quite conceivable that boiling the water might precipitate such a metal. There are probably many metals, known

* *Revue de Chirurgie*, June 10, 1908.

and unknown, that would fulfil the conditions; it will suffice to mention silver as an illustration. This, if taken into the body, would withdraw so much of the available iodine as inert silver iodide, that the thyroid must enlarge to obtain the indispensable minimum.

Major McCarrison, who has been observing endemic goitre amongst the Gilgit highlands in North India, has lately brought forward fresh arguments in favour of a bacteriological theory of its causation. He has induced a definite swelling of the thyroid both in himself and in natives by drinking the muddy residue on the filter; the filtered water, in a short experiment, did not give rise to goitre, nor did boiled water.

No organism could be found in punctures of the gland. Goats given water to drink contaminated by the fæces of goitrous patients in some cases, though not in others, developed a certain amount of swelling of the thyroid gland, and in man ten-grain doses of thymol, used as an intestinal antiseptic, reduced the size of a goitre in some patients. Hence, McCarrison believes that the disease is due to an intestinal organism. The evidence does not seem very conclusive; chemical substances permeating certain geological formations we are acquainted with, but pathogenic bacteria having a special soil distribution would be a novelty. According to Wilms, Bircher, and others,* the water of goitre wells retains the power of inducing thyroid enlargement in rats after

* Bircher, *Deut. med. Wochensch.*, 1910, No. 37; Wilms, *Deut med. Wochensch.*, 1910, No. 13; Kolle, *Korrespond. f. schweiz.. Arzte*, 1909, No. 17.

passing through a Berkefeldt filter. It is true that a very few tiny bacteria are filter-passers, but the immense majority are held back. It is easy to cause enlargement of the thyroid by various means; Bircher shows that food contaminated by the fæces of normal rats causes goitre in other rats.

There are goitre wells in England. One is known to the writer near Berkeley, in Gloucestershire. Its water is used by only one or two families, but four cases of goitre have resulted. It is usually the growing children who suffer.

IODOFORM AND THYROIDISM.

The conclusions which modern physiology has reached with regard to the relation between iodine compounds and the thyroid gland lead us to some further important explanations of obscure problems. We are now able to understand the toxic effects of iodoform, and the beneficial action of iodides on arteriosclerosis, aneurysm, and gummata.

Iodoform poisoning has become a well-recognized condition, and every text-book on pharmacology or toxicology gives a clear description of the clinical picture, which the writer has verified by consulting the reports on some 100 cases scattered through the literature, not including the very numerous records of dermatitis or erythema following its local use. A long list of well-described cases (not always very convincing) is given by Cutler.*

* *Boston Med. Soc. Journal*, 1886, ii, pp. 73, 101, 110.

There are four main varieties of iodoform poisoning :—

1. Skin eruptions, such as dermatitis, erythema, and swelling.

2. Persistent subjective taste and smell of the drug long after its application has been discontinued

3. Toxic amblyopia (5 cases), and optic atrophy (1 case).

4. Acute thyroid symptoms, comprising rapid pulse, delirium, headache, vomiting, and a variable amount of fever. The most characteristic sequence is when the pulse is very rapid but the temperature normal.

Of the above groups we are now concerned only with the last.

It will be noticed that the clinical picture corresponds exactly to that seen after the administration of excessive doses of thyroid extract. Iodoform causes its toxic effects by stimulating the internal secretion of the thyroid gland, with the production of acute thyroid intoxication.

I have described a case in which *chronic* thyroid intoxication, that is to say Graves' disease, clearly followed the application of iodoform to an absorbing surface. There was certain proof that too much iodoform was absorbed, because for weeks after the drug had been withdrawn the patient was haunted by its smell and taste. The tachycardia and wasting were first noticed a week or two after this symptom developed. The Graves' disease was still present in a mild form one year later, but eventually disappeared.

Hunt and Seidel have shown that after dosing

a dog with iodoform, the iodine content and the activity of the thyroid colloid are both increased greatly. The thyroid secretes into the blood, as iodothyrin, the iodine derived from the iodoform. When strychnine is excreted by the kidneys the excretion is merely discharged from the body, and therefore the drug can do no more harm. But the increased secretion of the thyroid is discharged not externally but into the blood, and may poison the patient.

ACTION OF IODIDES ON GUMMATA AND ATHEROMA.

A similar increase in the thyroid secretion may be obtained by giving iodides, but apparently the gland is not able to utilize these as readily as it does iodoform, for large doses do not so easily cause acute thyroid intoxication. Here we find the explanation, so long sought in vain, of the effect of iodides on gummata, arteriosclerosis, and aneurysm. The beneficial agent is really the increased internal secretion of the thyroid gland.

Two important results of observation and experiment confirm this theory.

In the first place, in cases of myxœdema, arteriosclerosis is early and intense. The same is true in animals after removal of the thyroid. Eiselsberg gives a number of very convincing photographs of intense atheroma of the aorta in his cretin lambs in which the thyroid had been removed in early life. In the second place, thyroid extract has a wonderful power over young connective tissue, as is seen by the

way in which it absorbs the subcutaneous thickening of myxœdema and cretinism. It is not surprising, therefore, that it should be able to deal also with gummata and atheroma. By its absorptive effect on the atheroma, it may work some improvement in aneurysm.

I have found thyroid extract quite as effectual as iodide of potassium in healing tertiary syphilitic ulcers.

EXOPHTHALMIC GOITRE.

The arguments in favour of the hypersecretion theory of this disease appear to almost all observers to be of overwhelming strength. The thyroid gland is enlarged, vascular, and soft in most cases; occasionally it is normal in size. Microscopically, the acini are dilated and irregular, and the contents too watery. These are just the changes seen in the actively secreting fragment left after a sub-total thyroidectomy. The colloid contains too much iodothyrin as compared with the normal gland. The wasting, restlessness, and quick pulse may all be reproduced with constancy in man or animals by thyroid feeding, and exophthalmos has also been obtained occasionally in both man and the monkey. The underlying *cause* of the hypersecretion is still unknown. A few cases may be lighted up by fright or by iodoform poisoning.

PRACTICAL DEDUCTIONS.

We may seek here to summarize the conclusions, in so far as they are of importance to the clinician,

that the New Physiology has reached. We learn that parenchymatous goitre is an hypertrophy of the thyroid gland, designed to enable it to obtain sufficient iodine from the blood, this element being an essential constituent of its internal secretion. The deficiency in iodine is in some complicated way connected with the drinking-water. In the early stages, iodides, thyroid feeding, or probably iodoform will work improvement, and the water should be boiled, or the supply changed. Should operative measures be adopted, we learn that the whole gland must not be removed, or myxœdema may result, and that the four small parathyroids lying behind it must also be respected, or the patient may develop tetany. In some cases the loss of the parathyroids on one side only has caused this unpleasant sequel. An attempt should therefore be made, in removing one lobe of the thyroid for goitre or adenomata, to leave these little glands intact and *in situ*, and to preserve their blood-supply. They will not be injured if the posterior part of the capsule of the thyroid is left.

If myxœdema or tetany do follow the operation, they may be remedied by thyroid and parathyroid feeding respectively. There is some evidence that even the medical varieties of tetany are due to loss of the internal secretion of the parathyroids ; according to Kocher, this has been proved in the case of the tetany of pregnancy, and other observations have since been made in which the parathyroids were diseased when tetany was present. Parathyroid feeding should therefore be worth a trial in such

cases also. Macallum* recommends the administration of calcium salts, or milk, which is rich in calcium salts. He has shown experimentally, and Edmunds† has confirmed the statement, that these salts will cure tetany. Thyroid and parathyroid grafting have both been undertaken in man for cretinism and tetany respectively, with the idea of relieving the patient from the necessity of taking drugs all his days. In a few cases success has resulted, but unfortunately the graft becomes absorbed as a general rule, and soon ceases to function.

In a case recently described by Brown, of Melbourne, parathyroid feeding and calcium salts both failed to relieve tetany in a patient who had been treated by a too extensive thyroidectomy for Graves' disease. The in-grafting of parathyroid tissue from dogs and monkeys gave pronounced relief for about twelve days, but she relapsed after each operation. Human parathyroid was then grafted, and the cure seemed to be permanent. I have seen a case apparently cured by the grafting of human parathyroid.

We see also that exophthalmic goitre is due to hypersecretion of the iodothyrin, as is proved by the artificial imitation of the disease by excessive thyroid feeding, by the excess of iodine present in the colloid in Graves' disease, and by the character of the histological changes. Thus we have reason

* *Journal of Experimental Med.*, New York, 1909, vol. xi, p. 118.
† *Journal of Path. and Bact.*, 1910, p. 288.

to expect good from partial removal, which has been very successful in the hands of Kocher, the Mayos, and others. It would be reasonable also to try the effect of iodine starvation, by eliminating vegetables and ordinary tap-water from the dietary, and substituting for the latter the water of a goitre well. It is well known that exophthalmic goitre and parenchymatous goitre show a sort of geographical antagonism, and the effect of the water in reducing the amount of iodine available for conversion into iodothyrin would be valuable.

Further, we are helped to understand and to recognize cases of iodoform poisoning, and to learn caution in the use of this drug on absorbing surfaces. It is safer in children than in adults, possibly because the thyroid in children contains less iodine. It ought not to be used in patients who have ever shown a tendency to thyroidism, lest acute poisoning or an attack of Graves' disease be precipitated.

Finally, we obtain a clue at last to the remarkable action of iodides in arteriosclerosis and gummata, and it is reasonable to hope that organic compounds of iodine, which cause acute thyroidism more readily than the alkaline salts, may be yet more effectual in stimulating the activity of the thyroid gland. In fact, thyroid extract itself may prove to be the best remedy of all.

Seeing that the activity of thyroid extracts depends only on the iodothyrin, these should be standardized chemically if they are to be given as drugs. Leading chemists now issue an extract

which contains not less than 0·2 per cent organic iodine.

REFERENCES.

RICHARDSON.—"The Thyroid and Parathyroid Glands," Philadelphia, 1905.

ALLBUTT'S SYSTEM OF MEDICINE, vol. iv, part. 1, p. 333, 1907 Edition (a full bibliography).

HUNT AND SEIDEL.—"Studies on Thyroid," *Hygienic Laboratory Bulletin of Public Health*, Washington, 1909.

A. RENDLE SHORT.—*Bristol Medico-Chirurgical Journal*, 1910, p. 122.

KOCHER, HECTOR MACKENZIE.—"Discussion on Exophthalmic Goitre," *Brit. Med. Journal*, 1910, vol. ii, pp. 931, 935.

MCCARRISON.—"Milroy Lectures," *Lancet*, 1913, i.

CHAPTER VI.

THE PITUITARY AND PINEAL GLANDS.

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.

IT will be remembered that the pituitary gland is lodged in the sella turcica of the cranium, in an exceedingly secluded position in the body, and it is only recently that its functions have been recognized. It may be that the interesting researches of Schäfer, Paulesco, Cushing, and others, will prove to have opened up a very important and useful chapter in medicine as well as in physiology.

The gland consists of two distinct portions, anterior and posterior, closely fused in man, but with a well-marked line of junction in the dog. The anterior part is glandular in structure, consisting of columns of epithelial cells which generally contain colloid. In young animals these cells line tubules; later, the central lumen disappears. Large blood sinuses are present. The posterior lobe consists of vascular neuroglia. Between it and the anterior lobe is a cleft containing glairy fluid. The anterior portion is derived from a pit in the dorsal wall of the pharynx of the embryo; the posterior is budded out from the brain.

All the ductless glands are 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 are arching of the back, low temperature, shivering, and death in unconsciousness. Achsner, Handelsmann and Horsley, Morawski and others, however, find that death is by no means inevitable after enucleation either of the anterior lobe or the whole gland, and positive evidence of survivals must outweigh statements to the contrary.

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 very convincing photographs showing that these changes are quite marked.

Another consequence is a remarkable influence upon the metabolism of sugar. We shall see 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 grams of glucose are taken at a dose, some will overflow in the urine. If the action of the pituitary was subnormal, judging by the results of animal experiments and a few observations on man, even a larger dose than this would not cause glycosuria.

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 secretion of milk in animals, but it is not yet proven that it does so in the human subject.

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 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 7 ft. 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. This train of symptoms will recall the effects of total or partial removal of the gland in animals.

Not only the bones, but also the viscera, may be increased in size in acromegaly: the kidneys, liver,

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* E. Fawcett, *Jour. Royal Anthropological Institute*, 1909, vol. xxxix. p. 196.

pancreas, and even the auriculo-ventricular 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.

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.

A year or two 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; probably it is not.

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.

It is true that cases of acromegaly may eventually develop impotence, sterility, and amenorrhœa; this

is explained as hypopituitism succeeding an excess. The same alternation is seen in diseases of the thyroid gland.

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. Acromegaly and gigantism do not usually require anything to 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.

Patients suffering from the Fröhlich type may be treated by pituitary feeding, the whole gland of cattle being used. The dose is about 12 grains a day. This may be worked out by its influence on the sugar tolerance. Remarkable results have been obtained in a few cases. 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.

THE USES OF PITUITARY EXTRACT.

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. A very valuable effect is that it promotes peristalsis even when purgatives fail or are vomited, as in cases of 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 is a powerful diuretic. As a galactagogue its success so far has been doubtful. Feeding with the gland may be valuable in some forms of amenorrhœa.

Pituitary extract must not be given frequently at short intervals, or its effect may be reversed.

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 persist 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 it contains in children 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!

REFERENCES.

CUSHING.—"The Pituitary Gland and its Disorders," 1911.
BIEDL.—"The Internal Secretory Organs," 1913.
KIDD.—*Med. Chron.*, 1912, vol. xxiv, p. 154.

CHAPTER VII.

STUDIES IN THE CLINICAL PHYSIOLOGY OF THE ALIMENTARY CANAL.

Movements of digestion—Sensation in the alimentary canal—Causes of variations in the hydrochloric acid of gastric juice—The physiological effects of gastro-jejunostomy—Feeding after gastrostomy—The process of secretion of pancreatic juice—The bile—The absorption of proteins—Absorption in the large intestine—The value of nutrient enemata.

WE shall not repeat here the now well-known researches of Pawlow and Edkins, described in our previous editions, showing the importance of two factors in provoking a flow of gastric juice: the first the appetite reflex through the vagus, and the second due to the production of gastric secretin by various extractives.

THE MOVEMENTS OF DIGESTION.

Very important and far-reaching advances in our knowledge of the movements of various parts of the alimentary canal have been made by the introduction of the method of skiagraphy, or direct observation with the fluorescent screen after feeding men or animals on milk, mush, or other food impregnated with bismuth salts. For this purpose the subnitrate should be avoided, as it has led to nitrite poisoning when large doses are given. Barium sulphate is now

replacing bismuth salts to some extent. The great advantage of the method is that it is absolutely physiological; no pain is caused, no operation is needed, and permanent records can be obtained by photography. Cannon in America, and Hertz in England, have contributed most to our knowledge in this field of study. The bismuth can be given by mouth or per rectum.

Movements of the Œsophagus may be dismissed in a few words, as the clinical importance is not great. It is found that the mere contraction of the pharyngeal muscles is able to shoot fluids a long way down the œsophagus, quite apart from any contraction of that tube. When corrosives are swallowed, the upper part of the œsophagus may therefore escape injury.

The peristaltic wave in the gullet, unlike that in the small intestine and stomach, is dependent on a succession of impulses arriving from successive nerve-cells in the vagus nuclei, whereby segment after segment is led to contract in regular order from above downwards. In man, the wave takes about six seconds, from the first contraction of the pharynx to the opening of the sphincter at the cardiac orifice of the stomach. This sphincter is relaxed by vagus influence.

If the vagi are cut, the œsophagus is paralysed for some days. After a little time, however, the muscle recovers, and peristaltic waves can pass, so that swallowing is once more possible.

The cardiac orifice is maintained closed by a chemical reflex; the acid in the stomach causes a

spasmodic contraction of the sphincter which is relaxed only during swallowing, vomiting, or eructation of gas or fluid.

