THE ENDOCRINES IN THEORY AND PRACTICE

This article is the first of a series on Endocrinology contributed by invitation

THE PRESENT POSITION OF ENDOCRINOLOGY

BY

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In a subject of such rapid growth as endocrinology the practitioner may well feel lost among what appears to be a maze of disconnected facts. It is therefore with a feeling of relief that we can see a plan beginning to emerge which may in some measure act as a guide.

The first phase of our knowledge of endocrines led to a conception of an autonomous system acting independently of the central nervous system. *A priori* this might have been realized as unlikely, considering that complexity of structure demands some central control. The newer conception places the controlling centre in the diencephalon, which is closely linked up with the expression of the emotions. 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.

Integration of the Endocrine System

The first hint as to the method of integration of the endocrine system came from Langley's generalization that the effect of adrenaline on any part was the same as stimulation of the sympathetic nerves to that part. Indeed, the cells of the adrenal medulla actually replace a part of the sympathetic nervous system. But the significance of this substitution of a chemical for a nervous mechanism was missed for a time. That emotion could influence secretion had long been recognized; the tears of sorrow, the dry mouth of fear, the polyuria of nervousness, were proverbial. What was not recognized was that these were merely special instances of a general law, that the messages transmitted by the nerves are ultimately translated by chemical messengers. And that phrase—chemical messengers—at once recalls that this was the very description which Starling gave to hormones when he originally introduced the term. It adds point to that description to find that one particular hormone—adrenaline (or, as Cannon holds, a closely similar chemical substance)—is liberated at the final ending of every sympathetic nerve when stimulated, while Dale showed that acetylcholine is similarly liberated at parasympathetic endings. Hormones, then, are highly specialized instances of chemical messengers which are by no means outside nervous control.

In addition to this method of direct control there is an indirect control through the anterior pituitary, which has gradually come to be recognized as the leader of the endocrine orchestra, as I ventured to describe it. The way in which it exerts its influence on the others has been made more intelligible 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: these are bodies of comparatively small molecular weight, and most of them

have been isolated in crystalline form, some having actually been prepared synthetically. In this respect the posterior pituitary belongs to the second group.

Type of Cell in the Pituitary

In this task the anterior pituitary has been credited with the production of an inordinate number of hormones, but now there is a reaction against this view. It appears more probable that its task is to produce an accelerating and an inhibitory substance which can stimulate or diminish the activity of other glands in accordance with the needs of the body. On that view these two substances would correspond to Sharpey-Schafer's original distinction between a hormone and a chalone respectively. The three types of cell to be found in the anterior pituitary were allotted their appropriate functions: the chromophobe cell, the undifferentiated parent cell which gave rise both to the eosinophil or growth cell, and the basophil or sex cell. But further observation and reflection has thrown doubt on this simple distinction, and it has been suggested that the eosinophil cell produces the accelerator hormone and the basophil cell the inhibitor. Cushing's description of the syndrome known by his name has aroused much discussion, and we must not anticipate what is to be said on this subject in another article. Suffice it to say here that while this syndrome may apparently be initiated by changes in the pituitary, thymus, adrenals, or ovary alike, Crooke's generalization appears to be confirmed—that the only factor common to these various manifestations of the syndrome is a hyaline change in those basophil cells which does not appear to be degenerative, but probably an expression of altered physiological activity. He regards this change as of fundamental importance.

The Endocrines and Sex

This naturally leads to the consideration of the influence of the endocrines on sex. That the anterior pituitary produces something which is necessary to sexual maturation is generally accepted, and the cells producing it appear to increase for a time in number when sexual activity is reduced by operative intervention or by the menopause, as if to stimulate a system that is flagging. The ovary and anterior pituitary are complementary; too much oestrin depresses pituitary activity, and too little makes it unusually apparent. The influence of the anterior pituitary-like substance extracted from pregnancy urine in helping sexual maturation is strikingly seen in the successful treatment of many cases of undescended testis. At first sight it seems extraordinary that a female hormone should have a masculinizing effect. McLellan has recently made an interesting suggestion based on the complementary actions referred to above. He thinks that the boys who respond to this treatment may, during intrauterine life, have been subjected to an excessive amount of oestrin or to a deficient amount of anterior pituitary substance. In that case the anterior pituitary-like substance obtained from pregnancy urine simply rectifies at a late stage the hormonal balance. There is, however, another possibility. The male and female hormones are closely related chemically, and, as we shall see later, there is a considerable amount of overlap between the effects produced by a number of such substances; in other words, they do not appear to be strictly specific.

