A British Medical Association Lecture

ON

THE PRINCIPLES OF INTERNAL SECRETION.*

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I TAKE it we all believe, though perhaps to a varying extent, that the functions of the body can be controlled by chemical means. Otherwise we could hardly justify to ourselves our daily administration of drugs. And justification can be found in the fact that the body regulates itself by drugs which it specially prepares.

To a certain extent every product of cell activity has an effect on every other tissue. It is of interest to note that the more widely tissues differ, the more they can make use of the end products of the other's metabolism. Thus while animals ultimately depend on vegetables for their food, the CO_2 excreted by animals is actually a food for plants, and their urea, once it has undergone ammoniacal decomposition, acts as an important source of nitrogen to them. For animals such substances are merely stimulant in the sense that they contribute to the process of their own removal. Thus CO_2 is a respiratory stimulant and in small doses actually improves the contractions of the heart. By this action on respiration and circulation its excretion is facilitated. Similarly urea is a diuretic, which is an obvious advantage. But neither CO_2 nor urea can act as a food to animals, or quicken their vital processes in any other way. It is true that an intermediate product of metabolism, creatin, which is produced by muscles, is a stimulant to gastric secretion and increases the rate of growth. But it may be asserted in general terms that the more similar tissues are the less can the one make use of the other's end products of metabolism. They require a specially elaborated secretion to produce a beneficial action. Of such secretions the hormones produced by ductless and other glands are outstanding examples. Another thing which we can learn from comparing animal and vegetable processes is the powerful effect of even infinitesimal doses. In recent years we have found that, in addition to a proper ration of protein, carbohydrates, fats, and salts, animals require minute doses of vitamins. Such vitamins appear to be produced solely by vegetable tissues, though they may remain stored up in the tissues of animals that have consumed such vegetables. In the absence of such vitamins certain deficiency diseases develop, showing again the dependence of animal upon plant life. Vitamins are as characteristic of vegetable as are hormones of animal life, and chemically they are not greatly dissimilar, while both are intensely effective in minute doses. That the lack of either may produce somewhat similar effects can be seen on comparing (1) rickets (due to the absence of vitamin A) with osteomalacia; (2) the neuritis of beri-beri (due to the absence of vitamin B) with that of diabetes; and (3) scurvy (due to the absence of vitamin C), with the form of purpura due to acute adrenal deficiency. McCarrison's recent observation on the endocrine changes produced by vitamin defect are interesting in this connexion. He showed that while the adrenals and pituitary enlarged, the other endocrine glands showed more or less atrophy. Whether such enlargement is compensatory or not we cannot say as yet, but it illustrates, at any rate, the close relationship between hormones and vitamins.

Yet another *a priori* proposition I would commend to your notice is that response to chemical stimuli is only to be expected when we remember that before a nervous system developed it was to such stimuli alone that primitive animals could react. As Starling pointed out in enunciating his hormone theory, the development of a nervous system enabled much more rapid reactions to occur. We might express it by saying that a nervous system is to a multicellular organism what the telegraph is to an organized community. As I have elsewhere pointed out, the first and most essential purpose for which such rapid reactions would be required would be for self defence. In accordance with this the lowest level of the

nervous system, the sympathetic, is pre-eminently defensive in its action. But we should expect that the newer rapid method would remain associated with the older slower methods, so that as the chemical reactions became specialized in the endocrine glands, these glands interacted especially with the sympathetic nervous system. This association is particularly well seen in the case of the adrenals. In a former lecture¹ I pointed out that originally there were cells in the central nervous system which were the common ancestor of both the sympathetic ganglion and the adrenalin-secreting cell. As the sympathetic system develops in higher vertebrates the adrenalin-secreting cells become gradually restricted to the medulla of the adrenals. Thus the nervous element steadily acquires predominance over the chemical element in the partnership.

Another generalization we can make is that many of the endocrine glands are closely associated with the reproductive organs. The moment animal life passed from unicellular to multicellular forms it lost its personal physical immortality. When a protozoön multiplies by simple fission, as Milnes Marshall said, the parent disappears without having died, and the children appear without having been born. But in all multicellular organisms special cells are set apart for carrying on the race. Multicellular animals having appeared before a nervous system was developed, we should expect the reproductive glands to remain closely associated with the older chemical reactions now specialized in the endocrine glands. The endocrine glands, the reproductive organs, and the sympathetic nervous system therefore remain as a basic tripod, and it is not likely that a disturbance will occur for long in one limb of this tripod without affecting the other two. As this relationship is most clearly seen in the endocrine group of adrenal, thyroid, and pituitary, I will deal with these first.