Shape, Position, and Movements of the Stomach.—The stomach consists of two distinct parts, which behave quite differently during digestion. The cardiac end and the greater part of the body form an oval reservoir lying vertically, with a well-marked angular ring separating it off from the horizontal or ascending narrow tubular pyloric antrum. After death, or under an anæsthetic, this distinction is lost, but it is often seen in formalin-hardened bodies. Just after a meal, the greater curvature forms the lowest point, and in men while standing it falls a few centimetres below the umbilicus. Later, as the stomach shortens, the pylorus becomes the lowest point.

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. In man, the waves are about three to the minute, and keep on so long as there is food present. 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. Even then peristalsis may not cease (Hertz), but the pylorus lies open, and bile and duodenal contents pass in and out without causing any discomfort.

The effect of the principal food-stuffs 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.

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.

For clinical purposes, skiagrams after a bismuth meal (one or two ounces of bismuth oxychloride in milk or porridge) are of distinguished value. The patient should be examined both standing and lying down, and at varying intervals. Gastroptosis, gastric dilatation, pyloric spasm, and hour-glass contraction become quite evident. In the last case the connection of the two sacs is between their upper portions, not at the lowest point—the latter appearance is of little significance. Percussion and auscultation may frequently be proved inaccurate by skiagraphy.

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 bismuth 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. 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 bismuth meals or bismuth 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.

Hertz 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 food-stuffs. Skiagraphy after bismuth meals shows that the last few inches of the ileum remain full for four or five hours after the stomach is empty. 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 ileo-cæcal sphincter is reflexly inhibited, and the last contents of the ileum pass through.

The rectum is of course under direct control of the centre near the tip of the spinal cord, the motor path being the pelvic visceral nerves from the second to the fifth sacral roots; the sympathetic system also supplies the rectum. The physiology of defecation is well known, and need not detain us.

In the cæcum and the ascending, transverse, descending, and pelvic portions of the colon, however, 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, but not over great lengths of the bowel. In the small intestine antiperistalsis is rare and pathological. Three or four times a day, and 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 observers. Here we have the explanation of "lienteric" diarrhœa immediately following a meal, and also of the pain after food met with by some sufferers

from chronic constipation. The bismuth meal normally reaches the pelvic colon in about 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.

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. This drug has been used for years in Vienna and Germany, though but little in England. 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.

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 described by Sir Arbuthnot Lane, and demonstrated by skiagraphy by Jordan, in which the lower end of the ileum is kinked. This is one of the causes of chronic intestinal stasis. Another cause is adhesions round the appendix, which perhaps leads to prolonged contraction of the ileocæcal sphincter. In these cases there is delay in the small intestine.

The saline aperients do not induce any hastening of its contents through the small intestine, and as they may produce purgation in less than four hours, it is possible that they are absorbed in the stomach, carried by the blood, and re-excreted in the colon (Hertz, Schlesinger, and Cook).

Large bismuth enemata are able to force the ileocæcal valve and enter the small intestine.

In animals, lateral union of two coils of intestine induces much more stasis than end-to-end anastomosis.

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 often cures 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.

SENSATION IN THE ALIMENTARY CANAL.

In his recent Goulstonian Lecture, Hertz 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 distension 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.

VARIATIONS IN THE HYDROCHLORIC ACID OF THE STOMACH.

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. The total gastric acidity is about 50 c.c. of decinormal acid.

The contradictory results obtained by various workers are worthy of explanation. The significant figure, the 0·1 per cent of HCl, means (*a*) HCl which has already got to work on and combined with protein in the food, *together with* (*b*) any free HCl still unattached. Obviously, a larger or more albuminous test-meal would reduce the *free* HCl still further in any stomach, however normal the acidity. In spite of this, some still prefer to estimate the free HCl and to regard it as the significant figure; they take the normal to be 0·02 per cent after a test-meal, the remaining 0·08 having combined with the food.

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

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* *Lancet*, 1905, i, p. 1566.

The most reliable test for the presence of HCl is Gunsberg's (phloroglucin and vanillin); this is too well known to need description. It is merely a qualitative test.

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 gastric ulcer, so much so that an analysis of a test-meal is of diagnostic importance. It is also seen in duodenal 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 characteristic symptom of this 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 alkalies. 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 anti-pepsin 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 anti-pepsin 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 frequently 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. Another evil consequence of excessive HCl is spasm of the pylorus, which may lead to dilatation of the stomach. A curious and suggestive symptom is pyrosis, a periodical copious secretion of saliva, probably designed to neutralize the acidity when swallowed.

In infants, Willcox and R. Miller have stated that

there are two types of dyspepsia causing pain, wasting, vomiting, and constipation. One is congenital stenosis of the pylorus, in which the HCl is subnormal but the pepsin (which may be conveniently tested by the curdling effect on milk) is excessive; and mucin is also in excess. The other is "acid dyspepsia," in which the HCl is excessive and the ferments are subnormal. In this case peristaltic waves may be seen, but the pyloric tumour is not felt. The prognosis is very much better than in congenital stenosis, and operation is not needed as it so often is in the more serious condition.

Enough has been said to show that hyperchlorhydria and its advertisement, "hunger-pain," are more than an inconvenience to the patient; they are in many cases the consequence and in other cases the precursor of serious organic mischief which may lead to dilated stomach, to chronic gastric ulcer—which in its turn is very apt to become malignant—or to an abdominal catastrophe from perforation of the stomach or duodenum.

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 thirdly ulceration.

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 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 patients with symptoms of gastric ulcer operated on at the Bristol Royal Infirmary, 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 sphincter remains tightly closed and produces back-pressure. In other cases there may be irregular gastric peristalsis and hyperchlorhydria as a nervous reflex.

The treatment of hyperchlorhydria is as follows. Medical means will often give a large measure of relief. Taking food, and especially a hard-boiled egg, when the pain comes on will generally abate the symptoms. Alkalies are indicated, especially magnesia, which has two advantages: it does not dissolve and exert all its effect in a few minutes, and it does not give off carbon dioxide as the carbonates do. The bismuth lozenges of the B.P. are convenient to carry and very successful in stopping the discomfort. We will barely mention such useful

measures as rest in bed, milk diet, and lavage. Pawlow on theoretical grounds recommends fats and oils to check the flow of the gastric juice. These measures are of course not applicable in the presence of an acute ulcer causing hæmorrhage.

If these means are not successful, it is very desirable to perform laparotomy and to explore the stomach, duodenum, appendix, kidney, and gall-bladder. If gastric or duodenal ulcer is present, gastrojejunostomy is of course indicated. If no abnormality can be discovered in either stomach or duodenum without opening into them (which is seldom if ever called for), it may be that some adhesions or kinking of the appendix may be found, and removal of the organ will effect a cure in many of the cases but not all. It is shown by Paterson, the Mayos, Sherren, and others that about 75 per cent of the many hundreds of cases of dyspepsia without ulceration treated by removal of the appendix are cured. It might be well to do a gastrojejunostomy at the same time; one of Paterson's failures was subsequently relieved by this means. This operation may lead to a permanent cure of pain, vomiting, or hæmatemesis, even when no abnormality can be found.* The important point is that it is not right to do the short-circuiting operation on a normal stomach

* This statement has been denied by one or two reviewers of the first edition, but is nevertheless persisted in. Admittedly the results are not so good as when a definite ulcer is found, but out of ten cases treated by gastrojejunostomy in which nothing was discovered, six were much improved years afterwards. See A. Rendle Short, "End-results of Operations on the Stomach and Duodenum," *Bristol Med.-Chir. Jour.*, 1911, p. 220.

without also exploring the appendix and gall-bladder. Soltau Fenwick states that of 112 cases of hyperchlorhydria, in 34 the stomach and duodenum were normal; in 22 of these the appendix was at fault, and in 12 gall-stones were present. In 9 cases appendix trouble complicated gastric or duodenal ulcer. In 66 patients an ulcer was present in the stomach or duodenum; 4 of these were malignant.

It is a remarkable fact that severe and repeated hæmorrhage from the stomach may take place in the absence of any ulcer. Out of seven cases recently operated on for hæmatemesis at the Bristol Royal Infirmary, in only two was an ulcer found. A condition of universal weeping of blood, called "gastrostaxis," occurs in these cases, and with the gastroscope the mucous membrane may be seen to ooze blood wherever it is touched.

Hydrochloric Acid Deficient.—It is well known that the HCl in the gastric juice is deficient or absent in cases of cancer of the stomach, but the practical value of this is lessened by the fact that old-standing gastritis, or cancer of other organs than the stomach, may abolish the HCl. On the other hand, cancer more often than not is preceded by ulcer, and there will be a stage in which the hyperchlorhydria has not yet passed off although cancer is already present. Nevertheless, we cannot afford to neglect the chemical test in the diagnosis of cancer of the stomach, as the other early signs are often equally dubious.

In persons beyond middle age, absent hydrochloric acid is not uncommon without any apparent cause or consequence.

THE PHYSIOLOGY OF GASTROJEJUNOSTOMY.

What effect is produced upon the functions of the alimentary canal by the operation of gastrojejunostomy? We have to ask: (1) Does the food pass through the new opening or by the pylorus? (2) What is the effect upon the gastric juice? and (3) What is the effect upon the absorption of proteins, fats, and carbohydrates?

Some light has been thrown upon the first of these questions by watching with the *x*-rays the course taken by a meal containing bismuth oxide, and it would appear, as might have been expected, that both routes are followed, unless either the pylorus or the artificial opening is or becomes greatly narrowed. On this subject the writings of Cannon and Gray may be consulted.

The former used cats with a normal stomach on which the operation had been performed, and naturally the tendency was for the meal to take the pyloric route.

Härtel* has made a study by this means of 22 patients operated on months or years before. About half of them, including those in which pyloric stenosis was found at the operation to be severe, emptied only by the new opening; in the others the food took both directions. In one case it appeared to pass out only by the pylorus.

The effect upon the gastric juice is nil if it has previously been normal; if hyperchlorhydria was present, an *efficient* gastrojejunostomy appears

* *Deut. Zeit. Chirurg.*, 1911.

invariably to restore the amount of acid to normal. Stenosis of the opening may be followed by a return to the greater acidity. If the HCl is absent, however, the operation will seldom, if ever, cause it to appear.

That there cannot be any serious loss of power to digest and absorb food-stuffs is shown by the remarkable way in which the great majority of cases operated on become fat and flourishing after gastrojejunostomy for non-malignant affections, the improved condition being maintained for many years. There is at least one patient who at the age of seven was described by his father as strong and healthy, with good appetite and exceedingly good digestion, after a gastrojejunostomy at the age of eight weeks for pyloric stenosis. Paterson has proved that the amount of fat and protein passed in the fæces without assimilation is very little greater than in the normal individual. In four cases it was only about 2 per cent above normal; that is, the fæces contained about 9 to 9·5 per cent of protein nitrogen taken as food instead of the normal 7·7 per cent. Much less favourable results previously published by Jöslin were due to the fact that he used cancerous cases on which to experiment. Paterson's results are confirmed by Cameron,* who finds that the only ill-effect is some slight diminution in the power of absorbing fat.

The relief afforded by a gastrojejunostomy in conditions where there is no organic obstruction depends on two main factors: it drains away the acid juice, so that no excess can accumulate, and

* *Brit. Med. Jour.*, 1908, i, p. 140.

when pain is being caused by strong gastric peristalsis against a spasmodically closed pylorus it provides a safety-valve. The beneficial effect on ulcers and hæmatemesis is probably due to the withdrawal of the acid and the prevention of distention.

Feeding after Gastrostomy.—Pawlow's experiments, above referred to, give a valuable hint as to the feeding of patients who are unable to swallow and have suffered a gastrostomy. It is well known that they may fail to make progress even when the operation has apparently not been postponed too long. Sometimes they will request that they should still be allowed to take food into the mouth "just to taste it." Evidently they lack the first secretion of gastric juice due to the relish with which the food is tasted and swallowed, and digestion may in consequence be very imperfect. This may be overcome by the simple device of adding some form of extractives to the feed, such as beef-tea, gravy, soup, or a meat essence. Thus the chemical mechanism is brought into play though the nervous reflex fails. Excellent practical results have been obtained by this expedient.

THE SECRETION OF PANCREATIC JUICE.

This was first thought by Pawlow to be due to a reflex through the vagus, but it has been shown by Bayliss and Starling that the stimulus is in reality chemical, though it is not impossible that a secretion can also be induced by the vagus. When the hydrochloric acid of the gastric juice touches the mucous

membrane of the duodenum, a soluble chemical substance is formed called " secretin," which passes into the rootlets of the portal vein, is carried to the liver and heart, and thence all over the body. Some of it in due course reaches the pancreas, and a flow of pancreatic juice is at once instituted and continues as long as the acid contents of the stomach continue to enter the duodenum. The secretion acts chemically on the pancreatic cells, liberating steapsin from pro-steapsin, amylopsin from pro-amylopsin, and trypsinogen from pro-trypsinogen. There is some evidence that secretin stimulates also the activity of the liver cells, thus pouring into the bowel not only pancreatic juice but bile.

We find in this mechanism a clear indication for the administration of hydrochloric acid in cases where that of the gastric juice is deficient. At least we may be able to preserve for the patient the activity of his pancreatic juice, which is likely to be suppressed when the usual stimulus is lacking. The exhibition of secretin itself has so far been a failure ; it is not absorbed from the bowel, and giving it subcutaneously produces dangerous depression, due apparently to other substances, which we do not know how to separate, extracted along with it from the duodenal mucous membrane.

Pawlow and his followers have described a marvellous adaptation of the various pancreatic ferments to the work in hand ; thus, they thought that a meat diet called forth much trypsin, and a starchy diet much amylopsin. These statements were made before we knew that the flow of pancreatic juice

was started by secretin, which in its turn depends on the amount of HCl coming through from the stomach. A still more disturbing factor is the action of the ferment in the intestinal juice called enterokinase, without which trypsin is inert, being secreted in an inactive form called trypsinogen and only activated by the enterokinase. More recent work, taking these new facts into account, shows that the composition of the pancreatic juice does not vary. It is probable, however, that other substances besides hydrochloric acid have the power of calling forth pancreatic juice, and, indeed, if it were not so, patients with cancer of the stomach would usually starve. Workers in Pawlow's laboratory have demonstrated that the most important of these are fat and soaps, and the action is similar to that of the gastric juice, namely, by exciting the formation of a secretin. It is very probable, also, that the sight and smell of food set up a flow of pancreatic juice, but it is difficult to be sure of this.

Pawlow's operative experience in making pancreatic fistulæ in dogs and in the after-treatment may suggest devices for surgical practice. To obtain a permanent fistula it was necessary to bring the duct out on the abdominal wall, and still to preserve its natural orifice, otherwise it closed rapidly. Therefore a small square of duodenum containing the opening of the duct was transplanted to the skin. With careful nursing and treatment, such dogs would live for months or years.

There were two principal points in the after-treatment. At first there was great difficulty on account

of tryptic digestion of the skin around the wound, such as is so trying for surgeon and patient in some cases after operation for acute pancreatitis, pancreatic cysts, rupture of the pancreas, or artificial anus in the small intestine. One of Pawlow's dogs, suffering in this way, kept on tearing down mortar from the wall to lie upon, and by so doing greatly improved the condition. The hint was acted upon, and afterwards a bed of sand or mortar was always provided, and the excoriation avoided.

About a month after the operation, most of the animals became very weak and refused food, and several died. Yet there had been no loss of weight, there was no peritonitis, and merely ligating the pancreatic duct produced no such symptoms; indeed, no special harm resulted. Pawlow concluded that the loss of juice must be the cause of the trouble, so a diet of milk and bread, which excites the smallest flow of secretion, was substituted for meat, which excites the greatest flow, and alkalies were given regularly by mouth. By these means the dangerous symptoms were entirely averted.

Both the above experiences may help us in dealing with some special difficulties in surgical cases after operations on the pancreas. For the sand or mortar, bags containing some drying powder would probably be substituted.

THE BILE.

We may dismiss the recent researches on the bile in a very few words, as their clinical bearing is not yet apparent.