Perhaps the clearest indication of the way in which endocrines can influence sex is to be gained from a consideration of certain ovarian tumours—the arrhenoblastomas which occasionally occur in the rete of the ovary and simulate seminiferous tubules. It therefore appears that the ovary is a bisexual organ. Virilism in women can be produced by: (a) a direct overgrowth of the masculine rudiments in the medulla of the ovary; (b) by an overgrowth of cells of similar origin in the adrenal cortex; or (c) anterior pituitary disorders which disturb the balance between the female cortex and the male medulla of the ovary. That a thymic growth disturbs this balance in the same direction is known, but how disease of this infantile gland effects this is at present quite obscure.

Specificity of Hormones

We must next consider two new aspects of endocrinology: the degree to which hormones are specific, and the competence of the tissues to respond to their stimulation. As to the former, E. C. Dodds has shown that simpler compounds than those prepared by the body can have the same biological effect to a less or even greater extent. The basal group with the simplest chemical structure that can produce the biological effect he calls the "skeleton key," which picks the physiological lock. He also showed that the same basal group could produce more than one biological effect, and to such groups he gave the name of "pass keys."

Following this line of thought, more particularly with regard to stimulants of growth, we may adopt Needham's classification of substances affecting normal and pathological growth. He differentiates them into those which act by providing for optimum nutrition, and those which act by specific stimulus, whether hormones (both glandular and non-glandular), vitamins, or drug-like substances. 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 bile 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.

Relation of Hormones to Vitamins and other Substances

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 the role of vitamin E in reproduction is 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.

Physical Chemistry of the Cell

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. Mark that phrase, "certain cells," for now we pass to an aspect of hormonal action which is only just becoming recognized—that there are two distinct factors concerned, not only the power of the hormone to excite, but the competence of the tissue to respond. True, it is a good many years since Sir Arthur Keith, musing over a specimen showing hypertrophy of one side of the face in a case of hyperpituitarism, pointed out, with his subtle intuition, that there must be some local receptive agent to respond thus partially to a generally distributed excess of hormone. To-day we have some precise facts which confirm that intuition.

Thyroxine is known to promote metamorphosis in the tadpole. In doing so it will simultaneously excite proliferation of the limbs and degeneration of the gills in immediately adjacent areas. Histologically the division between these two is quite clear-cut; rapidly dividing cells are seen in one area, and degenerating cells in the other. Such a state of affairs postulates an entirely different capacity for response in each. Embryologists speak of this as the "competence" of the tissue to react. This competence clearly varies as life goes on, and hence the different response to hormones at different epochs. Indeed, it has been shown that at the menopause the altered response of the reproductive organs plays quite as large a part as the failure of hormonal stimulus. The onset of senility may well be determined by such factors. Competence may be altered by drugs. Thus Zondek maintained that barbitones impede the entrance of thyroxine into the cell, thus providing scientific sanction for the increasing empirical use of such drugs in hyperthyroidism. Indeed, a new pharmacology is springing up, based on a study of these receptive mechanisms. The barrier which atropine offers to the acetylcholine liberated by vagal stimulation, and the reinforcement that physostigmine and its derivatives provide it with, are familiar examples. In the same way ergotoxine bars the entrance of adrenaline into the cell.

Here we are on the threshold of the physical chemistry of the cell, where at present only the biochemical expert

can enter. He hints darkly at surface tensions and ionic equilibrium, and there the practising physician must leave him, in full expectation of more results in the near future. Nor does Collip's conception of anti-hormones help us much yet, though it may clarify our ideas before long.

Conclusion

Amid all these rapidly accumulating facts and changing theories it is not surprising that organotherapy lags behind endocrinology. Clearly some of the extravagant hopes indulged in are not going to be realized as yet, if ever. Indiscriminate prescription of endocrine products, without reference to the possibility of their physiological or pharmacological activity, merely impedes progress and brings discredit on an important subject. It would be well for the practitioner to familiarize himself with doses in terms of international units where these have been determined, and it is one of the aims of the present series of articles to provide him with such information as will help him to realize the scope and limitation of endocrine therapy. As a preliminary to such information, it may be well to sum up the present position of endocrinology in a few dogmatically stated conclusions.