ADRENALS.

While the medulla is an outgrowth of the sympathetic nervous system, the cortex is developed from the Wolffian body which also provides the interstitial cells of the reproductive glands. Conformably with their origin, disturbances of the medulla chiefly affect the sympathetic nervous system, and of the cortex the reproductive system. The influence of tumours of the adrenal cortex in producing premature sexual development is an example of the latter.

Stimulation of the sympathetic nervous system produces a whole series of effects all calculated to facilitate violent action in the direction of fight or flight. The pupil dilates to increase perception of light, the blood pressure rises to assist circulation, and the heart beats faster. The skin sweats to cool the body heated by exertion, and the blood sugar increases the better to feed the active muscles, even overflowing into the urine if it is not made use of. In some animals the hairs become erect to render them more formidable. Now an injection of adrenalin, which is a secretion purely of the medullary part of the gland, produces in every particular the same effect as the stimulation of the sympathetic. Their action is reciprocal, for the sympathetic stimulates the secretion of adrenalin, while adrenalin increases the sympathetic response. We have little evidence in disease of overaction of adrenalin, though it is possible that some conditions of raised blood pressure with glycosuria in later life are due to this, since they may be induced by overstrain and worry, which irritate the sympathetic, and adrenalin excess would raise both the pressure and the sugar of the blood. But we have a clear-cut example of adrenalin defect in Addison's disease, in which all the symptoms can be attributed to loss of sympathetic action. Failure of its inhibitory action on the stomach would tend to vomiting, and of its stimulating effect on the vaso-constrictor nerves to low blood pressure and a relaxed condition of the peripheral vessels which would lead to pigmentation. The asthenia is not only due to low blood pressure, for adrenalin has a tonic effect on striped muscle. Conformably with all this we find in Addison's disease a rise in sugar tolerance—the reverse of the condition exciting glycosuria. When the medulla of the adrenals is destroyed suddenly by haemorrhage instead of gradually by tuberculosis, an acute condition arises instead of the more chronic condition of Addison's disease. But the conditions are strictly comparable—purpura replacing pigmentation.

* Delivered to the Suffolk Branch.

It has generally happened that the fully developed form of a morbid condition has been recognized before the minor degrees. Thus ataxia was first regarded as a necessary part of tabes, and slighter non-progressive forms escaped diagnosis. Thus also myxoedema and cretinism were identified long before the minor forms of hypothyroidism. The same is true of hypo-adrenalism. Remembering the strain thrown on the sympathetic in responding to prolonged mental and physical conflict or to infection, it is only to be expected that adrenalin exhaustion might ensue. This has actually been proved in an acute infection such as diphtheria (Elliott and Tuckett), as well as in more chronic diseases. It has been suggested with every show of reason that adrenalin exhaustion enters into many war neuroses and other functional states characterized by lack of vascular tone, vasomotor instability, and myasthenia, especially when accompanied by a low blood pressure.

THYROID.

There is an equally close association between the thyroid gland, the reproductive organs, and the sympathetic. The thyroid tends to enlarge at puberty, marriage, and in pregnancy, while myxoedema is most apt to occur just after the climacteric. Amenorrhoea is common, even in the minor forms of hypothyroidism. The effect of sympathetic irritation in producing thyroid enlargement and Graves's disease is now recognized. Cushing showed that if in cats he sutured the phrenic nerve to the cervical sympathetic so that every respiration stimulated the latter, he could produce the symptoms of Graves's disease. The influence of distressing emotions in producing hyperthyroidism was well shown during the air raids on London. Epidemics of Graves's disease also followed the Kishineff massacres and the San Francisco earthquake. Again, if a distressing emotion has a matrimonial origin it is particularly likely to induce Graves's disease, for here each limb of the basic tripod is involved. The disease has been compared with a state of continuous fear, a description which tallies with its general appearance.