The secretion of bile by the liver cells is excited by secretin, just as is the pancreatic secretion. No bile, however, enters the duodenum except when food is there, two hours after a meal. The quantities of bile and pancreatic juice poured into the intestine rise and fall exactly together. The reflex contractions of the gall-bladder which determine this flow of bile are brought about by the presence of fat or of extractives in the duodenum. Here probably we find the explanation of any virtue which olive oil may have in getting rid of gall-stones, because it is highly questionable whether any of the oil is actually excreted by the bile, or in any other way brought into contact with the concretions so as to dissolve them.

Of the many functions which have been charged upon the bile, the most important is that of an intensifier of the action of the pancreatic juice. The pancreatic ferments have their activity enhanced threefold in the presence of the sodium taurocholate and glycocholate of the bile. Moreover, these salts dissolve fatty acids, and so help in the absorption of fats.

ABSORPTION OF PROTEINS.

There remains to be described a fundamental change in our views of the digestion and absorption of proteins. It was formerly taught that the gastric and pancreatic ferments converted the albumin of the food into soluble, diffusible bodies called peptones; that these passed through the intestinal wall into the blood-stream, and in so doing were by some means built up again into the proteins of the blood. Some

readers may recollect a Cleavage Theory, suggesting that half of these peptones were further acted on by the trypsin of the pancreatic juice and broken down into two aminoacids called leucin and tyrosin, whose fate was in doubt. The modern view is very different. The researches of Fischer, Kossel, and others have thrown a flood of light on the composition of the protein molecule. We now know that protein consists of a complicated chain of the bodies called aminoacids (that is, organic acids of which a hydrogen has been replaced by the NH_2 group). These may be classified as monoamines (as leucin, glycin), diamines (as arginin, lysin), and aromatic amines (as tyrosin, tryptophan). By the trypsin of the pancreatic juice proteins are resolved into their various components, and consequently a mixture, in differing proportions, of these aminoacids is found in the intestine. Some peptone appears to resist further disintegration by the pancreatic ferment, but there is a ferment in both the pancreatic and intestinal juices called erepsin, which completes the action of the gastric and pancreatic juices by converting all the peptones into aminoacids.

Neither albumin nor peptone can be absorbed by the intestine. They must first be converted into aminoacids. These are the actual substances which traverse the intestinal wall and enter the blood-stream. They do not circulate as serum albumin, but as aminoacids, and are taken up by the tissue proteins according to their needs. Should these require more of the aromatic amines, they will abstract tyrosin or tryptophan from the blood, and

so on. Any aminoacids that are in excess of the requirements of the body are broken down by the liver to urea, and excreted by the kidney. This constitutes the so-called exogenous origin of urea.

The evidence for these fundamental changes in our view of the absorption of proteins may be summarized briefly as follows :—We now know that

(*a*). Aminoacids are abundantly formed in the intestine.

(*b*). Feeding on aminoacids obtained by tryptic digestion, though not by sulphuric acid disintegration of protein, will sustain life. Gelatin will not sustain life, because it lacks the aromatic amines, but if it is given with tyrosin and tryptophan, the animal lives.

(*c*). During protein absorption, it is not the proteins (serum albumin and globulin) which increase in the blood, but the nitrogenous constituents of the plasma which are *not* coagulated by heat.

(*d*). Van Slyke has demonstrated a marked rise in the quantity of aminoacids in the blood during protein digestion, although it seems to last only a very short time. These acids disappear from the circulating blood within a few minutes of injection.

Carlyle said that an error is never proved to be an error until it is shown how the error arose, and this is possible in regard to the older theory, that peptones were converted by the intestinal epithelium into albumin. The disappearance of the peptone in contact with the intestinal wall was taken to indicate a conversion into albumin, because the nature and function of the ferment erepsin were not then known.

The erepsin had converted the peptone into amino-acids.

We must not hope therefore when we feed a patient on peptonized foods, that we have completely saved him the necessity of digesting them. We have carried the process only part of the way. It is not feasible, perhaps, to feed him on aminoacids, because the prolonged pancreatic digestion makes the food unpleasantly bitter and might cause diarrhœa; aminoacids are not normal occupants of the stomach.

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 aminoacids), 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.

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 no amino-acids are formed from the peptone of the enema. The crucial experiment is, Can aminoacids be absorbed?

To determine this the writer, with Dr. Bywaters, has made daily analyses of nitrogen in the urine by the Kjeldahl method in patients to whom enemata were given, either of milk pancreatized for twenty-four hours, so as to convert most of the protein into aminoacids, 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 aminoacid preparations used instead. In each of five patients the nitrogen output in the urine was greatly increased by the use of aminoacids in the nutrients. Figures of two such cases are given in the Appendix.

We conclude, therefore, that aminoacids 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. 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 haematemesis, 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.

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.

REFERENCES.

PAWLOW.—" The Work of the Digestive Glands." Translated by W. H. Thompson. 2nd Edition. Griffin & Co., 1910.

STARLING.—" Recent Advances in the Physiology of Digestion." London, 1906. (Gives an excellent list of authorities.)

LANGDON BROWN.—" Physiological Principles in Treatment." 2nd Edition. London, 1910.

HERTZ.—" The Sensibility of the Alimentary Canal." Oxford Med. Public., 1911.

SOLTAU FENWICK.—*Proc. Royal Soc. Med.*, Surgical Section, 1910, p. 177.

PATERSON.—*Ibid.*, p. 187.

CANNON.—" The Mechanical Factors of Digestion." Arnold & Co., 1911.

WILLCOX.—*Lancet*, 1905, i, p. 1566; 1908, ii, p. 220.

WALTON.—*Ibid.*, 1908, ii, pp. 17, 85.

GROVES.—*Proc. Royal. Soc. Med.*, vol. ii, 1909, part iii, Surgical Section, p. 121.

LANGDON BROWN.—*Proc. Royal Soc. Med.*, Therapeutics Section, 1911, p. 63.

HERTZ.—*Jour. of Physiol.*, 1913, vol. xlvii, pp. 54, 57.

SHERREN.—*Brit. Jour. of Surg.*, 1914, Jan., p. 390.

RENDLE SHORT and BYWATERS.—*Brit. Med. Jour.*, 1913, i, p. 1361.

CARLSON.—*Amer. Jour. Physiol.*, 1913, p. 8.

CHAPTER VIII.

THE HÆMORRHAGIC DIATHESIS.

The physiology of the coagulation of the blood—Fibrinolysis—Hæmophilia—Pathology of hæmophilia—Treatment of hæmophilia—The therapeutics of calcium salts.

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.

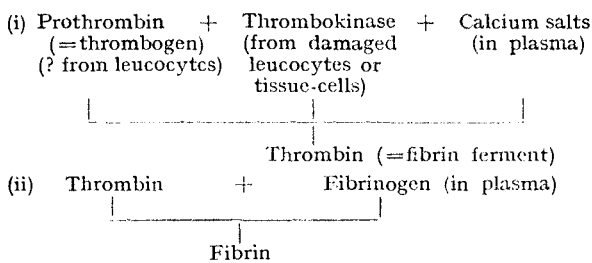
The phenomena of blood-clotting are beautifully designed to avoid two opposing evils; if no provision was made for fibrin formation every injury would be fatal; but on the other hand, if all the essentials for the process were already present in the plasma, the circulation would immediately be brought 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 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.

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 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 hypodermically to absorb young fibrous tissue, may possibly be due to the production of ferments such as these.

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 over 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.

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

PATHOLOGY OF HÆMOPHILIA.

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 five to ten minutes; hæmophiliac blood may take anything from fifteen to ninety minutes to solidify, although the eventual yield of fibrin is copious and firm. Addis has shown 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 hæmophiliacs 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. Hæmophiliac fibrinogen is as readily clotted by normal or by hæmophiliac thrombin as is normal fibrinogen, and normal fibrinogen is easily clotted by thrombin from a bleeder. But the hæmophiliac blood must stand a long time before any 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 hæmophiliac 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 hæmophiliac 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 hæmophiliac 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 has 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 hæmophiliac 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 hæmophiliac 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 hæmophiliac blood to clot as it does, because any thrombin in the former would be overpowered and destroyed by the antithrombin 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.

TREATMENT OF THE HÆMORRHAGIC DIATHESIS.

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 grains for adults, and 15 grains for children, at once, followed by 10-grain doses three times a day for three days for adults, with a corresponding reduction for children. Calcium salts reverse their effect after three days.

To the same authority we are indebted for the suggestion that we should administer carbon dioxide gas, either from a Kipp's apparatus containing marble and hydrochloric acid, or from a cylinder of the gas. Venous blood is much more coagulable than arterial. Dyspnœa should be avoided.

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 hæmophiliac blood, and that is to supply normal blood.

Goodman has published a well-written, almost dramatic description of his treatment of a Jewish boy, aged 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 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. Both made an excellent recovery. The donor required to rest in bed for a few days.

The above-described case by no means stands alone; excellent results have been obtained in septicæmia and in coal-gas poisoning as well as in hæmophilia. It will not do to use animal's blood, because bloods of different species are mutually destructive.

The connection between the two patients may be made by dissecting out a short length of artery and vein respectively under local anæsthesia, and uniting them either by a short oiled glass tube or by Carrel's immediate suture. Of course great care must be taken not to inject clots or air, and the technical difficulties may be considerable.

When a healthy adult supplies blood to an infant, the donor suffers no ill-effects, except that rest for a few days is desirable. In many cases, however, especially if older children or adults are to be transfused, it would be well to provide two donors, either simultaneously or successively. But probably it is not necessary to transfuse large quantities. We have seen that quite a trifling addition of normal blood will make it possible for hæmophiliac blood to clot promptly, and there is no need in most cases to do more than stanch the bleeding. Rest, fresh air, plenty of fluids, and iron, will speed the convalescence.

THE THERAPEUTICS OF CALCIUM SALTS.

So much interest has lately attached to this subject that brief mention only will be called for of the uses to which calcium salts have been put. It has long been recognized by physiologists that they are essential to the continued success of perfusion fluids, and now we know that they control the coagulation and viscosity of the blood, and probably the functions of the ovary and parathyroid glands also.

Remarkable results have been obtained in many cases by giving calcium lactate in 15-gr. doses thrice a day, for three days only, in the following conditions:

Transient or functional albuminuria.

"Lymphatic" headache frequently recurring in anæmic young women.

Some urticarial eruptions.

Chilblains. In this common complaint it may work like a charm.

All varieties of tetany.

The symptoms of the menopause are sometimes greatly relieved by calcium lactate.

In all the above, however, there is one constantly recurring source of fallacy. The power to absorb calcium from the bowel varies much in different people, and some observers record negative results after giving the drug. Magnesium salts will sometimes be more effectual if calcium fails to get into the blood.

REFERENCES.

MELLANBY.—*Jour. of Physiology*, 1909, p. 28.
SIR ALMROTH WRIGHT.—Allbutt's System of Medicine, 1909, vol. v, p. 918.
ADDIS.—*Quart. Jour. of Medicine*, Oct., 1910, p. 14; *British Medical Jour.*, 1910 (ii), p. 1422.
GOODMAN.—*Annals of Surg.*, Oct., 1910, p. 457.

CHAPTER IX.

THE PHYSIOLOGY OF URIC ACID AND OTHER URINARY DEPOSITS.

Uric Acid: Derivation from foodstuffs; Derivation from the tissues; The purin bodies; Calcium oxalate—Cystin

THE substances which may form a crystalline deposit in the urine are many, but we shall here refer only to three, namely, uric acid and the urates, oxalate of calcium, and cystin.

URIC ACID AND THE URATES.

For many years totally erroneous views were held by physiologists with regard to the origin of these substances. It has been customary to argue the physiology of the mammal from that of the bird, with disastrous results. Removal, or rather isolation, of the liver in geese was shown by Minkowski to diminish the output of uric acid, whilst ammonium salts and lactic acid were increased in the urine. Hence it was concluded that uric acid was formed in the liver from ammonium salts and lactic acid; and for birds and reptiles this is true. In mammals, the metabolism is totally different. The end product of protein metabolism in birds and snakes is uric acid; in mammals it is urea. It by no means follows, therefore, that uric acid is formed in the

mammalian liver. We may say at once that urea *is* formed in the mammalian liver.

We now believe that *uric acid in mammals is derived partly from certain substances in the food, and partly from the breaking down of cell nuclei, which takes place in most organs in the body, notably in the spleen.* From these organs it is carried to the kidney, and excreted thereby. As we shall see, however, there is a curious complicating factor, in that any uric acid which chances to reach the liver instead of the kidney is changed into urea. The liver, like all other glands, furnishes a little uric acid to the blood, but it probably destroys more than it supplies.

The researches of Fischer and his pupils have demonstrated that uric acid belongs to a group of bodies containing a hypothetical nucleus, the purin ring. Other members of the group are xanthin and hypoxanthin, which occur in muscle and meat extracts; caffeine, which occurs in coffee; and theobromine, in cocoa. Many foodstuffs contain small quantities of these bodies; amongst vegetables, peas, beans, lentils, and asparagus may be mentioned as yielding them; there is also a small quantity in beer. Milk, eggs, and most vegetables contain practically no purin bodies.

The nuclei of all cells in the animal body contain a special form of protein called nucleoprotein, in which the protein is combined with nucleic acid. On ultimate analysis this substance yields, amongst other products, certain purin bodies, called guanin and adenin.

The uric acid and other purin bodies in the urine (xanthin, etc.) are derived from two sources, referred to as *exogenous* and *endogenous*. By *exogenous origin* we mean that substances capable of yielding purin bodies taken as food are broken down by the digestive juices, the purin bodies are then liberated and absorbed by the blood, carried, with or without alteration, to the kidneys, and by them excreted in the urine. These have never been built up into the protoplasm of the living cells of the body. By *endogenous origin* we mean that purin bodies are end products of the breaking down of certain of the constituents of the living protoplasm of the individual. In other words, the purin bodies of the urine may be derived from the food, or from the living tissues of the body. The normal man on an ordinary diet excretes exogenous and endogenous purin in about equal quantities.

Variations in the amount of uric acid excreted may be affected, then, by variations in the food, or by variations in the breaking down of the tissues.

Considering first the effect of diet, it is found that on a purin-free diet the uric acid and the purin bodies in the urine drop to about half the ordinary amount. Feeding on meat, broths, coffee, etc., increases the excretion of the uric acid and other purin bodies, and the same effect may be obtained by feeding with hypoxanthin itself. Again, any tissue rich in nucleoprotein, that is to say rich in cell-nuclei, will, if given by the mouth, increase the output of uric acid and purin bodies. Calf's thymus, the roe of fishes, liver, and pancreas (sweetbread) all have this effect. To

sum up, uric acid and other purin bodies are derived from feeding on :—

1. Purin bodies in meat, broths, coffee, etc.
2. Nucleoproteins.

Strange to say, feeding on uric acid itself causes no increased output in the urine ; instead, there is a greater excretion of urea. If urates are injected into the blood-stream, uric acid and urea are both increased in the urine, only part of the uric acid injected being recovered as such. Evidently then some organ is capable of converting uric acid into urea. This organ is the liver, and a uricolytic ferment, destroying uric acid, may be obtained from it.

The whole of the purin body given by the mouth does not appear as purin body in the urine. A good deal appears as urea. There is a fraction, constant for the species, representing to what extent this takes place. In man, half the purin body absorbed is destroyed by the liver. In the dog, nineteen-twentieths are destroyed. The difference appears to depend on the differences in relative size of the blood-vessels of the liver and kidney in the various species, those of the dog's liver being very large.

It has yet to be explained how it is that adenin and guanin—derived from nucleoprotein—and xanthin and hypoxanthin—derived from muscle—come to be excreted partly as urea, partly as uric acid, and partly as less oxidized purin bodies.

It is now known that many organs of the body, notably the spleen, contain a remarkable series of ferments acting upon these substances. Thus there have been obtained :—

Nuclease, splitting nucleoprotein, and liberating guanin and adenin.

Guanase, converting guanin ($C_5H_3N_4O \cdot NH_2$) into xanthin ($C_5H_4N_4O_2$).

