THE PRESENT POSITION OF ENDOCRINOLOGY.*

By SIR WALTER LANGDON-BROWN, M.A., M.D., D.Sc., F.R.C.P.

(*Emeritus Professor of Physic in the University of Cambridge. Consulting Physician to St. Bartholomew's Hospital.*)

Endocrinology is a subject of such recent growth, and facts have accumulated so rapidly that it is a relief to find a plan beginning to emerge which can in some measure act as a guide.

I would stress three recent lines of advance which are leading to a clearer conception of the integration of the endocrine system.

1. The diencephalon has been conclusively shown to be the nervous structure concerned with the expression of the emotions.
2. The pituitary, which is so closely associated with the diencephalon, has become recognized as the leader of the endocrine orchestra.
3. It is now realized that all nervous impulses have a chemical mediator between the neuron and the tissue cell, and indeed between one neuron and another.

I shall hope to show how these three points are leading to a new conception of the unity of functioning of the body.

The diencephalon has ties in three directions, with the cortex of the brain above, with the pituitary below, and with the sympathetic nervous system of which it appears to be the head ganglion. In this way a psychical experience may record its effects either through the chemical mechanisms initiated through the pituitary, or through the sympathetic acting on the viscera or on other ductless glands.

From the experiments of Sherrington it has been known that if the higher parts of the brain be severed from the diencephalon in a dog, the animal responds to ordinary stimuli in an exaggerated way by an explosion of what he terms "sham rage." Cushing has reported similar explosions in a patient suffering from a cerebral tumour which similarly destroyed these connections. On the other hand, if this region be completely destroyed by a tumour, the power of emotional expression may be lost altogether as in a case reported by Naish. There is a close anatomical connection between the diencephalon and the pituitary body. Beattie has described a well defined bundle of nerve fibres, coming chiefly from the nucleus supra-opticus, and passing by the stalk of the pituitary into the posterior lobe. There is almost certainly a close physiological connection as well. Herring some years ago described the passage of hyaline bodies from this lobe into the hypothalamus and Frank has shown that the parts of the hypothalamus which do not ordinarily yield posterior lobe hormones, may after hypophysectomy take on the function of secreting these hormones. The difficulty in deciding whether certain cases of diabetes insipidus, adiposity and genital atrophy are due to hypothalamic or pituitary lesions is further evidence of the functional association between these structures. Interesting examples of this functional association

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between emotional centres and pituitary secretions can be given. Thus the cow which refuses to yield milk when deprived of its calf can be made to do so either on hearing the call of the calf or by an injection of pituitrin. Injections of the lactogenic principle of the pituitary will lead to the demonstration of maternal behaviour in the unimpregnated animal.

Having thus established the connection between the activities of the diencephalon and the pituitary we may proceed to establish the position of the pituitary as the leader of the endocrine orchestra. Cushing some years ago laid down the principle that polyglandular syndromes had their primary focus in some pituitary disturbance. The close association between the pituitary and the other endocrine glands is now generally admitted. We recognize three types of cell in the anterior pituitary—the chromophobe which resists staining, the eosinophile and the basophile. The chromophobe is probably the parent cell of the other two. An adenoma composed of chromophobe cells diminishes pituitary function. Fröhlich's syndrome of obesity of the limb-girdle type and genital hypoplasia was originally recognized in a case of this sort. Milder cases occur without the presence of an adenoma. They may be attributed to a delay in the differentiation of these chromophobe cells; puberty may be delayed but the outlook is not so serious. That the eosinophile cells are the source of a growth hormone can be definitely accepted. The experimental evidence as to the production of gigantism in rats, the clinical evidence derived from acromegaly and acromicry, from Simmonds' disease both in children and in adults seem alike satisfactory. The basophile cells became regarded as the source of the sex hormone after the researches of Evans and Simpson, and still more so after Cushing's description of the syndrome of pituitary basophilism. We may accept the view that the growth and sex hormones are antagonistic, and that it is not until the latter gains the upper hand that puberty occurs, but there are strong reasons to doubt the basophile cells as the source of the sex hormone. After the recognition of the growth and sex hormones, claims for other hormones secreted by the anterior pituitary multiplied rapidly. Of these the thyrotropic, adrenotropic, lactogenic and diabetagenic are best established. But we were a little too ready to conclude that the syndrome of pituitary basophilism confirmed the idea that the sex hormone originated in the basophile cells. Woollard was the first, as far as I am aware, to point out that if this were so, it is unreasonable to suppose that in women virilism and decay of sexual function should follow excess of it. Injection of pituitary gonadotropic hormone produces nothing like pituitary basophilism, but may produce gonadal atrophy. He therefore does not believe that the basophile cells are the source of the sex hormone; rather, he envisages them as the inhibitors of the acidophilic activities. He thinks the evidence warrants the statement that the pituitary plays no part in sexual differentiation, but exerts its effects on either the testis or the ovary, bringing each to its structural differentiation and to its full endocrine activity. Levy Simpson and also Leschner and Robb-Smith have come to a similar conclusion, that the basophile cells are the source of some depressive inhibitory substance.