But not only does the sympathetic stimulate the thyroid; the thyroid secretion also lowers the threshold to sympathetic stimulation. Thus a vicious circle is established. In time the thyroid gland may become exhausted, and symptoms of myxoedema become combined with those of Graves's disease. This accounts for those remarkable cases of thyroid instability described by Rothschild and Leopold Levi, striking instances of which I have seen myself. The impending thyroid exhaustion shows itself in little spurts of over-secretion imposed upon a background of continuing myxoedema. It is a condition of irritable weakness, as seen in various other nervous disorders, particularly the occupation neuroses, and it calls for the cautious administration of small doses of thyroid extract to steady the fluctuating secretion. Like adrenalin, thyroid secretion mobilizes the blood sugar; in hyperthyroidism the sugar tolerance is lowered, and there may be glycosuria. As is well known, it is easy to produce glycosuria by over-dosage with thyroid extract.

Fully developed thyroid insufficiency, as expressed in myxoedema and cretinism, are too well known to detain us. We are chiefly indebted to Hertoghe for our knowledge of its minor degrees. He pointed out that the thyroid both governed the building up of the cells and regulated the destruction of the protein molecule and its elimination. Therefore with thyroid insufficiency there will be defective growth, which will be most noticeable in the young subject, while in the adult there will be accumulation of material which should be katabolized. He attributes to a minor degree of thyroid insufficiency such symptoms as relaxation of the articular ligaments, particularly in the knee, heel, ankle, and thoracic vertebrae, causing knock-knee, painful heel, flat-foot, and lordosis. Infiltration of tendons and fascia may produce rheumatoid pains. He attaches considerable importance to the loss of hair in the outer half of the eyebrow. Enuresis he believes to be frequently due to the same cause. Thyroid inadequacy diminishes the coagulability of the blood, which explains the tendency to haemorrhage. Infiltration of the nerve centres causes mental slowness, partial or entire loss of memory, and difficulty in expressing ideas. Sometimes there are hallucinations of sight and hearing. Headache, giddiness, and somnolence are not uncommon. The liability of myxoedematous subjects to develop atheroma

suggests the use of thyroid extract in premature arterial degeneration.

PITUITARY.

The pituitary body also shows the twofold association with the reproductive organs and the sympathetic nervous system. Like the adrenals, it has a double origin, a glandular portion growing up from the epithelium of the buccal cavity, partly surrounding an outgrowth from the central nervous system. In both cases it is the nervous part which produces a well-recognized secretion. The anterior glandular part of the pituitary appears to have an effect on body temperature, growth, the cutaneous tissues, and the reproductive organs. Removal or disease of this lobe leads to a subnormal temperature, and an injection of its extract then causes a febrile reaction, a point of diagnostic value. If the anterior lobe be removed in young animals, the development of both primary and secondary sexual characters is much interfered with, while that infantile gland, the thymus, remains large. In human beings over-secretion shows itself, as in acromegaly, by overgrowth of the skeleton and the skin, and hypertrichosis, while under-secretion leads to a smooth, hairless, plump condition of the skin, with amenorrhoea or impotence.

I am sure that minor degrees of hypopituitarism of this type are not uncommon. The condition of the skin and subcutaneous tissues recalls myxoedema, but the mental state remains active. The obesity is very marked. A curious point, to which I have not seen attention called, is the frequent occurrence of polycythaemia. I believe adiposis dolorosa is a related condition, and I recently saw an example of it in which a skiagram showed an enlargement of the pituitary fossa into which the anterior clinoid process dipped down.

The intermediate part of the gland, though closely adherent to the posterior, is derived from the anterior lobe. It influences carbohydrate metabolism. In excess its secretion lowers sugar tolerance, and may excite glycosuria; when it is in defect, giving even very large amounts of sugar will not cause glycosuria.

The secretion of the posterior lobe, pituitrin, is mainly a stimulant to plain muscle, and also to the secretion of milk. Its action on plain muscle is better seen in an emergency than under normal conditions. Thus it does not usually influence a normal blood pressure, but raises it when lowered by shock; it acts on a failing heart, but not on a normal one; it has little effect on the plain muscle of the bowel, except when it is paralysed as in post-operative conditions; it does not cause contractions of the uterus until labour has begun and inertia is present. The way it acts on diuresis is still a matter of controversy, but it is clear that disease of the posterior lobe is often the cause of diabetes insipidus. Stimulation of the sympathetic nerves to the gland may cause both glycosuria and polyuria. Probably hysterical polyuria is thus produced. But the reciprocal action of the gland on the sympathetic is not so clearly seen as in the adrenals and thyroid, unless the examples quoted above may be taken as instances. Like the thyroid it enlarges in pregnancy, producing a curious and characteristic effect on the facies. The glycosuria of pregnancy is no doubt due to its stimulating effect both on the thyroid and pituitary.