Adenase, converting adenin ($C_5H_3N_4 \cdot NH_2$) into hypoxanthin ($C_5H_4N_4O$).

Oxidase, converting xanthin ($C_5H_4N_4O_2$) and hypoxanthin ($C_5H_4N_4O$) into uric acid ($C_5H_4N_4O_3$).

If spleen pulp, which is rich in nuclei, is left to digest itself at a suitable temperature, xanthin and uric acid are formed *in situ*.

The purin bodies, then, split off from nucleoprotein in the body or derived from food containing purin bodies or nucleoprotein, are acted on in the spleen and in all other organs by these ferments, and eventually uric acid would be produced. This is excreted by the kidney as rapidly as it is formed, so that it is not possible to isolate it from normal blood.

Side by side with this, the liver is exercising its destructive function on so much of the uric acid as may be brought to it. The products of its action are urea, and probably glycine (amino-acetic acid). If the liver is largely shut out of the circulation by means of Eck's fistula (putting the portal vein into the inferior vena cava), uric acid appears in the blood even on a purin-free diet, because now so much of it escapes the activity of the liver cells. The same effect is observed if the aorta is tied above the cœliac axis, both the liver and the kidney being shut off by this operation.

A little remains to be said with regard to the endogenous origin of purin bodies. They are derived

from two main sources, the xanthin of the muscles and the nucleoprotein of all cell nuclei. Much of the purin bodies split off from these is oxidized into uric acid by the above-mentioned ferments, but only that which chances to be carried to the kidney before it reaches the liver appears in the urine as uric acid or urates. That which finds its way to the liver appears in the urine principally as urea.

The excretion of purin bodies on a purin-free diet is of course entirely endogenous, and the daily output is a constant for the individual, depending roughly on the weight of his muscles. It is, however, increased greatly by muscular exercise. Whilst the hard work is proceeding the uric acid output falls a little, while the xanthin output rises correspondingly; the muscles take up so much oxygen that there is none to spare to oxidize xanthin. After the work is over, the uric acid rises. Unaccustomed work is much more effectual than routine work. There is also a considerable rise in any conditions where cell nuclei are rapidly broken down. As is well known, there is an increase of both uric acid and purin bodies in the urine in fever, and especially in leukæmia. In gout, less uric acid than usual is passed.

It appears that purin bodies are not utilized by the body in the synthesis of nucleoprotein in the protoplasm. It seems to be formed from proteins.

Indeed, it is very doubtful if purin bodies serve any useful purpose. It is certain that they are powerful stimulants in some cases; caffeine is of course one of the most powerful and satisfactory stimulants

known, producing a really increased capacity for mental and physical work. Every one knows how a cup of strong tea, coffee, or beef-tea will refresh the weary and give new energy to the student. We know that squads of soldiers doing forced marches are greatly helped by caffeine. It has been repeatedly proved in every army that the cold-tea brigade comes in first, the water men second, and the alcohol squad a bad third. But we must set against this the certainty that purin bodies produce earlier degeneration of the arteries, and occasionally they are responsible for very severe types of migraine.

We shall not attempt here to discuss the difficult and rather barren problem of the pathology of gout.

We are now in a position to arrive at some practical and clinical deductions from the work of the physiologists. An explanation is furnished of the appearance of the uric acid or urates deposit in the urine so common in functional or organic affections of the liver; this organ is evidently less active than usual in destroying uric acid. We may draw the following conclusions with regard to the prevention of calculus or gravel in those threatened with these complaints. Meat and broths should be restricted, also tea, coffee, and cocoa; muscular exercise must be mild, and warning given that fever is dangerous. Of course if uric acid crystals tend to form, plenty of fluid must be taken, and alkaline citrates, acetates, or tartrates given. Salts of lithium used to be preferred, since lithium urate is the most soluble of the urates, but potassium is cheaper and better. The uric acid

shower of crystals may often be prevented by Gee's treatment, consisting of a large cupful of whey three times a day.

A simple apparatus for determining the amount of total purin in the urine has been invented by Walker Hall. It is readily used for clinical work. The principle adopted is to precipitate the phosphates with magnesia mixture, then add ammoniacal silver nitrate, leave standing for twenty-four hours, and read the amount of the silver purin precipitate.

CALCIUM OXALATE.

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 causes 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 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.

CYSTIN.

Cases of cystinuria are not common. Sometimes the deposit forms a yellowish-green waxy calculus; more often, flat hexagonal crystals are passed.

In the chapter on the digestion and absorption of proteins, it was explained that our modern conception of the molecule is that of a long-linked chain of aminoacids, grouped as monoamines, diamines, and aromatic amines. The diamines ordinarily met with in a protein digest are called arginin, lysin, and ornithin. Of this group, cystin is a member, though it is not always present amongst the products of protein dissolution. Its formula is diamino-β-thiopropionic acid; it therefore contains the sulphur of the protein molecule. It has been obtained from hair by chemical disintegration.

It is suggested that in cases of cystinuria a physiological ferment is lacking which should convert the cystin into some simpler product. In a few of the patients, other abnormal diamines, such as cadaverin, have also been found in the urine; in some cases no abnormal amines except the cystin have been detected. In a number of cases leucin and tyrosin were being excreted as well.

Variations in the diet influence but little the output of cystin in a cystinuric. Feeding on arginin (a diamine) or tyrosin (an aromatic amine) makes no difference. Feeding on cystin itself merely increases the output of sulphates.

Cystin is soluble in ammonia.

It will be observed that we cannot exercise any useful control over the output of this deposit. It is a life-long abnormality.

REFERENCES.

Uric Acid and Gout.

L. Hill.—"Recent Advances in Physiology and Biochemistry," p. 387. Arnold & Co., London, 1906.

Von Noorden.—"Metabolism and Practical Medicine," edited by I. Walker Hall, vol. iii, p. 647. Heinemann, London, 1907.

Oxaluria.

A. Rendle Short.—Von Noorden's "Metabolism and Practical Medicine," vol. i, p. 148.

Cystinuria.

Garrod.—*Lancet*, 1908, vol. ii, p. 214.

T. S. Hele.—*Jour. of Physiol.*, 1909, vol. xxxix, p. 52.

CHAPTER X.

ACIDOSIS, ACETONÆMIA, AND DIABETES.

Conditions of occurrence of acetone, diacetic acid, and β-oxybutyric acid—Origin from fats—Sugar starvation the cause of acidosis—Acid poisoning—The diagnosis of starvation—The essential nature of diabetes—The treatment of non-diabetic acidosis—The prevention of post-operative coma in diabetics.

TEXTBOOKS of medicine published fifteen or twenty years ago introduced us to the fact that in diabetic coma, that tragic termination to so many promising young lives, the urine is loaded with three substances whose relations were not well understood—namely, acetone, diacetic acid, and β-oxybutyric acid. A constant study of the behaviour of these bodies by many observers has led to some settled conclusions of considerable interest and value.

It has been shown that they are not peculiar to diabetic coma, although in no other disease are they excreted in such quantity. They appear in the urine in the following conditions also :—

(*a*). Starvation.
(*b*). Periodic (cyclical) vomiting of children.
(*c*). Delayed chloroform poisoning.
(*d*). Salicylate poisoning.
(*e*). The toxæmias of pregnancy (pernicious vomiting, eclampsia).

Starvation may be voluntary, or due to such affections as gastric ulcer, fevers, acute abdominal

catastrophes, prolonged vomiting, or diarrhœa. The amount of acetone and other bodies is large only if the starvation is prolonged.

Cyclical vomiting is a curious and not uncommon condition, usually seen in young children, who for a few hours or days at intervals get bouts of drowsiness and vomiting, which are accompanied by the excretion of acetone and these acids. The attacks usually pass off harmlessly.

Delayed chloroform poisoning is considered at some length in Chapter XI.

It is known that an unusual sequence of overdosing with *salicylates* is drowsiness with vomiting, some collapse, and particularly hissing dyspnœa or air-hunger. Here again the above substances are excreted in the urine.

The presence of acetone, indeed, is perfectly physiological. On an ordinary diet we excrete about 0·01 to 0·03 gram of acetone daily in the urine and rather more in the breath, but these amounts are too small to be recognized by clinical methods. During starvation the excretion by the seventh day may be forty times as much (F. Müller). Diacetic and oxybutyric acids are not normally present in the urine.

ORIGIN OF ACETONE, DIACETIC ACID, AND β-OXYBUTYRIC ACID.

It was at first supposed that these were all derived from glucose, because of their appearance in diabetes; at a later time they were accredited to the proteins; but it is now definitely established that they are the

result of a peculiar abnormal process of breaking down of the fats.

The physiological process of dealing with fat is to resolve it into carbon dioxide and water. If we make a pound of fat into tallow candles and burn it, we shall obtain carbon dioxide and water, and a certain amount of heat will be evolved. If the pound of fat is eaten and absorbed by a man or an animal, it will be burnt to the same end-products, and the same amount of heat will be given out. But in certain circumstances, an abnormal mode of breaking down is followed, and there are produced first β-oxybutyric acid, then diacetic acid, and finally acetone. If this takes place on a large scale, the conversion into acetone fails to keep pace with the production of the acids. Therefore first acetone appears in the urine, then diacetic acid, and finally β-oxybutyric acid; the last may rise rapidly to an enormous figure: 30, 50, or even 180 grams may be passed daily in diabetic coma (Magnus Levy).

Feeding on fats will always cause some rise in the output of acetone and of these acids if they are already present; in starvation it will cause a very marked increase. Butter, which contains lower fatty acids (butyric, etc.), as well as fats, is particularly active in this respect.

It is of no great importance to us to know *where* in the body this process of breaking down takes place; the liver is usually supposed to have the power to effect it.

We next ask, What are the special circumstances in which the breaking down of fat deviates from

its normal course, and follows this dangerous route? The answer is clear and decisive. *When the tissues are unable to obtain sugar from the blood, fat is broken down via these abnormal acids to acetone, instead of to carbon dioxide and water.*

This remarkable proposition has been abundantly proved, and along several independent lines of research. Thus in one case, an experimenter (Satta) ate nothing for two days but milk sugar, and excreted the normal amount of 0·01 gram of acetone daily. Then he took a diet of 300 grams each of meat and fat, which is of course quite an adequate amount to sustain health, and the excretion rose to 0·8 gram and 1·1 gram on the two days of experiment. Thus:

Day 1.	Diet only lactose.	Excreted 0·01 grm.	acetone.
Day 2.	,, ,, ,,	,, 0·01 ,,	,,
Day 3.	,, meat and fat	,, 0·80 ,,	,,
Day 4.	,, ,, ,,	,, 1·10 ,,	,,

As we shall see, if the tissues can be supplied with glucose, pathological acetonæmia and acidosis are rapidly cured.

It now becomes evident why acetone and the acids are formed in the conditions above referred to. In starvation the tissues cannot obtain glucose because there is none in the blood. In cyclical vomiting of children, and in delayed chloroform poisoning, the conditions are a little more complex. Mild acetonæmia is set up in the first place either by abstinence from carbohydrate food for a longer time than usual, or by some toxic agent preventing the tissues from obtaining the requisite sugar for the blood by paralysing in some way their activity; in many

cases both these causes are combined, as when a patient with a perforated gastric ulcer, who has absorbed nothing for hours, is given chloroform. The vomiting induced by the acetonæmia of course prevents the retention of carbohydrate food, and so the bad becomes worse.

Salicylates presumably act by paralysing that function of the tissues which enables them to take up sugar from the blood. As we shall see, this is also the pathology of diabetes. The tissues, starved of sugar, break down the fat to acids and acetone instead of to carbon dioxide and water. With reference to the acidosis of pregnancy, some unpublished observations by Statham, made at the Bristol Royal Infirmary, show that in addition to the acidosis of pernicious vomiting, in which probably starvation is a factor, there is constantly an increase in the ammonia nitrogen ratio in the urine in the pre-eclamptic state as well as in eclampsia; usually there is diacetic acid present, but not always. If the patient is kept on glucose, the nitrogen ratio becomes normal soon after delivery, but not before.

THE MECHANISM OF POISONING IN ACIDOSIS AND ACETONÆMIA.

Neither acetone, diacetic acid, nor β-oxybutyric acid is poisonous, except in enormous doses. Why then do such marked and indeed fatal symptoms occur when they accumulate?

The blood is normally alkaline. All the functions of the tissues are attuned to a medium of a particular alkalinity. If this alkalinity is greatly reduced,

almost to a point of neutralization, the symptoms produced experimentally are not dependent on the particular acid used. They include dyspnœa, vomiting, and coma. In diabetic coma the alkalinity of the blood is much reduced by the increase of diacetic and especially of β-oxybutyric acids in the plasma. This condition is called "acidosis." It would perhaps be going too far to say that absolutely unlimited quantities of β-oxybutyric acid may be formed and tolerated if sufficient alkali is supplied to neutralize it; there is a point beyond which even sodium β-oxybutyrate becomes toxic; and by keeping the urine alkaline, although we may greatly delay, we do not altogether prevent the onset of diabetic coma.

The body is able for a long time to defend itself against the increased production of diacetic and β-oxybutyric acids, by furnishing enough alkali to neutralize them more or less completely. First, the reserves of sodium and potassium are called upon, but the main defence is the production of large quantities of ammonia. In normal metabolism the proteins of the tissues split off their effete nitrogen in the form of ammonium salts (carbonate, carbamate, etc.), and these are converted into urea by the liver. When diacetic and β-oxybutyric acids are present, these unite with the ammonia, and it escapes conversion into urea; consequently there will be an increase of ammonia nitrogen in the urine (as ammonium diacetate and ammonium β-oxybutyrate). At length, however, the production of the acids becomes so excessive that the supply of ammonia from the

tissues fails to keep up with them. Then the normal alkalinity of the blood falls, and dyspnœa, collapse, and coma begin to appear.

DIAGNOSIS OF STARVATION.

It may become very important to know if a patient is or is not obtaining adequate nourishment. This is particularly the case when on account of vomiting, hæmatemesis, or typhoid fever, mouth feeding has to be restricted or becomes altogether impossible. It is easy to find out. Daily estimates of the urea output will show if the protein absorbed is adequate, and tests for acetone, diacetic acid, and oxybutyric acid will show if the supply of carbohydrate has fallen too low. The normal ratio of ammonia nitrogen to urea nitrogen is about 5 per cent. If it rises to 10, 15, or 20 per cent, there is severe acidosis present, due to starvation, but masked by the ammonia supplied to neutralize it. When the supply of ammonia fails, fatal coma will follow.

THE ESSENTIAL NATURE OF DIABETES.

Seeing that it is in diabetics that the most terrible consequences of acidosis are exhibited, it will be well very briefly to consider just in what way the metabolism has gone wrong in this disease.

Glycosuria may be experimentally induced in animals by the following means :—

(*a*). *By puncture of the medulla.*—This is perhaps a vasomotor effect, the increased blood-flow washing glycogen out of the liver. Or there may be some interference with secretory nerves to the liver.

Stimulation of the central end of the divided vagus acts in the same way. To this class belong those clinical cases in which transient glycosuria follows head injury or cerebral compression.

(*b*). *By very excessive feeding on sugars.*—Doses of over 150 grams of glucose or cane sugar will set up a sort of overflow glycosuria; smaller quantities of lactose or maltose (from beer) will do the same.

(*c*). *By administration of phloridzin,* which is a glucoside occurring in the bark of plum and cherry trees. This drug has the remarkable power of compelling the secretory epithelium of the kidney to break down serum-albumin so as to yield sugar; the glycosuria is not therefore associated with any increase of sugar in the blood.

It is of course conceivable that human diabetes, in some cases at least, might be of renal origin in a similar manner, and an attempt has actually been made in France to separate off a class of renal diabetics, but very few English, German, or American authorities allow the justifiability of this. Phloridzin glycosuria would be devoid of practical interest if it were not that it has recently been taken up by the surgeon for diagnostic purposes. When a patient has severe tuberculosis of, shall we say, the right kidney, but the condition of the left is doubtful, it would of course be a serious risk to remove the right kidney, and indeed a fatal result has several times been recorded. Of the methods of investigating the function of the left kidney, one of the best is to give phloridzin. If sugar fails to appear in the urine, both kidneys are seriously diseased; if it does

appear, there is still an efficient amount of renal substance. To give precision to the test it is usually wise to catheterize both ureters, and to analyse the urines separately.