Crooke has described a characteristic hyaline change in the basophile cells in Cushing's syndrome, whether that syndrome be associated with basophilic adenoma or a neoplasm of the adrenal cortex. He did not regard this as a

degenerative change, but as an expression of altered physiological activity. In Addison's disease he, in conjunction with Dorothy Russell, found an extreme reduction in the pituitary basophile cells. They think this may be the cause of the low blood pressure and possibly of the hypoglycæmia in this disease ; it is certainly in sharp contrast with the high pressure and hyperglycæmia found with basophilic adenomas. These two authors together with Horace Evans have described two cases of such adenomas in which most of the characteristic symptoms of the syndrome were lacking, cardiovascular hypertrophy being the salient feature. Nevertheless, they are not prepared to go as far as Cushing in regarding essential hypertension as due to increase in the number of basophile cells. Broster and Vines regard an excess of fuchsin staining material as the essential change in the adrenal cortical cells which produces virilism. This change may be absent in pituitary basophilism. The way in which a growth in the thymus gland, usually regarded as antagonistic to sexual development, may simulate the basophilic syndrome adds to all these doubts concerning the sexual functions of the basophile cells.

The functions controlled by the anterior pituitary have multiplied until the existence of a separate hormone for each function has become almost incredible. As P. E. Smith puts it, "That this small gland, which in man averages less than half a gram in weight, secretes this number of hormones as separate entities throughout the entire secretory process taxes the imagination. The differentiation into two highly specialized secretory types suggests perhaps the formation of a corresponding number of basic secretory products which may be altered to give these specific responses. There can be no certainty until physiologically pure extracts are secured as to how much these impurities may modify the response." One might add to this the fact that somewhat violent chemical measures have been adopted to isolate these pituitary hormones even in only an approximately pure state. It seems more probable that such measures have produced alterations in the basic products.

In view of these facts, this newer conception of the anterior pituitary producing an accelerating hormone in the eosinophile cells and an inhibitory one in the basophile cells seems a rational one—the functions and the staining reactions of these cells being alike diametrically opposed. One may regard the anterior pituitary as largely controlled by the diencephalon and putting down the loud or soft pedal, as it were, on the other glands.

Fresh light on the whole subject has been thrown by Dodds who classifies hormones under two headings. The first are complex protein bodies formed by the anterior pituitary, which act on the other endocrine glands causing them to form the secondary type of hormones which are bodies of comparatively small molecular weight, most of which have been isolated in a crystalline form and some of which have actually been prepared synthetically. It will be noted that in this respect the posterior pituitary belongs to the second group. In conjunction with Cook he has carried out a brilliant series of researches into these secondary hormones and has shown that simpler compounds than those prepared by the body can have the same biological effect to a less or even greater extent. This basal group with the simplest chemical structure that can produce the biological effect he calls the "skeleton key" which picks the physiological lock. Even more striking was his demonstration that the same basal group could produce more than one biological effect. To such groups he gave the name of "pass keys."

It is accordingly by no means fanciful to regard the anterior pituitary as receiving the impulses from the diencephalon and producing an activating and an inhibitory hormone of a protein character according to demand, which can speed up or inhibit the secretion of the simpler grade of hormone in the other endocrine glands; hormones which are of allied chemical structure and which, in some instances may even be interchangeable in their action. At any rate, it is a unifying hypothesis which deserves further and careful consideration.

This is perhaps the appropriate place to consider the position of hormones in the scale of substances influencing normal and pathological growth. The best examples of non-glandular hormones are to be found in the "organizers" of the embryo, which are not cellular structures but chemical substances. They are not ferments for boiling actually liberates them in an active condition in parts of an egg, where they never normally so appear. The best known of these is the one which organizes the first appearance of a central nervous system in the embryo. This is a sterol closely related chemically to oestrogenic compounds, which in their turn are chemically related to carcinogenetic substances on the one hand, and to pile acids and vitamin D on the other. This chemical relationship between various stimulants to normal growth and those to abnormal growth is both interesting and important. That there is also a functional relationship was clearly brought out by Dr. Needham in his paper read at the Oxford meeting of the British Medical Association. Let us consider some illustrative instances.