Some of the main functions of this group of endocrine glands may be expressed in tabular form thus:

	Sex.	Growth.	Vasomotor System.	Glycosuria.
Thyroid ...	+	+	Dilator	+
Adrenals—				
Cortex ...	+	+	0	0
Medulla...	0	0	Constrictor	+
Pituitary—				
Anterior ...	+	+	0	0
Intermediate ..	0	0	0	+
Posterior ...	Galactagogue.	0	Constrictor	0

It will be noted that the main functions of these glands are katabolic. They throw sugar into the blood stream for active consumption, they co-operate with the sympathetic

in defensive activities, they divert the stream of energy outwards, they are accelerators.

STOMACH, DUODENUM, AND PANCREAS.

I now turn to a group of glands whose main functions are anabolic. These co-operate with the vagus—that is, the parasympathetic rather than the sympathetic—they divert the stream of energy inwards, they are not spend-thrifts, but economizers. I refer to the endocrines of the stomach, duodenum, and pancreas, and also to the parathyroids. Gastric digestion is started by the appetite and the taste of food reflexly stimulating the vagus, but it is continued by a hormone in the pyloric glands, which spur the fundus glands on to renewed effort. Thus gastric secretion is continued after the hunger is appeased and the appetite satisfied. In its turn the acid gastric juice, entering the duodenum, acts on its mucosa to form *secretin*, which is the hormone for the secretion of pancreatic juice. But, as is well known, the pancreas forms an internal secretion as well—it is bipolar in its activity. This secretion promotes the assimilation of sugar, probably by linking it on to larger molecules both in the blood and in the tissues. Quantitative reductions in this secretion may give us all the stages between a slight lowering of the carbohydrate tolerance and a "total" diabetes. Co-operating with the parasympathetic as these glands do, they assist in its task, which Cannon has defined as the quiet building up of reserves against a time of strain and stress.

PARATHYROIDS.

The evidence is not quite so clear as to the parathyroids. Some have held that they are merely adjuvant to the thyroid, but at the present time they are generally regarded as antagonistic. The varying results of thyroidectomy in different animals can be explained according to whether the parathyroids were simultaneously removed or not. Severe nervous symptoms only occurred with their removal. MacCallum showed that the parathyroids in some way controlled the distribution of calcium in the body. When their secretion is deficient the tissues lose some of their calcium. As this calcium has a sedative action on nerve cells, this loss increases nervous excitability, which is particularly apt to express itself in tetany. Parathyroid extract has been found, both in animals and man, to be helpful in controlling tetany due to injury or removal of these glands. There are a number of other conditions in which tetany occurs, but it would appear probable that here, too, the symptom is due either to a deficiency of calcium salts or some impairment of parathyroid function, possibly of toxic origin.

OTHER ENDOCRINE GLANDS.

I need refer but briefly to the other endocrine glands. The interstitial cells of the reproductive glands no doubt form an internal secretion of great importance, particularly in the development of secondary sexual characters, but they have not been definitely isolated, and they appear to interact chiefly with the first group of ductless glands I described. The obesity which follows loss of such internal secretions is very likely due to their interaction with the thyroid and pituitary. A comparison of the results following ligature of the whole spermatic cord, with those of tying the vas deferens only, gives us the most definite idea of the action of such an internal secretion. In so far as the carotid and coccygeal glands have any action they would appear to be adjuvant to the adrenals. The thymus may be looked upon as mainly an infantile blood-forming organ. But overaction of the thyroid appears to cause hypertrophy of the thymus, particularly of its Hassell's corpuscles, which may possibly be of an antagonistic character. It is, at any rate, of interest to note that in exophthalmic goitre the thymus always hypertrophies. Its persistence in infantilism, and its disappearance with sexual maturity, points to a function which usually ends with childhood. The acquisition of the adult blood picture and the disappearance of the thymus are generally simultaneous. The enlargement of the thymus in status lymphaticus is usually only a part of a general adenoid enlargement. It may be regarded as part of an abnormally sensitive reaction to foreign proteins, such as is generally met with in those whose vagus response is increased. The extreme vulnerability of persons suffering from such a condition is shown in their liability to sudden death from

trivial causes. But this throws no light on any internal secretion formed by the gland, of which, indeed, there is no evidence.