(*d.*) *By variations in the blood-content of* CO_2.—Apparently either a marked rise or a marked fall in the amount of carbon dioxide in the blood may produce glycosuria. Prolonged deep breathing, for instance, reduces the CO_2 in the blood to a very low figure, and not infrequently transient glycosuria results. This has been adduced as the explanation of its occurrence after violent anger or after anæsthetics. Strong saline injections may also induce glycosuria.

(*e*). *The ductless glands and diabetes.*—There is probably an important and complicated relationship between the ductless glands and glycosuria. So far we only know a few isolated facts. Thus, adrenalin injection causes glycosuria of pancreatic type; in hyperthyroidism sugar may appear in the urine and the toleration limit of glucose may be very low (less than 100 grams may set up glycosuria); on the other hand, partial excisions of the pituitary gland raise the toleration for glucose above the normal 150 grams.

(*f*). *Pancreatic diabetes.*—Removal of the pancreas in dogs or other animals if complete induces fatal diabetes exactly corresponding to severe cases of the disease in man; a sub-total removal brings about a milder type of the disease. The symptoms are improved by pancreatic grafting. If less than four-fifths of the pancreas is taken away, no glycosuria

follows. After complete removal, but not after removal of four-fifths, sugar will continue to appear in the urine even when all carbohydrates are excluded from the food, being derived in this case from the breaking down of food and body protein.

In ordinary human diabetes, the pancreas is found at autopsy to present some abnormality in such a large proportion of cases that the smaller group in which nothing is found amiss may safely be attributed to functional deficiency apart from organic disease. To quote an analogy, mental defect is so often associated with gross changes in the brain that we think we are justified in assuming that there must be some functional derangement of that organ, even when in cases of insanity it appears to be quite normal.

In what way may destruction of the pancreas conceivably produce diabetes?

The present-day teaching is that the pancreas supplies to the blood some internal secretion, some chemical substance, which is carried to the muscles and other tissues to enable them to make use of the sugar brought them by the blood. The tissues are positively in *need* of sugar. It is probably an essential source of muscular energy. A beating mammalian heart, through which a solution of salines containing sugar is repeatedly passed, will use up that sugar. It is a principal source of heat. It is probably a necessity for nearly all the functions of the protoplasm of the tissues. The blood always contains sugar (about 0·1 per cent) to supply this need; the whole process of glycogen-storing in the liver is designed to keep the percentage at a constant level

in the blood. The internal secretion of the pancreas is the link whereby the tissues may take hold of and utilize this circulating sugar. In diabetes the internal secretion of the pancreas fails, and the link is missing. The tissues are in the position of the hungry boy outside the sweet-shop; he longs for the sweets and the supply is abundant, but he has not the means to purchase. So the sugar in the blood, lacking a market, goes on accumulating till it reaches a figure of 0·2 or 0·3 per cent; it runs to waste in the urine, but the tissues cannot touch it. Like a starving town through which rich convoys are passing, the plenty comes to their very doors, but cannot be utilized. Urgent messages for food are sent to the liver, to other organs, to the intestine; these are depleted of all their reserves of glycogen, and even the proteins themselves are broken down wastefully to obtain sugar, some of which slips out into the blood and is permanently lost to the tissues. So we see the patient losing flesh, and not only sugar but also excess of urea appear in the urine, derived of course from the proteins.

Naturally, in most cases matters have not progressed quite so far; a *little* of the pancreatic secretion continues to be supplied, and if carefully husbanded, as by reducing the carbohydrate in the food, may suffice for the bare needs of the body. To return to the illustration, the hungry boy is not quite penniless, and if he spends his money wisely he may yet keep himself going by alternating periods of self-denial and mild indulgence.

It must be admitted that some researches of the

past few months have taught us to be cautious in coming to the conclusion that the problems of diabetes are solved. A year or two ago Starling and Knowlton advanced what appeared to be most interesting evidence, that after removal of the pancreas the surviving beating heart of a dog is unable to make use of dextrose perfused through it, but that if pancreatic extract is added, the power to utilize sugar is restored. This of course exactly fitted the theory. But now Starling finds that the supposed results were due to experimental error, and that the diabetic heart is well able to use up sugar.

Various authorities have tried to go further with the explanation of human diabetes, and have stated that the internal secretion is derived from the clusters of cells called islets of Langerhans, whereas the digestive juices are derived from the acini; it has further been stated that in diabetes sometimes the islets are destroyed whilst the rest of the pancreas is normal. Ligature of the pancreatic duct causes atrophy of the secreting cells of the alveoli, but not the islets, and is not followed by glycosuria. Some observations by Dale, supposed to tell against the theory, are not confirmed. It is true that in some cases of human diabetes the islets appear to be normal. Perhaps we must look to some alteration in the internal secretions of the ductless glands for an explanation of these cases.

Again, such wide currency has been given to an experiment of Cohnheim's, that it is necessary to state and refute it. He taught that muscle extract

with pancreatic extract was able to break down sugar, but that neither was able to do so without the other. It has since been abundantly proved that muscle extract can break down sugar just as well by itself. Von Noorden considers that the pancreatic secretion is necessary to enable the tissues to build up sugar ($C_6H_{12}O_6$) into the more complex glycogen ($C_6H_{10}O_5)_n$, where the *n* may stand for a very high figure; glycogen he takes to be a necessary stage in the absorption of sugar into the molecule of protoplasm. Certain it is that both in experimental and human diabetes, glycogen is absent from the liver and muscles in all but mild cases.

Returning to the question of acidosis in diabetes, we are now able to understand why it is so marked and so fatal an occurrence. We saw that the cause of acidosis was the failure of the tissues to obtain sugar. Obviously severe diabetes will be a far more potent factor in leading up to this condition than even starvation. And indeed, of severe cases of diabetes, that is, cases in which complete deprivation of carbohydrate food will not abolish the glycosuria, about four-fifths die in coma. Most of us have known instances. It may have been a young man or woman, the victim of diabetes certainly, but otherwise apparently in good health, with only the fatal red fringe on touching the urine with ferric chloride to hold out any warning. There was a long walk, a feverish cold, an anæsthetic; or some physician too suddenly instituted a severe deprivation of carbohydrate food, and within a few hours coma had set in, and death was inevitable.

THE TREATMENT OF NON-DIABETIC ACIDOSIS.

It will probably be agreed that the time has now come when no examination of the urine in cases of diabetes, of abdominal catastrophes, of vomiting, or of starvation, will be complete unless we record the presence or absence of acetone and diacetic acid as well as of albumin and sugar. Unfortunately there is no simple clinical test for β-oxybutyric acid. It has been usual to estimate it by the amount of lævo-rotation of a ray of polarized light, from which of course must be deducted the dextro-rotation due to any glucose which may be present.

A fairly simple qualitative test is Stuart-Hart's: Take 20 c.c. of urine, add 20 c.c. of water and a few drops of acetic acid. Boil the mixture till the bulk is reduced to about 10 c.c.; thus acetone and diacetic acid are driven off. Add water to restore the bulk to 20 c.c.; put 10 c.c. into each of two test-tubes, A and B. To A add 1 c.c. of hydrogen peroxide; just warm it, but do not boil, for one minute. Cool. Add to A and B ½ c.c. of glacial acetic acid, a few drops of fresh sodium nitroprusside, and overlay with 2 c.c. of ammonium hydrate. Stand four hours. If β-oxybutyric acid was present, it will have been oxidized to acetone, and a purple-red ring will form where the fluids meet in A, but not in B. The presence of sugar does not interfere with the reaction.

The presence of acetone cannot be definitely excluded without distilling the urine, but too delicate tests are usually less valuable than more approximate

ones, because, as in this instance, a trace may be found normally. The presence of diacetic acid is of more clinical importance.

Tests for acetone in the urine :—To 3 c.c. of urine add a few drops of fresh sodium nitroprusside (a crystal in 5 c.c. of water). Cover with strong ammonia. A magenta ring appears at the line of junction, and spreads upwards (Jackson-Taylor). Or, to 5 c.c. of urine add ½ c.c. of 5 per cent sodium nitroprusside ; make just alkaline with caustic soda, and acidify with acetic acid. A reddish-violet colour develops. Diacetic acid also gives this test.

Acetone is excreted in the breath as well as in the urine, and the sweet odour is perfectly apparent to many medical men, more so to some than others ; some can smell a diabetic excreting acetone at a great distance. It is remarkable how the flies may congregate about a diabetic in a ward.

Test for diacetic acid in the urine :—To 3 c.c. of urine add a few drops of liq. ferri perchlor. A deep red colour which *disappears on heating* is positive. The test is often performed on a white slab as a contact test. One must not be deceived by the frequent reddish *precipitate* of iron phosphate from a normal urine.

Turning now to the prevention and treatment of acidosis, we may clear the ground by reserving diabetic coma for a special word later on in the chapter, and delayed chloroform poisoning for consideration in Chapter XI.

We saw that the *cause* of this peculiar perversion of metabolism is inability on the part of the tissues

to obtain sugar, and that the fatal element in the poisoning is the swamping of the blood with acids. Therefore prevention lies in the supply of glucose, and treatment is to introduce alkalies. In practice, as might be expected, glucose alone is better than alkalies alone; probably both together would give the best results.

On account of vomiting it may not be possible to administer either by the mouth. They may be given by the rectum, or directly into a vein. If the case is urgent, the latter method would be adopted; if not, the former. Glucose should be given in either case in 6 per cent solution in warm distilled water, using two or three pints. Sodium carbonate may be given in doses of 4 drachms to the pint, again using two to three pints. It should be the object of the treatment to make the urine alkaline.

In milder cases, it will of course be possible to give remedies by the mouth. The addition of enough starch or sugar to bring the daily supply of carbohydrate up to 150 grams (5 ounces) will effectually banish the pernicious acids in the urine. Alkalies are best given in the form of sodium citrate, 30 grains or more three times a day, until the urine is alkaline.

It is important to bear in mind the danger of this auto-intoxication, that is, poisoning by the products of the patient's own internal processes, in all the numerous conditions in which insufficient food may be absorbed, so that serious or fatal symptoms may be warded off. Diarrhœa, wasting, or vomiting, from whatever cause, should lead to an examination of the urine for diacetic acid, and the same is specially

necessary when a patient is being fed only by the rectum.

The old-fashioned treatment of rheumatic fever, by combining alkalies with the salicylates, will prevent acidosis from the use of the latter.

The Prevention of Diabetic Coma.—In the treatment of a severe case of diabetes the physician is on the horns of a dilemma. To relieve the ordinary symptoms of diabetes, which are due to the excess of sugar, and to enable the patient to make the best possible use of what little internal secretion of the pancreas he has left, the indications are *to reduce or exclude the carbohydrates* from the food, replacing them by fats and proteins. To prevent the formation of the abnormal acids from fat in the absence of available sugar, the indications are to reduce the fats and *to supply carbohydrates.* The one has to be weighed against the other.

The general treatment of diabetes is not discussed here. The writer has neither the space nor the special experience which would be necessary. We shall confine ourselves to the physiological problem of averting diabetic coma.

Let it be an axiom that no case of diabetes is suddenly to be put on a carbohydrate-free diet on first acquaintance. Particularly would this be dangerous if he already had diacetic and β-oxybutyric acids in the urine. If they are absent, that is, if there is no red colour on bringing the urine into contact with ferric chloride, a strict diet will be safe and valuable.

It would be going too far to say that severe limitation of the carbohydrates is *never* indicated when

diacetic acid is present. Von Noorden has a daily quantitative analysis made of the excretion of β-oxybutyric acid, and with this safeguard, which of course involves a complicated procedure, strict dieting is often safe. Patients with the acids in the urine may live for many years.

Apart from an analysis of the excretion of β-oxybutyric acid, it will usually be justifiable to limit the carbohydrates, provided that the patient is carefully watched for any slight drowsiness, vomiting, or air-hunger, and, further, *that the urine is kept alkaline with sodium citrate.* Fortunately, feeding diabetics on fat does not greatly increase the excretion of acetone bodies, if the lower fatty acids in butter are washed out with cold water before it is taken.

When there is severe acidosis, as evidenced by the quantity of diacetic and β-oxybutyric acids in the urine, or when there are threatening symptoms such as a little tendency to drowsiness or vomiting, it is necessary at all costs to get in carbohydrate at once. The most effectual method of doing so, and one which only very slightly increases the glycosuria, is to adopt von Noorden's *oatmeal treatment.* He allows nothing for three or four days but seven or eight ounces of oatmeal, given as gruel every two hours, with butter, eggs, and vegetable protein, tea, coffee, wine, or whisky. Then for a day or two he gives nothing but vegetables.

The effect on the acidosis is usually very marked, the ferric chloride reaction disappearing in a few days. The glycosuria also may improve to a considerable extent. It is extraordinary that so much

starch as the oatmeal contains should not make the glycosuria worse, but apparently it does not do so. A diet restricted to potatoes may have the same beneficial effect.

At the same time, alkalies should of course be administered, either by mouth, rectum, or intravenously.

It may be asked, Of what avail is it to give carbohydrates, when the tissues will not be able to make use of them owing to the absence of the internal secretion of the pancreas? If the internal secretion were actually *absent*, the case would of course be beyond treatment, but there is always hope that a little may still be available to assist in the assimilation of glucose by the protoplasm; and if the sugar has been expelled from the blood by severe dieting, so that acidosis has resulted, the administration of carbohydrate may save the situation.

Again, it may be asked, Why not give extract of pancreas as a drug? Unfortunately, it has been thoroughly tried and has failed. Most probably the active principle is either destroyed by digestion or is not absorbed from the bowel. Pancreatic grafting gives some temporary relief in animals.

It is well known that diabetic coma may be precipitated by a surgical operation. In some cases matters are so urgent that there is no time for precautions to be taken to avoid this calamity, but if a day or two can be secured first, it should be possible with our present knowledge to banish this bugbear from surgery. It will be much safer to give ether than chloroform, on account of the danger of

delayed chloroform poisoning. If the urine contains no diacetic acid this precaution will be sufficient. Should the red coloration with ferric chloride be present, however, the patient ought to be put on the oatmeal diet, and alkalies introduced by mouth, rectum, or intravenously, until the acid reaction of the urine disappears. These measures must be kept up for a day or two after the operation, until the danger has passed.

Perhaps we are scarcely yet entitled to speak of the *treatment* of diabetic coma. It is true that after intravenous injection of two or three pints of a solution of sodium carbonate (ʒiv to the pint), patients have made a marvellous rally, and, as in one case in the writer's experience, may be so far recovered as to sit up in bed, eat an orange (without leave), and talk to friends. But the symptoms soon recur, and proceed to a fatal termination. The alkaline injection must not be given subcutaneously, but intravenously; the former method will often cause gangrene.

REFERENCES.

L. HILL.—"Recent Advances in Physiology and Biochemistry," Arnold & Co., London, 1906, p. 312.

VON NOORDEN.—"Metabolism and Practical Medicine," Heinemann & Co., London, 1907. Edited by I. Walker Hall. Vol. i, p. 169 (Acetone Bodies); vol. iii, (Diabetes Mellitus).

VON NOORDEN.—"Diabetes Mellitus," J. Wright & Sons Ltd., Bristol, 1906; "Acid Auto-intoxications," J. Wright & Sons Ltd., Bristol, 1904.

STARLING.—*Jour. of Physiol.*, 1913, October.

CHAPTER XI.

IMMEDIATE AND REMOTE POISONING BY CHLOROFORM.

Sudden death under chloroform—The fatal adrenalin-chloroform combination—Delayed chloroform poisoning.