We know that parathormone and vitamin D each control calcium metabolism, though in a different way. Again, vitamin A is as necessary for the growth of the hind legs of an embryo pig as thyroxine is for the development of the tadpole's limbs. The old distinction between endogenous hormones and exogenous vitamins loses its validity now we know that the animal body forms vitamin A from carotene, that the embryo chick can synthesize its own vitamin C, and that irradiation of the skin will lead to the production of vitamin D. Oestrogens, moreover, are found in plants, and human oestrin can cause daffodils to flower all the year round.

Lack of vitamin A causes xerophthalmia and a defect in the visual purple. But if a sow be deprived of this vitamin her litter suffer a much graver ocular damage—the eye cup and lens fail to form at all. Now the normal stimulus to the formation of the lens resides in an "organizer" found in the eye cup. Moreover, even synthetic oestrogenic hydrocarbons have actually been shown to act as organizers of the nervous system in the embryo.

Carcinogens can excite oestrus and oestrin can have carcinogenetic effects. Human skin heated to a very high temperature will yield a tarry substance which is as carcinogenetic as any derived from coal tar. A strongly carcinogenetic substance has also been synthesized by Cook from deoxycholic acid, a sterol in bile. Therein is a hint at the explanation of the known close association between gall-stones and cancer. Again, if fertilization is delayed in amphibia, the organizer may escape from its proper site and set up teratomata capable of wide metastasis. This throws new light on the origin of these so-called "included twins." In this connexion it is interesting that Aschheim has found the gonadotropic hormone in the urine of patients suffering from a teratoma even in the case of a man. This may provide a test of real diagnostic value. The rôle of vitamin E in reproduction is also instructive. In its absence the embryo throws

out a rapidly proliferating "lethal ring" of new growth, thus committing suicide by cutting itself off from its own food supply. Here the vitamin appears to impose order on what would otherwise be a disorderly growth, just as vitamin D controls irregular ossification.

From this collection of amazing facts two definite conclusions emerge: (1) the overlap between the activities of these various stimulants to growth is very considerable; (2) from sterols normally occurring in the body a deranged metabolism may produce specific carcinogenetic substances which will stimulate certain cells to wild proliferation.

The question has not been simplified by the claims made for the existence of antihormones. Collip showed some time ago that parathormone gradually lost its effect on repeated injections. One might imagine that this failure could be adequately accounted for by its destructive action on the calcium content of bone and muscle, but he now thinks that there is an antihormone both to the pituitary growth and thyrotropic hormones, and advances the hypothesis that the production of antihormones may be responsible for hypoglandular states. He regards a hormone-antihormone linkage as the normal condition, which can readily be disturbed. The purposive character of such antihormones is hard to see; certainly thyroid administration is effective when continued over many years. The claim for the existence of a catechin in the blood which is antagonistic to thyroxin, if substantiated, suggests a simpler explanation, namely that various chemical substances can destroy hormones, just as we know the acetylcholine and adrenaline set free on nerve stimulation are rapidly destroyed in the blood or tissue cells.

And this leads me directly to my third point. It has long been common knowledge that emotional states may modify secretion; the tears of sorrow and the dry mouth of fear are proverbial. In such instances it is obvious that a nervous impulse has produced or prevented a chemical process. But it is only quite recently that we have realized that all nervous impulses have a chemical mediator between the neuron and the tissue cell, and indeed between one neuron and another. In Hopkins' phrase, chemical substances are produced which translate for the tissues the messages received by nerves. We have indeed been curiously blind to the fact that the chemical changes produced in a gland by nervous stimulation is only a special case of a general law. I say curiously blind, because this century was only a year old when Langley found a clue which was not really followed up for years. We knew that adrenaline is manufactured by the cells of the adrenal medulla, which are actually formed out of sympathetic ganglion cells. Langley enunciated the law that the effect of adrenaline on any part is the same as if the sympathetic nerves to that part were stimulated; an extraordinarily interesting example of a chemical substance imitating a nervous response. The adrenal medulla was seen to represent the postganglionic element in the sympathetic. In 1907 W. E. Dixon made some tentative experiments on the liberation of a chemical substance in the heart after vagus stimulation; later the work of Loewi and of Dale has proved that acetylcholine is liberated at the terminals whenever sympathetic or parasympathetic preganglionic fibres are stimulated, and adrenaline at the sympathetic postganglionic terminals. So Dale speaks of cholinergic and adrenergic fibres and incidentally shows how this conception explains Langley and Anderson's cross-suturing experiments. You can cross-suture cholinergic with cholinergic or adrenergic with adrenergic, but you cannot successfully cross-suture

cholinergic with adrenergic fibres. Cannon thinks that the substance liberated at the sympathetic postganglionic terminal is not identical with adrenaline ; he thinks he can extract a slightly different one after an excitant action from that appearing after an inhibitory one. The non-committal name of adrenergin has consequently been introduced.