The liver, as the most important metabolic workshop of the body, throws many substances into the blood stream, such as sugar from the stored glycogen, urea, unsaturated fats which it has prepared for combustion, antitoxins, and something which influences the coagulability of the blood, but none of these can be regarded as hormones in the sense here defined. The spleen, although the largest of the ductless glands, appears to form no internal secretion. Hence it is that diseases of the spleen have so few symptoms apart from the enlargement of the organ, unless of such a character as to set up splenic anaemia. And it would appear that not one but several diseases of the spleen are capable of producing this destructive change in the blood.

CLASSIFICATION OF ENDOCRINE GLANDS.

The endocrine glands would therefore appear to fall into two main groups: (1) the adrenals with other chromaffin cells, the pituitary, thyroid and interstitial cells of the reproductive glands; (2) the mucosa of certain parts of the alimentary tract, the pancreas, and the parathyroids. The first group interact chiefly with the sympathetic and are accelerators, the latter with the parasympathetic, and are retarders. The former display kinetic energy, the latter store potential energy.

GENERAL PRINCIPLES OF INTERNAL SECRETION.

To get a general conception of the principles of internal secretion it is necessary to start from the premise that the development of each individual recapitulates, briefly and with modifications, the history of the race. And it is helpful to remember that while life has been present on the earth for millions of years, man did not appear more than a comparatively few thousand years ago. Every time an individual repeats the history of the race he does it more easily as the result of practice. Thus it happens that the fetus in nine short months of pre-natal life recapitulates the history of millions of years, while his longer infantile life only repeats the history of a few thousand years. That even an adult may speedily revert to the instincts and habits of a cave man the war has abundantly shown. Later veneers of civilization are easily cast aside.

Now the most primitive forms of life multiplied by simple fission. The unfertilized ovum is the nearest approach to the primordial cell that we know. Like the primordial cell it starts to divide by simple fission, forming two polar bodies. Millions of years ago simple fission was found inadequate for a complex animal, yet every ovum starts on this course till it is abruptly brought up by the consequent exhaustion of its powers of growth. But when fertilization has remade its nuclear network a tremendous impetus is given to growth. When growth is expressed as a fractional increase of body weight it will be found that its curve continuously diminishes from fertilization onwards. In other words, the impetus thus derived gradually wears itself out. A new life may be compared to a projectile travelling with a constantly diminishing acceleration. But unlike an ordinary projectile it is supplied by intrinsic regulators, capable of increasing or diminishing its velocity. These regulators are the two groups of endocrine glands and their associated nervous mechanisms. In the first few years of life the original impetus is so enormous that a brake is needed—which seems to act through the thymus. By seven years of age this brake is needed no longer, and should it continue to be applied from any cause, infantile features persist. With the aid particularly of the thyroid and pituitary, active growth continues until puberty gives another twist to the mechanism from the active development of another set of glands—a new position of equilibrium has to be found. With adult years a part of the energy is diverted from growth of the individual to providing a supply for the next generation; and again the regulators have to provide a new adjustment. Another jolt—often a violent one—is given to the mechanism by the climacteric, and yet a new position of equilibrium has to be acquired. From this point on, the dying down of the initial velocity is marked; the accelerating thyroid seems to die down before the sedative parathyroid—calcium fixation goes on unchecked, therefore; the intercostal cartilages grow rigid, the chest

becomes emphysematous, greatly diminishing the bodily activities by restricting respiratory exchange, the arteries become calcareous, diminishing the blood flow to every part of the body, while childish and even infantile characters may reappear as the organism slows down for the terminus.