ENTHUSIASTIC advocates of chloroform as the ideal anæsthetic (usually hailing from the north) used to say, "Chloroform kills your patient to-day, and ether kills him to-morrow." They referred of course to the pulmonary complications which used to follow the use of the latter drug in the days when it was given by a Clover's inhaler throughout the operation, instead of by the open method. We are now finding out that chloroform too may not claim its victims until to-morrow.

Chloroform may cause a fatality in three distinct ways: first, by sudden arrest of the heart; secondly, by poisoning the heart and vital centres in the medulla of the brain; and thirdly, by inducing acute fatty degeneration of the viscera, and acidosis. We shall here only consider the first and third.

SUDDEN ARREST OF THE HEART.

Some of the most tragic calamities of surgical practice are due to sudden death from chloroform, and few and happy are the surgeons who have never seen it. Here we must place those cases where the

patient is far from under, perhaps struggling and shouting, and then without warning draws a few deep breaths and dies. Here also, those who seem to be under, but whose heart and respiration cease on being lifted into position for the surgeon. Here, again, those who have been given a mere whiff of the anæsthetic for a trifling operation, and whose life ebbs away at the bare touch of the knife.

Until recently, it was supposed that these fatalities were due to sudden reflex stoppage of the heart by way of the vagus, and that view was given in our previous editions. Very important research work by Goodman Levy appears to demonstrate that the chloroform acts directly on the ventricular muscle, and causes it to fibrillate, that is, to enter into flickering irregular contraction of individual fibres, instead of performing its proper rhythmical systoles. Working with cats, Levy was able repeatedly to observe fatal ventricular fibrillation, usually heralded by cardiac irregularity, and always when the chloroform anæsthesia was light, not deep. Stimulation of sensory nerves under a light anæsthesia frequently caused death in this way; in other cases, the animal recovered. The effect was just the same if both vagi were previously cut. Levy found great difficulty in discovering exactly by what means the sensory stimulus affected the heart. The connection is probably complex. If the chloroform is given in a perfectly continuous manner without intermissions, sudden death—in cats at any rate—can be avoided. Struggling, both in man and animals, is dangerous.

An apology must be made for saying again what we

all know, yet never can know too well. It is courting disaster to hurry the patient under. We must feel the pulse all the time, as well as watch the pupil and the respirations. " Whiffs " are far more dangerous than proper anæsthesia. No lifting, or cutting, or painful pressure is permissible until the patient is properly under. There is no danger of an overdose during quiet breathing if the mask is kept half an inch away from the face. If Levy's results are to be accepted, the mask must not be entirely withdrawn if struggling occurs, but every effort made to keep the administration constant.

What is to be done if the calamity is not successfully averted, and the heart and breathing cease? The books advise a dozen expedients. A moment's consideration of physiological principles will lead us to put most of them aside. How can amyl nitrite, which is simply a vasodilator, possibly help a heart that is fibrillating? Strychnine and brandy are perfectly futile. It is no use giving oxygen to a patient who is not breathing. " Galvanization of the phrenics " is equally likely to galvanize the vagus.

There are just four measures which matter. The *first* is to have the head low, so as to keep the vital centres alive. The *second* is, of course, artificial respiration, which fills the auricles with blood as well as the lungs with air, averts death from asphyxia, and so gives the heart a chance to recover if it can. The *third* is to stimulate the heart to contract again by manual compression, if possible through the diaphragm. The *fourth* is to administer as quickly as possible atropine, which must be injected right

into the heart by a long hypodermic needle.* Its value in overcoming chloroform inhibition has been abundantly proved by Dixon and others in dogs, and though its use in such cases in man is but recent, successes are already recorded. That there have been failures is admitted, but there is good reason to hope for recovery with immediate injection into the heart itself. There is ground for hoping, also, that a preliminary injection of scopolamine, now becoming popular for employment before the administration of a general anæsthetic, may help to eliminate these terribly sad occurrences.

Several patients apparently passed beyond the shadowy Rubicon which separates the living from the dead have been brought back to life by rapidly opening the upper abdomen and rhythmically squeezing the heart against the chest wall through the diaphragm.

THE FATAL ADRENALIN-CHLOROFORM COMBINATION.

In Bristol, it has been well recognized for seven or eight years that the combination of chloroform anæsthesia with injections of adrenalin, as for instance into the mucous membrane of the nose to check hæmorrhage in a nose operation, is a peculiarly deadly association of remedies. There have been several fatalities, and a number of narrow escapes. Levy has done most valuable service in working out

* Atropine solutions are apt to grow a mould which is very poisonous. If such a growth is observed, the solution must no be used.

the subject upon animals, and in demonstrating that adrenalin has a peculiar power in bringing on the ventricular fibrillation which is the particular danger of a light chloroform anæsthesia. A number of deaths have now been recorded from this cause in medical literature. The adrenalin-ether combination appears to be safe.

DELAYED CHLOROFORM POISONING.

The third danger is subtle and unexpected; it has been recognized only recently, and we do not know how to treat its symptoms.

In Chapter X. reference is made to the remarkable process of abnormal decomposition of fats which may take place when the amount of glucose supplied to the tissues by the blood is deficient. In these circumstances, β-oxybutyric acid, diacetic (or aceto-acetic) acid, and acetone are produced, and the patient is poisoned by the acids, while the acetone imparts a sweet odour to the breath and urine. We saw that starved patients and diabetics were particularly liable to this condition of "acidosis" or "acetonæmia," as it is variously called. Fat children and sufferers from peritonitis are frequently the subjects of acidosis after operations in which chloroform has been used, and there is greater danger if there has been a long interval between the last feed and the anæsthetic. A prolonged administration is more dangerous than a brief one. The train of symptoms is referred to as delayed chloroform poisoning. A hospital of 200 beds may perhaps furnish one or two such cases annually, if chloroform

is used frequently as the anæsthetic of choice. The signs are incessant vomiting, drowsiness or unconsciousness, and a sweet acetone odour in the breath. Acetone and aceto-acetic acid are present in considerable amount in the urine. A *trace* may often be found after any anæsthetic. Death follows within a few days. At the post-mortem examination the liver, kidneys, and other organs show signs of acute fatty degeneration. Whether this is the cause or the consequence of the acidosis may be in doubt, but the vomiting and drowsiness are almost certainly due to the effect of the acid intoxication on the brain. Most surgeons who are aware of the condition can recall sad cases where an operation promised well, but this fatal complication stepped in and banished all hope of a favourable issue. Recently it has been found possible to imitate the condition in experimental animals. To draw the practical lesson, we can at present hope only to prevent, not to cure. Every patient to whom it may be necessary to administer chloroform should be guarded as far as possible against this complication. The urine should be tested with ferric chloride. A prolonged starvation should be avoided. Glucose and alkalies have been advocated as remedies likely to prevent trouble, and the former would appear to be the better. If possible, ether should be given to patients who have been starved, to fat children, and, especially, where the urine strikes a red colour with ferric chloride. Diabetics require special care. If prolonged vomiting follows recovery from the anæsthetic, the poison should be diluted by a

large injection of saline into the rectum, which often works wonders. If acetone can be smelt in the breath, glucose or alkalies, or both, should be introduced into the blood by transfusion, but success is not very probable, as these remedies cannot restore the fatty liver and other viscera to normal.

Whether the acidosis is the cause of the vomiting, or whether the starvation consequent on the vomiting causes the acidosis, is not yet certain, but we may safely attribute the drowsiness to the acids in the blood, and they probably share in bringing about the fatal termination.

REFERENCES.

GOODMAN LEVY.—*Brit. Med. Jour.*, 1912, ii, p. 627.
GOODMAN LEVY.—*Heart*, 1913, June, p. 319.

CHAPTER XII.

NERVE INJURIES.

The effects of nerve section—Epicritic, protopathic, and deep sensibility—Causation of trophic lesions—Diagnosis of partial nerve section—How degenerated nerve is regenerated—The results of primary and secondary nerve suture—Methods of dealing with wide gaps.

IT will be necessary in compressing this immense subject into the limits of a single chapter simply to mention the better-known phenomena, and refer to the original monographs those who wish to become more fully acquainted with the interesting results here alluded to.

THE EFFECTS OF DIVISION OF A NERVE.

The effects of division of a nerve are as follows :—

(*a*). Flaccid paralysis of the muscles supplied, with loss of reflexes.

(*b*). Loss of epicritic sense over the anatomical area supplied by the nerve. Loss ot protopathic sense over an area, usually smaller and encircled by the former. Sometimes loss of deep sensibility over an area smaller still. (These terms are explained subsequently.)

(*c*). Reaction of degeneration.

(*d*). Wasting of muscles.

(*e*). Paralysis of the pilomotor nerves, so that the hairs lie irregularly, and " goose skin " does not so readily occur.

(*f*). Paralysis of sweating in the area supplied.

(*g*). Vascular dilatation (transitory).

(*h*). Trophic changes, such as glossy skin, onychia, sensitiveness to injury, ulceration, and certain histological changes.

(*i*). Wallerian degeneration of the distal part of the nerve cut off from its nerve cell.

(*j*). Nissl's degeneration (chromatolysis) of the nerve cells from which the nerve fibres are derived.

Concerning two of these headings a few words of explanation may be useful.

The terms *epicritic*, *protopathic*, and *deep sensibility* were introduced by Head and Sherren to denote some very important distinctions, failure to observe which has led to endless mistakes and confusion in the past.

We may take as an illustration the consequences of section of the ulnar nerve at the elbow.

Epicritic Sense will be lost over the whole of the little finger, over the ulnar half of the ring finger, and over a corresponding area of the ulnar surfaces and border of the hand, both back and front; that is to say, over the region described in the anatomy books as supplied by this nerve. In this area the patient will be unable:

(i.) To detect a light touch;

(ii.) To detect mild ranges of heat or cold;

(iii.) To distinguish two points of an opened compass as separate; and

(iv.) His localization will be imperfect.

In the glans penis epicritic sense is normally absent.

Protopathic Sense will be lost over the whole of

the little finger, and over a small area of the ulnar border of the hand. In this region the patient will be unable to detect :

(i.) A pin prick ;

(ii.) Extremes of heat and cold.

Deep Sensibility will be lost over a smaller area still, of variable dimensions. That is to say, deep pressure will no longer be appreciated by the nerve endings in the tendons, joints, and bones.

It is easy to deduce from the above that serious pitfalls await the unwary observer in testing such a case. He may make pressure on the little finger over the metacarpo-phalangeal joint, or over the ulnar border of the ring finger, and on being told by the patient that both are readily felt, may conclude quite incorrectly that the ulnar nerve is intact. Testing with a pin point will probably bring out an area of anæsthesia smaller than that currently supposed to be supplied by the ulnar nerve.

The only reliable method of testing for anæsthesia in such cases is to make the patient close the eyes, and ask him to indicate with a finger of the opposite hand each point touched as lightly as possible by a pencil of wool. In testing hairy parts, the hairs should be shaved, or protopathic or deep sensibility may be excited. If these directions are followed, an area of anæsthesia will be mapped out corresponding to the anatomical distribution of the nerve.

It is astonishing, at first sight, to find that a patient can feel a pin-prick or pressure in a region to which the anatomist can trace only one nerve, and that one known to be divided. By what path

is he made aware of the stimulus? We must remember that tiny nerve twigs are to be found in unexpected places; in fasciæ, tendons, and bone, entering them far up the limb; in the walls of cutaneous vessels; also that there is always a considerable overlap of the distribution of neighbouring nerves, at any rate of their finest terminals, to be followed only by the microscope. The deep distribution both of the ulnar and radial nerves, in the instance given, is wider than their cutaneous distribution. It is probable, though not certain, that extremes of temperature and painful stimuli are effective because they penetrate to the subepithelial tissues.*

We do not now refer the so-called "trophic changes" to loss of innervation by special nerve fibres whose *sole* function is to maintain the nutrition of the part. The vulnerability of the parts to injury or invasion by bacteria can be accounted for without any such theory. To find the simpler explanation, we have to ask how a particular part of the body is able to obtain a better blood-supply at need. The answer is twofold. There is *a local chemical action* independent of nerves. A nerveless limb will show hyperæmia when a mustard plaster is applied. A

* Head denies this, believing that there is a different and more primitive sensory apparatus, the protopathic, detecting extremes of heat and cold, and a more recently acquired sensory apparatus, the epicritic, detecting the smaller ranges. He bases his opinion principally on the examination of a small area in his own arm after division of the radial nerve: in this area epicritic sense was intact, but protopathic sense was lost. He also states that the viscera possess only protopathic sense: it is, however, probable that the stomach and colon have no temperature sense at all.

limb all but amputated—left connected with the body only by its main artery and vein—will show active hyperæmia if its blood-supply has been stopped for a minute and then released. The chemical substances liberated in starved, fatigued, or damaged tissues exert a local action on the small arteries supplying them, causing them to dilate. But there is also *a vasomotor reflex*, whereby a message is sent to the spinal cord and vasomotor centre in the medulla asking for more blood, and in consequence vasodilator impulses are sent to that part, and vasoconstrictor impulses to the rest of the body. Normally, these occurrences are the inevitable result of every insult or injury, of every invasion by a few bacteria, and we know nothing of them in consciousness. But when the nerves of the part are cut, the vasomotor reflex fails, and the local hyperæmia takes place too late to check the mischief.

One may illustrate the circumstances by the analogy of a guarded frontier. An armed raid is made by an enemy; the nearest garrison is too weak to repel it, and telegraphs to the base to urge a hasty concentration of troops. The message goes astray because the wire has been cut. The garrison must make what resistance they can with the aid of local volunteers and small levies summoned by runners. The analogy fails in this particular, that the bacterial invaders of the human frame will not remain constant in numbers till the belated defending forces are at last mustered against them, but will multiply a thousand-fold in the interval and do

irreparable damage. This is the pathology of "trophic lesions."

We pass from the effects of total nerve section to those of an incomplete division. If less than one-third of the fibres are cut, there may be no symptoms at all except perhaps pain. In general the sensory disturbance is greater than the motor, except in such a nerve as the musculospiral, even complete section of which may cause no anæsthesia.* Epicritic sense is more affected than protopathic. If any muscular weakness is present, a very characteristic electrical reaction may be obtained, the faradic response being lost, but the galvanic response being brisk, not sluggish, and K.C.C. greater than A.C.C. It will be remembered that with complete division, the galvanic response is sluggish, and A.C.C. is greater than K.C.C.† Pain and mottling of the skin are often more evident with partial than with complete divisions of the nerve.

REGENERATION.

Much discussion and research have been devoted in the past decade to clearing up the problem as to how the nerve fibre is reproduced when it has been cut off from its nerve cell and has degenerated in consequence. We know that the fibres peripheral to the section degenerate; we also know that if the cut ends are brought together, whether at once

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* It is often forgotten that the radial nerve is joined in the forearm by branches of the musculocutaneous.

† I do not explain these terms, because only an expert would undertake the investigation of the electrical reactions.

(primary suture) or many months later (secondary suture), medullated nerve will in time be reproduced and the function restored. There are two schools of interpretation. The one holds that the central cut end buds out new fibres which find their way down the old track to their old destinations. This is the theory of central regeneration. The other school contends that the severed piece of nerve, after degenerating, eventually recovers itself, and the continuity of its fibres is restored, though admittedly very few of them, if any, acquire a medullary sheath. It only needs, according to this school, that the nerve thus regenerated should be put into continuity with its old stump for its function to return and the medullary sheath to develop. This is the theory of peripheral regeneration.

The arguments in favour of the latter theory were as follows :—

(*a*). A nerve is cut across, and the cut ends are kept apart. After some months, it is said, long beaded fibres may be demonstrated by suitable staining methods, running continuously the whole length of the nerve. They are not, in ordinary, surrounded by a medullary sheath.

It is objected to this that more reliable staining methods show only the discontinuous fibres which make up ordinary white fibrous tissue ; and that no nerve elements are present at all in the degenerated piece of nerve thus cut off from its trophic centre.

(*b*). It has been claimed repeatedly that if in man a nerve is divided and not sutured for many

months, the patient may have some degree of recovery of sensation in the anæsthetic area within a few days after the belated suturing. We know that if the nerve had been restored by primary suture, it would have been months before any recovery could have taken place. The deduction would be that the isolated segment of nerve had regenerated its continuity, and only needed to be put into communication with an efficient nerve to become efficient itself.