This leads me to an aspect of endocrinology which is urgently demanding attention. Some thirty years ago Langley and Elliott independently postulated the existence of a receptive substance between the nerve ending and the tissue as necessary to explain the facts then known. If such a postulate was required then, how much more is it needed today. Just as the appropriate chemical material, such as pilocarpins or atropin, may get into this receptive substance so may a toxin. G. N. Myers has shown that a therapeutic drug may seize on the receptive substance and thus bar the way to the ingress of the toxin. It seems to me that the pharmacology of the future will have to concern itself with the natural history of these receptive substances, and find out in what way they can be helped by drugs both positively, by facilitating their reactions, and negatively, by blocking the way against the entrance of toxins. Nor is this topic remote from my subject, for Zondek maintains that the adsorption of a hormone, such as thyroxin, is decreased in the presence of narcotics such as the barbiturates, which are able to adhere to the cell surface and thus to displace the hormone from it. But it is also germane to my subject in a wider sense. We are still entirely without any conception why a particular cell should be sensitive to a particular chemical substance or why the same substance should augment the activity of one type of cell and inhibit that of another. He indicates indeed precisely the problem to which many minds are beginning to devote themselves, the nature of these receptive substances. The nature of the stimulus has been intensively studied, but it is now clear that this is only half, and perhaps the simpler half of the question. The importance of the responsive capacity of the receptor tissues was clearly indicated by Harrison in his Harvey Lectures for 1934. He showed that when transplantation is effected between embryos of species of different sizes, the transplant responds according to its inherited growth capacity rather than to its new endocrine environment. As Keith pointed out some years ago, the partial gigantisms in certain cases of hyperpituitarism can only be explained on the theory that the locally hypertrophied tissues had developed a special sensitiveness to the growth hormone. H. M. Evans has recently shown that the response of the dachshund and of the sheep dog to injections of the pituitary growth hormone is entirely different. Indeed, if such things were not so, it would be difficult to account for the structural plasticity of dogs in the hands of the breeder. Thyroxin can speed up changes in tissues in the direction in which they are going. Thus it will precipitate the degeneration of the tadpole's gills and hasten the development of the limbs. Here the response clearly varies with the capacity of the tissue rather than with any change in the stimulating hormone.

Zondek considers that the potency of such minute quantities of hormones implies that they act as physical catalysts, which circulate in the blood in an inactive form until they are absorbed and activated in the tissue they excite. In the case of thyroxin however, Mansfeld maintains as the result of his experiments that it travels along the nerve fibre to reach the tissue cell in the same way as tetanus toxin and certain viruses. If this startling observation is confirmed it will have important biochemical bearings. It would render such pathological processes more comprehensible if there is a physiological path already open to them.

The influence of hormones on sex is too large a topic to discuss fully here; suffice it to state concisely the known facts with regard to hormones and sex reversal. It would appear that the testis is monosexual while the ovary is bisexual, with a male medulla and a female cortex, as it has been expressed. Therefore physical sex reversal can only occur in woman, and may be due to:—

1. Overaction of a basophilic adenoma in the pituitary which inhibits normal ovarian activity, allowing the rudimentary masculine elements to reassert themselves.
2. Overaction of the adrenal cortex, which is mesonephric and contains similar cells to those of the testis.
3. Overaction of mesonephric cells in the rete ovarii, which, as in some of the arrhenoblastomas first described by Pick, may actually develop convoluted tubules resembling the seminiferous tubules of the testis.

Closely similar syndromes of virilism may originate in any one of these three positions and are all due to absolute or relative overaction of masculinizing mesonephric structures. On the other hand, the testis being monosexual, sex reversal in man can only be psychogenic. There seems to be only one exception to this rule. A female-included twin may produce some degree of feminism in the masculine "host."

I will sum up what I regard as the present position of endocrinology in a few dogmatically stated conclusions:—

(1) Hormones are a special instance of metabolic energisers which are widely spread throughout the body and which may give rise to either physiological or pathological effects.

(2) They are of two grades—the first, of complex chemistry, are formed by the anterior pituitary, which uses them to stimulate or inhibit the secretion of the second, chemically simpler grade by the other endocrine glands.

(3) They are not entirely specific; the same basal chemical group can act as a "pass key" producing more than one biological effect.

(4) To a large extent they have come under the control of the diencephalo-pituitary apparatus.

(5) Their activity is largely conditioned by the competence of the tissues to respond to them.

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