This may be considered the normal course of events. That everybody should ultimately only die from senile decay is the goal of medicine. But apart from violent death, the regulators may become worn out, with consequent great increase of friction to the mechanism. Invasion by bacteria and their toxins may prematurely exhaust the endocrine glands, or endogenous poisons may produce a similar effect; metabolism becomes balanced on a razor edge, the sport of every wind that blows. Nervous shocks and strains excite a reaction of the sympathetic nervous system and, through it, of its associated chain of endocrine glands, with consequent exhaustion of them. And these two sources of endocrine exhaustion may interact, so that a psychic conflict may be produced because the body cannot adjust itself to a difficult environment largely because of an endocrine deficiency. Thus the two newest methods in medicine, psychotherapy and endocrinology become not opposed, but different aspects of the same problem. Or a body may start out ill equipped with a supply of endocrines, so that its growth curve suffers a steep descent, as in that rare condition progeria, where senility comes on in childhood and the patient dies "an enfeebled old dotard of five." In dementia praecox we probably have a mixture of such causes at work—an atavistic reversion in bodily structure, as shown in the monkey-like hands; a multiple endocrine deficiency, with a consequent persistence of the infantile outlook, hence a total failure of adjustment to the conditions of adult life; the mind defensively withdraws itself from its environment, and hence undergoes rapid involution.

But you will forgive me if I do not go further into conditions of pluriglandular disease. Fascinating though the subject is, it is still in a speculative stage, and it is essential to keep clear ideas on the simpler and better known phases. Suffice it to say that I look upon diabetes as probably of pluriglandular origin initiated through the sympathetic, which stimulates into activity those endocrine glands which mobilize the blood sugar, while inhibiting the pancreas, the one which leads to its assimilation.² Hence the gravity of glycosuria in early life when the accelerator group of endocrines are already called into full play, compared with its comparative mildness in later life when their activity is becoming a thing of the past. Hence also, in all probability, the frequently sterilizing effect of diabetes.

ORGANOTHERAPY.

Before we can apply organotherapy rationally we must have some clear ideas as to the chemistry of the hormones that the endocrine glands produce. Hormones appear to be bodies of comparatively small molecular weight, which, unlike ferments, are not destroyed by simple heating although they are rapidly destroyed by oxidizing agents. They do not appear in any of the excretions because they are destroyed in the tissues they excite. Unlike antibodies, they belong to the permanent and not the acquired defences of the body. Although hormones probably have a relatively simple chemical constitution, only those of the thyroid and adrenals have been isolated. It has been suggested that an application of the methods employed for the separation of the active principles of plants would yield valuable results. Recent work by Kendall goes to show that the active principle of thyroid secretion is an iodine compound of indol. Now, indol is a decomposition product of tryptophan, a constituent of the protein molecule. Hopkins, in studying the effect of depriving animals of certain protein fractions, found that although tryptophan only constitutes $1\frac{1}{2}$ per cent. of casein, its removal had a profound effect in checking growth, far more so than removing certain other fractions, which constituted nearly 30 per cent. of the molecule. He concluded that it is possible, and even likely, that tryptophan may be required for something other than structural purposes—that its indol nucleus, for instance, ministers to some dynamic function in the body. Now, thyroid secretion has such a dynamic function. The formation of the indol nucleus appears to be beyond the

powers of the body; it requires it ready-made. It is interesting to recall that indol is ordinarily split off by the action of intestinal bacteria; this raises the speculation as to whether we do not depend on these parasites, particularly *B. coli*, for the first step in the preparation of one of the most active and important hormones for us, a hormone that is essential to adult development—whether, in fact, we have not here another example of the interdependence of animal and vegetable life. Now, during the nursing period the child gets thyroid secretion from its mother's milk, and during that period *B. coli* are hardly present in its bowel. Herter has attributed one form of infantilism to persistence of the intestinal flora of the nursing period. We know that the suckling child has not a very active pancreatic secretion. Tryptophan is split off from protein by the pancreatic juice, and indol from tryptophan by bacteria. Normally, then, *B. coli* enter the bowel just about the time pancreatic juice becomes more active, and the child has to manufacture its own thyroid secretion. In this connexion I might refer also to McCarrison's observations on intestinal intoxication as a cause of thyroid enlargement, which on the hypothesis here suggested would be an example of a pathological exaggeration of a physiological process.