One might illustrate the two theories in this way. A telegraph wire near a town A has been cut, and the whole line from A to Z completely destroyed, leaving only the track of the broken poles. Villagers at B, C, D, etc., along the line effect a certain amount of rough repair, and finally restore a continuous wire from B to Z. After some months, when this has been done, a telegraph operator reunites the wire near A. Communication with Z is at once restored. This illustrates the theory of peripheral regeneration.

But let us vary the process, and suppose that the operator starts from A and unites a new wire to the cut end, and then works slowly through B, C, D, repairing as he goes, until finally he reaches Z. This would illustrate the theory of central regeneration. If it be true that communication can be restored within a few hours of the reunion of the wires, it is evident that peripheral regeneration must have taken place.

It is doubtful, however, whether the clinical observations of immediate return of sensation after

secondary suture are trustworthy. As we have seen already, there are many fallacies in testing sensation, and since these have been recognized there is no evidence that such immediate return of sensation has been proved to occur in any well-authenticated case. Patients are often over-sanguine as to the benefit of operations, and may deceive themselves. The irritation of the stump by the stitches may induce sensations referred to the surface. It is certain that in most cases improvement after secondary suture is not more but less rapid than after primary suture.

(*c*). Bethe and others have found that if a nerve is divided and not sutured, but a gap is left which prevents union, after a year or two a few medullated fibres may be seen in the degenerated peripheral segment, and feeble muscular contractions of the paralysed muscles may follow stimulation. He took this to indicate that peripheral regeneration had occurred. Langley and Anderson have, however, proved that these few medullated fibres are derived from some other nerve in the limb, which has grown down the old path, in obedience to the mysterious chemical attraction which is presumably the cause of central regeneration. Thus if the sciatic nerve was divided and the upper part cut away, any medullated fibres found in the tibial nerves will degenerate after section of the anterior crural or obturator. The observation thus becomes strong evidence in favour of the theory of central regeneration.

There is indeed abundant proof 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 μ 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, and indeed it is now almost universally accepted, whereas fifteen years ago it was losing favour.

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 gives 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.

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 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. Infinitely 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 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, or in Cargile membrane. There is some doubt as to whether the latter does any 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 nerve 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. To avoid this the hypoglossal is now utilized instead of the spinal acces-

sory. 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 somewhat damaged, and cannot take on more than ordinary work.* The method remains hopeful, however, for paralysis following other forms of nerve disease or injury.

REFERENCES.

A few recent papers of importance are :—

BALLANCE AND STEWART.—"The Healing of Nerves," London, 1901.

HEAD, SHERREN, AND RIVERS.—*Brain*, 1905, pp. 99, 116.

HARRISON, ROSS.—"Embryonic Transplantation and Development of the Nervous System," *Anatom. Record*, Balt., 1908, ii, No. 9. "Observations on the Living Developing Nerve Fibre," *Amer. Jour. of Anatomy*, 1907, vii.

KILVINGTON AND OSBORNE.—*Jour. of Physiol.*, 1909, vol. xxxviii, pp. 268, 276.

LANGLEY AND ANDERSON.—*Jour. of Physiol.*, vol. xxxi, 1904, pp. 365, 418.

MOTT AND HALLIBURTON.—*Proc. Roy. Soc. B.*, 1906, lxxviii, p. 259.

MOTT.—"Present Position of the Neurone Doctrine." Pres. Address, Pathological Section, Med. Chir. Soc., London, 1909.

SHERREN.—"Injuries of Nerves, and their Treatment," London, 1908.

BETHE.—"Allgemeine Anatomie und Physiologie des Nervensystems," Leipsig, 1903.

* See Murray and Warrington, *Lancet*, 1910, i, p. 912.

CHAPTER XIII.

THE SURGICAL PHYSIOLOGY OF THE SPINAL CORD.

The effects of division of the posterior nerve roots—The diagnosis and localization of tumours of the spinal cord—The exact diagnosis of injuries of the spinal cord.

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.

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 recently 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.

THE DIAGNOSIS AND LOCALIZATION OF TUMOURS OF THE SPINAL CORD.

Tumours of the spinal cord do not occur so commonly as tumours of the brain, but the results of surgical removal are a good deal better. It becomes important, therefore, to know how to make the diagnosis.

Before entering upon this subject, we must remind ourselves of the functions of the great paths or tracts running up or down the spinal cord.

DESCENDING TRACTS.—The *pyramidal tracts* convey motor impulses from the cortex, and particularly those acquired movements which call for skill and finesse. They also inhibit muscular tone. The *rubrospinal tract* (Monakow's bundle) controls stock movements such as standing, sitting, and walking. This tract starts in the red nucleus in the isthmus, and it is largely by its means that a man whose pyramidals have been destroyed in the brain may still be able to get about. It would appear, also,

that this tract carries down impulses that inhibit any excess of muscular tone. The *vestibulospinal* and other tracts pass down in the antero-lateral columns, from the region of the pons and medulla. They are important paths for motor impulses, at any rate in animals; in monkeys a section of these tracts produces more paralysis than one involving the crossed pyramidal. They appear to convey impulses *increasing* muscular tone, so that when the pyramidal fibres are damaged, as by a hæmorrhage in the internal capsule, muscular tone is increased and a spastic hemiplegia results. There are, however, other descending paths open to this class of impulses, some of them crossing in the cord.

ASCENDING TRACTS.—The *dorsal cerebellar tract* passes from the cells of Clarke's column of the same side to the cerebellum. It conveys sensations derived from muscles, joints, and tendons to the cerebellum, and so keeps it informed of the position of every joint and the state of contraction of every muscle.

The *ventral cerebellar tract of Gowers* is composite in nature. Most of the fibres are crossed. Some pass to the cerebellum, others to the mid-brain, and the important *spinothalamic tract* conveys sensations of heat, cold, and pain, and probably also tactile sense, to the brain.

The *posterior columns* (of Goll and Burdach) are also uncrossed in the spinal cord, and convey tactile sense, muscular sense, joint sense, and so-called "tactile discrimination," by which we determine whether two compass points are single or double;

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 sense cross, usually about six segments above their point of entry, and there is a cell-station in the grey matter. 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 two routes.

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.

(ii). *The pyramidal, rubrospinal, and vestibulospinal tracts* on the left side, causing paralysis of the left leg. Inasmuch as the pyramidal and rubrospinal tracts are involved, muscular tone will be

greatly increased; the impulses leading to this increase perhaps descend on the other side of the cord. 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.

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.

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 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 textbooks 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

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	Radial half of hand	
VIII, C. ..	Flexors of wrist; hand muscles	Ulnar half of hand	
I, D. ..	Hand muscles	(= that of ulnar nerve.) Ulnar border of forearm, one and a half fingers	Iris (pupillo-dilator fibres)
II, D. ..	Intercostals	Inner border of arm ..	Heart; parietal pleura.
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

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 first dorsal gives off sympathetic branches dilating the pupil.

The anatomy of the lumbo-sacral 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 Lasègne'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 antero-lateral 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 a 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.

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, and particularly in 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 Deiter's nucleus, because transection of the upper pons or mesencephalon does not cause spinal shock.

A total transection of the cord in man, not in animals, affects profoundly the functions of the segments below the injury, and either from the first or after the lapse of a little time they lose their reflex functions, the bladder and rectum and their sphincters become paralysed, and the effect is much the same as it would have been if the isolated portion of the cord had been removed *in toto*. In animals, the reflex functions persist.

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. In either case it is very seldom that any useful purpose will be served by operating, unless the injury involves the cervical region or the cauda equina.

When the cord is involved, but has not suffered a functional transection, the paralysis will probably be spastic in nature, and operation is more hopeful because there may be something exercising injurious pressure which can be removed.

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 (unless we accept the evidence of the famous Stewart-Harte case!) 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.

REFERENCES.

FORSTER.—*Zeitschrift f. orthopäd Chir.*, 1908, Bd. xxii, p. 203.

HEAD AND THOMPSON.—" The Grouping of Afferent Impulses in the Spinal Cord," *Brain*, 1906, p. 537.

A. RENDLE SHORT.—*Proc. Royal Soc. Medicine*, Surgical Section, July, 1911.

SHERRINGTON.—" Integrative Action of the Nervous System."

CHAPTER XIV.

CEREBRAL LOCALIZATION.

The causation and significance of optic neuritis—Localization in the cerebellum—Tumours in the cerebello-pontine angle. Localization of sensation in the cerebral cortex—Functions of the frontal cortex—Spasticity—Apraxia—Aphasia—Misleading localizing signs of cerebral tumour—The cerebrospinal fluid.

IT will be necessary here to assume that the reader has an ordinary acquaintance with the structure and functions of the brain. We shall confine ourselves to a brief reference to the most important advances of the past decade in providing evidence for the localization of tumours, abscesses, and traumatic lesions, and therefore for their successful treatment by operation.

OPTIC NEURITIS.

It has long been in doubt why optic neuritis should develop in cases of cerebral tumour. It has been attributed to the effects of chronic meningitis, and to over-filling of the third ventricle, with consequent pressure on the underlying optic chiasma. It is now definitely established by the experiments of Cushing and Bordley, and confirmed by clinical experience, that it is a pressure effect. The growth of the neoplasm causes a great and continued rise of intracranial pressure; this tends to dam back the lymph flow returning in the sheath of the optic

nerve. The usual consequence of lymphatic obstruction is produced, namely, œdematous swelling of the area drained. So the optic cup fills up, the disc is obscured by transudate, and the vessels are buried from view in the œdema fluid. All this may be exactly reproduced by intracranial pressure in dogs, and when the pressure is removed, restitution to normal takes place.

Several methods of raising the intracranial pressure were employed, the best results being obtained by the insertion of sponge-tent material inside the skull. Swelling and œdema of the disc, tortuosity of the veins, and over-distention of the lymph-sheath around the optic nerve were all marked. Relief of the pressure rapidly cured them.

Although we use the conventional term " neuritis," the histological changes are not those of inflammation. For instance, there is no arterial hyperæmia, and the principal infiltration is with cells of connective tissue origin, not leucocytes.

Further, it has been stated by many observers, and recently defended, with all his great authority and experience, by Sir Victor Horsley, that the degree of the neuritis in the two eyes is a most reliable guide as to the side of the tumour. It is not so much the amount of swelling that is to be taken into account as the age and extent of the changes. These nearly always commence at the upper nasal quadrant of the disc. Thus, optic neuritis best marked in the right eye is of great value in pointing to a right-sided tumour. The further forward the tumour, the more constant does this rule become.

It is well known that even if a cerebral tumour cannot be localized, palliative trephining should be performed to relieve headache and save the sight. If this is undertaken early, the optic neuritis passes off. As the tentorium transmits pressure badly, the trephining should be in the temporal region for supratentorial tumours, and in the occipital region for cerebellar tumours.

Another valuable observation which we owe to Cushing is that raised intracranial pressure, particularly by cerebral tumour, induces a considerable limitation of the field of vision for blue; indeed, there may be actual blue-blindness.

THE CEREBELLUM.

We have been in urgent need of some improvement in our means of localizing tumours and abscesses in the cerebellum. During the past ten years, at the Bristol Royal Infirmary there have been eight cases of temporo-sphenoidal abscess, all of which have been successfully diagnosed, and ten cases of cerebellar abscess, of which only three were correctly located; in three of these ten cases the cerebrum was explored in vain, and in two the lateral sinus was thought to be the cause of the symptoms. It remains to be seen how far the fresh light recently thrown on the subject and herein set forth will help us to obtain materially better results.

Sir Victor Horsley and R. H. Clarke have recently revised our knowledge of the functions and relationships of the cerebellum by an ingenious method. Reconstructions of a monkey's head have been made

by cutting frozen sections and then piecing them together again; by this means it was possible to build a frame of metal to fit about the head of a living monkey, carrying an insulated needle which could be thrust, through a small trephine hole, into any desired portion of the cerebellum, its cortex, or its deep nuclei (roof nuclei), the exact position of the point of the needle having been determined by a study of the head reconstructed from the frozen sections. By this means various parts could be stimulated electrically without doing any but the slightest damage to the overlying structures; moreover, by passing in a strong current and using a double needle shielded nearly to the points, small electrolytic lesions either of the cortex or of the roof nucleus could be made, and the resulting degenerations studied by suitable staining some weeks afterwards.

The general result was to prove that the cortex cerebelli is a receiving platform, and that its axons merely pass to the roof nuclei, from which the efferent tracts start. Stimulation of the cerebellar cortex by ordinary currents produces no obvious response; stimulation of the roof nuclei causes movements of the eyes and sometimes of the limbs. We see here the reason why laterally situated tumours or abscesses lie so quiet.

The classic signs of a lesion of the cerebellum, determined both by physiologists and by clinicians, are the following: — (1) Ataxia; (2) Atonia; (3) Asthenia; (4) Tremor: these all affect the same side as the lesion; (5). Nystagmus; (6) Vertigo.

1. *Ataxia.*—This, one of the most constant signs, is easily detected if the patient is able to walk. When he is in bed, it may be brought out by making him try to pronate and supinate rapidly for a minute or two ; or to make and unmake a fist quickly, over and over again. This sign is the more convincing if it is unilateral.

2. *Atonia* is very variable ; the knee-jerks may be absent, normal, or excessive, and may change day by day.

Thiele and others have proved that the great increase of tone noticed in man or animals after lesions involving the pyramidal and other long descending tracts depends on the integrity of Deiter's nucleus. This lies just at the junction of the pons and medulla, beneath the outer part of the floor of the fourth ventricle, and therefore in close relation to the cerebellum. If it is destroyed, or if it is cut off from influencing the spinal cord by a complete transverse division below Deiter's nucleus, the spasticity and increased reflexes which ordinarily follow lesions of the motor paths will fail to develop.

Some cerebellar abscesses and tumours press on the pyramids (above their decussation) but not on Deiter's nucleus. These cause increase of tone on the opposite side. Others destroy Deiter's nucleus, and cause loss of tone on the same side. Others do not involve either, and tone may be normal, or a little increased on the same side as the lesion.

3. *Asthenia* may be evidenced by weakening of the grip, tendency to fall, or drooping of the head on the affected side. It is not very constant.

4. *Tremor* is only occasionally in evidence.

5. *Nystagmus.*—These curious jerkings of the eyes are of considerable importance in the diagnosis of cerebellar affections, because, although seen in such conditions as disseminated sclerosis, they are very unusual with localized intracranial tumours. Unfortunately they are not constantly present even when the lesion is in the cerebellum, and, on the other hand, are usually to be observed in patients with disease of the labyrinth (vestibule and semicircular canals). Seeing that most cases of cerebellar abscess follow otitis media, it has been very difficult to be certain, in the past, whether any nystagmus in a patient with a suppurating ear was due to the labyrinth, or the cerebellum, or both.

Bárány, of Vienna, has shown that it is possible to induce nystagmus in a normal person by stimulating the labyrinth. This may be done either by rotating the patient, or by allowing hot or cold (not tepid) water to trickle in as far as the membrana tympani. Hot water in the right ear causes a nystagmus in which the eyes slowly turn to the left and are corrected by rapid jerkings to the right; with cold water the rapid jerkings would be to the left.

If a patient with a suppurating ear has nystagmus, and it is desired to know whether this is due to affection of the labyrinth or of the cerebellum, hot or cold water should be injected to see if the nystagmus can be reversed in direction. If it can, the labyrinth cannot be at fault; it must be the cerebellum.

Again, a patient with severe vertigo following on

otitis media may be suffering from labyrinthitis or from cerebellar abscess. If injection causes no nystagmus, the labyrinth is destroyed.

TUMOURS IN THE CEREBELLO-PONTINE ANGLE.

This is a very common location for cerebellar tumours, and a comparatively favourable one for surgery, seeing that in many instances the growth is simple, and can be enucleated without recurrence. Allen Starr finds in the literature sixty-nine cases cured by removal. In many of these there was restoration to good, in some to perfect, health. Diagnosis, therefore, becomes peculiarly important.