Tyrosin, another protein fraction, is chemically related to adrenalin, and it is tempting to relate the formation of adrenalin to the tyrosin of the food. A former house-physician of mine, Dr. Everard Williams, has made some interesting observations on the occurrence of pellagra in prisoners of war. Pellagra is accompanied by changes in the sympathetic nervous system, and he has suggested that a diet poor in tyrosin and tryptophan is specially liable to induce pellagra. Since the sympathetic nervous system depends on adrenalin for its activity, this association is of interest. But on the other hand the body is capable of making its own tyrosin, and Hopkins has shown that deprivation of tyrosin hardly influences growth. Moreover, in that congenital error of metabolism known as alkaptonuria, the body is unable to utilize the tyrosin of the food, yet no sympathetic symptoms appear. The evidence is, therefore, against the formation of adrenalin from the tyrosin of the food. Hormone therapy won its first triumphs with thyroid extract. There are two reasons for this: in the first place, the thyroid contains a larger reserve of secretion than any of the other endocrine glands; and in the second, its secretion was originally poured by the thyro-glossal duct into the alimentary tract, hence it can be readily absorbed from it. It is probably for the same reason that the parathyroid can be similarly absorbed; at any rate, quite small doses, such as $\frac{1}{2}$ grain, seem to produce a marked effect. That formerly thyroid was given in much too large doses is a clinical observation we owe to Leonard Williams. I always start with only $\frac{1}{2}$ grain twice a day, and seldom exceed 2 grains three times a day. In this way all its therapeutical effects can be obtained without exciting such toxic effects as tachycardia, tremors, and glycosuria. Its administration is indicated in all such minor degrees of hypothyroidism as I have described. Incidentally I might add that among the cases referred to me for an opinion I find that failures to recognize these minor degrees of thyroid insufficiency are still quite common.

One has no such confidence that adrenalin will be assimilated from the alimentary tract. Its administration by that route should therefore be restricted to cases where we wish to obtain its astringent effect on the gastric vessels as in haematemesis, or its inhibitory effects on peristalsis as in vomiting. Otherwise it must be used topically on mucous membranes or by injection. In this latter instance its effect is so sudden and so transient that its usefulness is limited. But in asthma and to restrict the spread of a local anaesthetic it is most useful. Its use in vasomotor paralysis has been largely replaced by pituitrin. Pituitrin, again, is probably scarcely assimilated from the alimentary tract, but when injected in vasomotor and intestinal paralysis is very helpful. Given thus its influence on diabetes insipidus is marked. Of its effect in labour I have no experience. The combined injection of adrenalin and pituitrin is sometimes very successful in asthma.

When we come to the other endocrine glands, our ignorance as to their active principles is a great hindrance

to intelligent therapy. That they must be used with care is well illustrated by the disastrous effects of experimental injections of secretin into animals—the resulting liberation of active pancreatic juice into a fasting intestine produced extensive self-digestion of its walls. Administration by the mouth is freer from risk, but possibly because of the uncertainty of absorption. But I do not wish to discourage the clinical use of such extracts, either singly or in combination, if it is made cautiously, and with due consideration of physiological principles. Empiricism has often won success where rational therapy has lagged behind, but I do deprecate the giving of extracts of glands that are known to have no internal secretion, such as the spleen and kidney.

If I have been able to give any guide to the principles which underlie organotherapy my object is achieved. That I have only been able to give a rough outline of those principles is inevitable, for the variety of endocrine activity is only exceeded by the infinite variety of life itself.

REFERENCES.

- ¹ Langdon Brown, BRITISH MEDICAL JOURNAL, 1920, ii, p. 191.
- ² Loc. cit.

EIGHTY-EIGHTH ANNUAL MEETING

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PROCEEDINGS OF SECTIONS.

SECTION OF NEUROLOGY AND
PSYCHIATRY.

HENRY HEAD, M.D., F.R.S., President.

DISCUSSION ON
EARLY SYMPTOMS AND SIGNS OF NERVOUS
DISEASE AND THEIR INTERPRETATION.

OPENING PAPER

BY

HENRY HEAD, M.D., F.R.S.

WHEN attempting to elicit the history from a patient it is a common experience to find that some early but significant symptom has been entirely omitted. For this he offers the excuse, "It was so slight and passed away so quickly that I did not think anything of it"; and this belief in the unimportance of slight transitory manifestations is not confined to the patient, but is frequently shared by his medical attendant.