In addition to the signs mentioned above, certain nerve-root symptoms may develop, and the pons may be pressed on. Mental trouble is quite unusual.

We may classify the evidence as follows :—

1. *General*: headache, vomiting, optic neuritis, slow pulse, blue-blindness, perhaps convulsions.

2. *Cerebellar signs*: staggering, vertigo, ataxia, weakness, tremor, and perhaps absent knee-jerk; these may be unilateral, on the same side as the growth. Nystagmus.

3. *Nerve-root symptoms* affecting the same side: pressure on the fifth, with corneal anæsthesia and loss of reflex, and weakness of jaw muscles; pressure on the sixth, with internal strabismus; pressure on the seventh, with facial weakness; pressure on the eighth, with tinnitus, loss of perception for upper notes (tested by Galton's whistle), or absolute deafness; pressure on the ninth, tenth, and eleventh,

with dysphagia, laryngeal palsy, cardiac attacks, etc.; pressure on the twelfth, with deviation of the protruded tongue. Of these, the facial and auditory nerves are most often affected, there being complete unilateral deafness in most of the cases. In cerebellar tumours these two nerves may be interfered with, but not to any considerable degree.

4. *Pressure on the pons*, causing crossed hemiplegic weakness, with exaggerated reflexes and extensor response. The cases may live for years, but there is a liability to sudden death by crowding of the cerebellum down through the foramen magnum.

LOCALIZATION OF SENSATION IN THE CEREBRAL CORTEX.

HEARING.—Although it is certain that monkeys which have suffered bilateral removal of the temporal cortex give every 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.

At any rate, there is a fair amount of evidence, both anatomical and clinical, to locate this function in the temporal region, and none to locate it elsewhere. The most convincing observation on record was made by Cushing, who stimulated the exposed temporal cortex in a conscious man, and the patient said that he noticed a buzzing noise.

VISION.—There is abundant evidence that visual sensations are received on the mesial surfaces of the occipital lobes, just above and just below the calcarine fissure. Histologically, the area is mapped out by the white line of Gennari; it barely encroaches posteriorly on the convexity of the hemisphere.

The left half of each retina is represented in the left cerebral cortex, and the right half of each retina in the right cortex. The fovea centralis of each eye has a bilateral representation. The upper half of each retina is projected above the calcarine fissure; the lower half of each retina below the fissure. Therefore a tumour of the left cortex above the calcarine fissure would render the upper left quadrant of each eye psychically blind, and the patient would be unable to see objects downwards and to his right.

A smaller lesion, however, does not produce a smaller patch of blindness; it merely reduces the visual acuity over the whole of the corresponding quadrant.

CUTANEOUS SENSATION.—It is universally agreed that the main receiving platform for cutaneous sensation is situated in the postcentral (ascending parietal) gyrus, just behind the fissure of Rolando, and that the general arrangement is the same as that of the motor centres; thus, the sensory centre for the leg is nearest the vertex, opposite the origin of the pyramidal fibres for the leg; next come the arm centres, and lowest of all those for the face and head.

The localization in the limbic lobe once advocated by Schäfer and others following him, has now been given up, even by its author. Doubt still remains,

however, whether the precentral or motor cortex takes any share in appreciating cutaneous sensation. If so, it is quite secondary to the part played by the postcentral convolution.

It is very difficult to be sure to what extent animals feel after the removal of small parts of either the postcentral or precentral convolutions, and very diverse views have been expressed; it is quite certain that a small lesion does not induce complete anæsthesia. It is probably wiser to put faith principally in the human evidence on such a subject. It is abundantly proved that lesions involving the ascending parietal convolution almost always cause a certain degree of interference with sensation, never amounting to a complete hemianæsthesia, which, indeed, occurs only in hysteria, or very transitorily after an apoplectic stroke. Bergmark quotes thirty-three cases of lesions of this gyrus with sensory symptoms but no paralysis.

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.

It is more difficult to be certain whether the ascending frontal or motor convolution has also any sensory function; if so, it is less obvious than in the case of the postcentral convolution. Naturally occurring lesions limited to the front of the fissure of Rolando, and carefully studied before and after death, are rare, and the evidence is conflicting; some showed paralysis but no sensory loss, whereas others had both motor and sensory impairment. Many years ago, before it was realized that the convolutions in front of and behind the fissure of Rolando differed in function, Ransom 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. Recently Sir Victor Horsley has published an account of the only case in which he has 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 were 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 convolution, the sensory symptoms, in his experience, would have been much more marked. The athetosis was cured.

Interference with sensation is of course no proof that a cerebral tumour is in the cortex; it may be found with a lesion of the optic thalamus, internal capsule, isthmus, pons, or medulla. In twenty-six cases of hemiplegia due to some trouble in the internal capsule, Bergmark found evidence of sensory impairment in all who were intelligent enough to be tested with accuracy by modern methods, although there was never complete hemianæsthesia to all forms of stimuli.

The relations of the cerebral cortex, optic thalamus, and mid-brain to various forms of sensation have recently been made the subject of an interesting research by Head and Gordon Holmes. The special character of interference with sensation in lesions of the cortex in the Rolandic area is the *untrustworthiness* of the response. The stimulus will be felt at one time but not at another; the sensation may persist after the stimulus is withdrawn, hallucinations may be present, and local fatigue, affecting sensation in the paralysed limb but not in the other, is easily induced. All forms of sensation, heat, cold, tactile, localization, stereognosis, and weight sense, may be diminished, muscular sense (sense of passive movements and of posture) being particularly liable to reduction.

It is the special function of the optic thalamus, or rather of its mesial nuclei, to impart emotional tone, pain or pleasure, to the sensation. These are thalamic, not cortical, in their appeal to consciousness. Fibres from all parts of the cortex converge on the lateral nucleus of the optic thalamus, and tend to control and inhibit excessive pain or pleasure arising from the impulses received from the spinal cord. When this lateral nucleus is destroyed, and only the mesial part of the thalamus left intact, stimuli are much more painful or (in the case, for instance, of stroking or of warmth) more pleasurable than on the normal side. Sometimes music produces a remarkable emotional effect in the affected limbs, especially if it is solemn or majestic.

There are of course other signs of involvement of the optic thalamus, such as hemianæsthesia, athetosis, and transient hemiplegia.

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.

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.

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. Thiele has demonstrated in animals that tone is *increased* by impulses from Deiters' nucleus in the medulla, and *inhibited* by impulses generated in the optic thalamus and conducted by the rubrospinal tract (Monakow's bundle). It is this tract which subserves the stock movements such as standing and walking, which can often be carried out after complete destruction of the pyramidal tract. 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. Pressure on the isthmus, pons, medulla, or spinal

* 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.

cord will probably damage the rubrospinal tract as well as the adjacent pyramidal tracts, and so set up spasticity, unless the whole cord is functionally divided, in which case impulses descending from Deiters' nucleus (possibly in the vestibulospinal tract), are also cut off, and a flaccid paralysis results.

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.

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 the 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 are apraxia of the left side and 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 as well, 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 (i) Aphasia which persists; (ii) Recurring convulsions; (iii) Flaccidity; (iv) 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.

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

The majority even of the nineteen cases allowed by these writers they consider to be inconclusive for various reasons.

Two cases of Burckhart's are of sufficient surgical interest to be worth quoting. In the first, he removed 5 grams 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.

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 the 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.

To sum up, we may express current opinion by accepting the existence of a large diffuse centre in the left temporo-parietal 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 ((?) of 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 temporo-sphenoidal abscess, for instance, are usually unable to name correctly objects shown them. Moreover, we receive encouragement 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.

MISLEADING LOCALIZING SIGNS OF INTRACRANIAL TUMOUR.

It is very disappointing when definite signs usually regarded as of importance in localization give colour to a diagnosis as to the position of a cerebral tumour, but on the operation table nothing is found in that region. It is more than disappointing, because unsuccessful attempts to find the tumour are more fatal than actual removals. Some study therefore of the physiology of the production of misleading signs may be useful.

The principal traps are furnished by the following:

1. CRANIAL NERVE PALSIES.—Paralysis of one or both sixth cranial nerves is quite common, and by

no means proves that the nerve itself or its nucleus is involved in the lesion. It has been accounted for by stretching, due to a supposed backward displacement of the whole brain late in the development of a growth; the abducent nerves run straight forwards and are slender, so the first sign of the displacement is a convergent squint.

Other cranial nerves, including the third, fifth, seventh, and eighth, are occasionally affected by displacements of the brain or by pressure.

2. Localized or General Convulsions.—Mistakes are particularly apt to arise if the fit starts in some definite area, follows a slow and orderly march to other areas, and perhaps affects only one side, consciousness being lost late if at all (Jacksonian epilepsy). It must, however, be remembered that all this may occur without any obvious cortical lesion; indeed, *the commonest cause of a localized convulsion is ordinary idiopathic epilepsy.*

Again, localized or general convulsions may give a wrong impression when arising late in the course of an intracranial tumour or abscess, especially if it presses on the ventricular system of the brain and dams back the cerebrospinal fluid, causing hydrocephalus. The accumulation of fluid in one or both lateral ventricles stretches the overlying cortex, and may give rise to fits, sometimes of a Jacksonian type.

3. Bilateral Spastic Paresis.—In many cases a hint is given of the true nature of these seizures by the presence of a slight degree of bilateral spastic paresis, with clumsiness of movement, exaggerated

reflexes, extensor plantar response, and a little rigidity.

Of course, if this should chance to be associated with paralysis of a cranial nerve, such as the sixth, the temptation to diagnose a lesion of the pons would be very great. Fortunately, this would not be of much surgical importance, as the pons is not an accessible structure. Pontine tumours are often unilateral, and optic neuritis is usually absent; whereas in the class of cases we are now considering, optic neuritis is marked and old-standing, and there is a long history of headache, vomiting, or other signs, previous to the development of spasticity or cranial nerve palsy.

In other cases, misleading localizing signs may arise from patches of secondary thrombosis, spreading œdema, or meningitis; but none of these is common.

The suspicious feature about all the signs here mentioned is their late development. Localizing symptoms appearing when headache, vomiting, optic neuritis, or other evidences have been present for months or years are little to be trusted. Early localizing signs, on the other hand, are trustworthy in the main.

A few words may be said about the significance of ataxia. This is of course evidence of a lesion of the cerebellum, but it may be seen in other conditions also. Putting aside ataxia due to affections of the labyrinth, Friedreich's ataxia, and other general nervous diseases, it may also be caused by a tumour in the neighbourhood of the red nucleus in the isthmus, or in the pons.

THE CEREBROSPINAL FLUID.

This fluid is clear, watery, and of low specific gravity; it contains almost no albumin, but some sugar. Until recently this reducing substance was thought to be a pyrocatechin body. It contains no cells in health, nor does it contain the antitoxins, opsonins, or alexins which are present in plasma, lymph, and most serous fluids. This explains the great liability to septic meningitis after injuries to or operations on the central nervous system. As urotropin is excreted into the cerebrospinal fluid when given by mouth, it may usefully be administered to prevent septic complications such as the above, or following on suppurative otitis media. Some success is already claimed for this procedure.

The fluid is secreted by the choroid plexus into the lateral and third ventricles; it passes by the Sylvian aqueduct into the fourth ventricle, escapes by the foramina in the roof into the subarachnoid space, and is absorbed, partly by the aid of the Pacchionian bodies, into the superior longitudinal sinus and other veins. Hydrocephalus is produced by blocking of the foramina in the roof of the fourth ventricle. If an exit is provided, large quantities of cerebrospinal fluid may be lost daily.

Lumbar puncture is a very valuable aid to diagnosis in various forms of meningitis, parasyphilitic affections, etc., and the fluid may be blood-stained after cerebral hæmorrhage or injury. It is also valuable in treatment as a means of reducing intraspinal and intracranial pressure, particularly if the trouble lies below the tentorium.

REFERENCES.

CUSHING AND BORDLEY.—"Observations on Experimentally Induced Choked Disc." *Bulletin Johns Hopkins Hospital*, 1909, xx, p. 95.

HORSLEY.—"Optic Neuritis." *British Medical Journal*, 1910, i, p. 553.

HORSLEY AND CLARKE.—"The Structure and Functions of the Cerebellum." *Brain*, 1908, xxxi, p. 45.

THIELE.—"The Optic Thalamus and Deiters' Nucleus." *Journ. of Physiology*, 1905, xxxii, p. 358.

ALLEN STARR.—"Tumours of the Acoustic Nerve." *Amer. Journ. of Medical Sciences*, 1910, cxxxix, p. 551.

BERGMARK.—"Cerebral Monoplegia." *Brain*, 1909, xxxii, p. 342.

CUSHING.—"A Note on Faradic Stimulation of the Post-central Gyrus in Conscious Patients." *Brain*, 1909, xxxii, p. 44.

WILSON.—"A Contribution to the Study of Apraxia." *Brain*, 1908, xxxi, p. 164.

COLLIER.—"Recent Work on Aphasia." *Brain*, 1908, xxxi, p. 523.

COLLIER.—"The False Localizing Signs of Intracranial Tumour." *Brain*, 1904, xxvii, p. 490.

HEAD AND G. HOLMES.—"Researches as to Sensory Disturbances from Cerebral Lesions." *Lancet*, 1912, i, pp. 1, 79, 144.

CHAPTER XIV.

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 very 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 on 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 in 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, *British Medical Journal*, 1910, i, p. 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 aminoacids. 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., aged 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, six 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.
,, 3–4 ..	32	9·3	9·53	7·70
,, 4–5 ..	31	0·5	9·02	

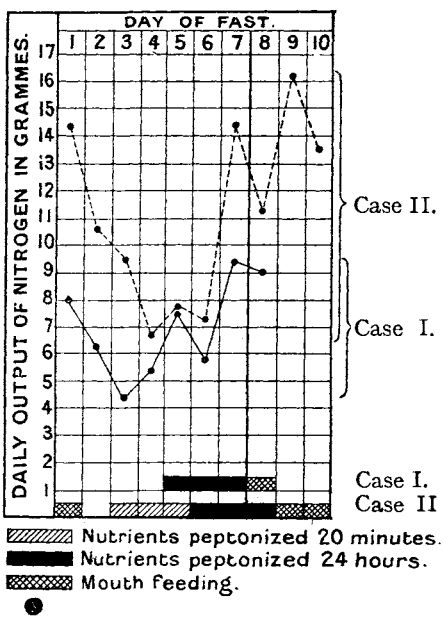
* Glucose not well retained.

It will be observed that instead of showing the usual steady fall, the nitrogen output is increased during the three days of feeding on aminoacids.

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 1	,,	,,	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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ADDENDUM.

THE ACIDITY OF GASTRIC JUICE.—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 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.

THE NERVOUS CONTROL OF MUSCULAR TONE.—A very interesting research has been published by Weed, affording a different explanation from that given in the text with reference to the nervous control of muscular tone. This has an important bearing on the explanation not only of the rigidity which is seen in the body and limbs of cats after section of the mesencephalon (decerebrate rigidity), but also of that which accompanies hemiplegia or monoplegia in man, and the occurrence of atonia in cerebellar lesions.

According to Weed's researches on cats, the centre which is responsible for the exaggeration of muscular tone is the red nucleus, and it does so in response to sensory stimuli reaching it from the posterior nerve roots by way of the ventral cerebellar tract, cerebellum, and superior cerebellar peduncle. Section

of any of the following will abolish decerebrate rigidity: the posterior nerve roots, antero-lateral region of the cord, superior cerebellar peduncle, or any part of the brain-stem below the red nucleus. Ablation of the cerebellum or of the cerebellar cortex also abolishes tone. Cutting the inferior cerebellar peduncle or the columns of Goll and Burdach do not influence it. It will be remembered that the ventral cerebellar tract enters by the superior peduncle.

On the other hand, the inhibitory path cut off when the mesencephalon is divided is supposed to be the fronto-pontic tract and middle cerebellar peduncle. Stimulation of either of these inhibits any excess of muscular tone.

The exact location of the tone centre probably has an important bearing upon the pathology of surgical shock.

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