Such symptoms as double vision or a passing weakness of one limb may have been of supreme diagnostic importance in the light of subsequent events. But the experience and outlook of the family physician leads him of necessity to a different attitude towards early signs and symptoms from that of the specialist. The former has seen so many apparently serious conditions pass away that he tends to become sceptical with regard to minor manifestations, which so often cause no permanent disability. On the other hand, the knowledge of the consultant leads him confidently to anticipate the worst. In many instances he is not told whether his Cassandra-like prophecies have been fulfilled or falsified, and he rarely knows if the signs and symptoms on which he laid such stress turned out to be important or not.

This sitting of the Section of Neurology and Psychiatry has been devoted to the early signs and symptoms of nervous diseases, in the hope that the combined experience of the meeting may show which of them are of diagnostic and prognostic value. Amongst nervous diseases we do not intend to include the results of gross organic destruction only; we hope that the discussion will touch on the early symptoms of those morbid conditions usually classified as the neuropsychoses. For in the early stages it is often extremely difficult to determine whether the symptoms are due to a primary psychosis or to some

structural change in the central nervous system. Thus cerebral syphilis may show itself first in a change of character or produce a condition which exactly simulates paranoïa or dementia præcox.

Early symptoms frequently produce so little discomfort that a medical man is not consulted. Nearly all histories of illness taken from the labouring population start from the moment when the patient was forced to leave his work. Amongst the well-to-do the story usually begins with the first visit of the doctor. But such symptoms as precipitate micturition or slight changes in articulation, though trivial manifestations, may be of profound diagnostic importance. How many patients in the early stage of a spinal lesion have been thought to be hysterical because the first signs of defective control over micturition were neglected! Women rarely confess to this symptom; but not uncommonly its occurrence can be elicited by asking "How long is it since you were able to go out to tea?" For a woman who suffers in this way cannot face the strain of sitting for some hours under the influence of a diuretic.

Early signs are not only neglected because they seem trivial, but the physician frequently omits to establish their true nature during the short period of their existence. For example, a patient suffering from a cerebral tumour may have had a slight convulsive attack, followed by transitory "weakness" of one hand. Careful examination would have shown that this was a definite loss of motor power accompanied by some changes in the reflexes, or that the defect was a disturbance of sensation of the cortical type. A few days later the hand may have recovered its normal functions, and the opportunity has been lost for discovering the true nature of this post-convulsive disorder.

On the other hand, any morbid condition with an acute or fulminating onset is liable to be accompanied by signs and symptoms far in excess of the structural changes on which it is based. Thus, embolism of one of the minute arteries supplying the internal capsule may produce severe paralysis of the opposite half of the body; this sometimes clears away so completely that little evidence of the stroke remains. The shock to the central nervous system was so profound that the functional activity of parts outside the area supplied by the blocked artery suffered severely.

Any sudden injury to the brain produces widely radiating effects within the structures of the nervous system. Sometimes a blow on the head or a cerebral wound may be followed by loss of motion and sensation so severe that it is difficult to believe the mid-brain has not been affected. The whole of one half of the body may be in a condition of flaccid paralysis, insensitive to touch, pain, heat and cold; and yet the rapidity with which this loss of function disappears shows that it was not due to gross structural changes in the lower centres.

All aspects of cerebral activity are liable to undergo similar profound and extensive changes in consequence of trauma; these are particularly evident in the phenomena which follow cerebral concussion. At first the patient lies in flaccid unconsciousness, with shallow breathing, scarcely able to swallow fluid placed in his mouth. Then the lower centres recover from the shock and he becomes restless and even violent. As consciousness returns he grows more amenable to control, and his conduct is no longer dominated by the activity of his lower functional levels; but his memory and power of concentrated attention long remain defective.

The widespread distribution and severity of these early shock-effects tend to lead to a mistaken idea of the permanent extent of the lesion. After a cerebral hæmorrhage producing a complete hemiplegia, the patient's friends are frequently told that he will never walk again. But, provided he can recognize the posture of the limb with his eyes closed, he usually recovers sufficient power to walk with the help of a stick. The leg always tends to recover to a greater amount than the arm, unless the structures which govern its motor and sensory functions are more directly affected than any other centres.

Frequently the significance of some symptom or sign is not appreciated owing to the adoption of a misleading general diagnosis. The early pains of spinal syphilis are thought to be due to "fibrositis." Disseminated sclerosis not unusually begins with short attacks of what is called "influenza"; the temperature is little if at all raised, but