1. Hormones are a special instance of metabolic energizers 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.

THE FUTURE OF THE INTERNATIONAL HEALTH ORGANIZATION

[BY OUR GENEVA CORRESPONDENT]

The devaluation of the Swiss franc will not adversely affect the financial resources of the League of Nations, whose budget has always been calculated in gold francs and whose investments are spread over many countries. This is fortunate for the Health Organization of the League, because next year the Rockefeller benefaction comes to an end. The grant of 300,000 Swiss gold francs annually was made in 1922 for a period of fifteen years, and is mainly spent in salaries of technical staff. It is already agitating the Health Organization and the Finance Committee of the Assembly as to how the work will be financed when this subsidy is withdrawn. The director of the Health Section has asked that the staff whose salaries are now paid out of the Rockefeller grant be placed on the League pay-roll. This matter will be decided next year, when the budget for 1938 comes up for discussion. No doubt the valuable services of the Health Organization, which everyone acclaims, will be the factor determining the decision. There is a proposal to standardize the amount which the League spends on health work at one million Swiss francs (some £50,000) instead of at 875,000 francs as at present, and it is said that at this figure it would be possible to continue the work unimpaired despite the withdrawal of the Rockefeller gift.

Work on Nutrition

The work on nutrition is still the subject of rather desultory debates, in which information is exchanged but

nothing in particular done. Mr. Geoffrey Shakespeare said the British Government endorsed the recommendations of Lord Astor's committee, the report of which was "un succès de librairie" in the United Kingdom. He described the steps taken to provide milk for school children, and said that the Government was considering the possibility of extending cheap milk schemes. A committee under the chairmanship of Lord De La Warr was being set up to co-ordinate information on nutrition in the British colonies. The Dutch delegate gave a rosy account of nutrition and public health in the Netherlands. The general death rate, the infant mortality rate, and the tuberculosis rate were all declining. The Norwegian delegate said that thanks to a Rockefeller donation an institute of public health had been established as part of the University of Oslo. A national health insurance scheme was about to be introduced into Norway. The Latvian delegate spoke of the organization in his country under official auspices of workers' refectories and public kitchens, all in accordance with the latest dietetic principles. Elaborate systems of milk production and control have also been set up in that country. A reminder of the economic side of the question came from the New Zealand delegate, Sir James Parr, in a reference to the high cost of transport, whereby apples which the New Zealand farmer sells at less than one penny a pound are retailed in Europe at eightpence or tenpence a pound.

Abuse of Narcotic Drugs

The debate on dangerous drugs was noteworthy for a speech by the Portuguese delegate, who calculated that the legitimate world requirements of narcotic drugs could be estimated at about 540 tons, and that world production in 1934, without taking account of the Chinese output of raw opium, was twice as great as world requirements. A distinction was drawn by one of the South American delegates between the chewing of coca leaf—which was a common practice in several South American countries—and the "drug addiction of the idle." He said that such chewing in moderation helped the natives in their work, especially in enduring forced marches and high altitudes. The Indian delegate, Sir Krishnama Chari, said that in 1935 exports of opium from India, other than for medical or scientific purposes, had ceased. This had not been done without financial sacrifices. The revenue from opium exports, which twenty-five years ago was over seven million pounds, had now entirely disappeared. The Canadian delegate complained of an extensive traffic in cocaine from Japan through Canada. Japan had declared that she was taking very strong measures, and her assurances on the subject were welcomed by the Canadian Government. Finally, the British delegate said that his Government would do all it could to assist China in her efforts to combat the opium evil, and was now applying to British subjects enjoying extraterritorial rights in China the penalties applicable in the United Kingdom.

According to S. Muntner (*Wien. klin. Woch.*, July 3rd, 1936, p. 850) treatment of post-encephalitic Parkinsonism by scopolamine is to be deprecated as having only a narcotic action and diminishing the excitability of those central nerve fibres to the exclusion of whose activity a portion of the syndrome is due. Further experience has confirmed the value of treatment by large doses of atropine, the toxic symptoms of which are neutralized by simultaneous administration of pilocarpine or physostigmine. The atropine dosage is increased to five drops of a 0.5 per cent. solution twice daily orally, with a pill containing 0.01 gram of pilocarpine twice daily. On two days weekly the morning and afternoon doses of atropine are replaced by a subcutaneous injection of 0.002 to 0.0025 gram. Medical exercises used at the same time include dancing or rhythmic upper limb responses to dance or march music from the gramophone. In refractory cases novatropine (homatropine methyl bromide) may be given in about one-third of the amounts prescribed for atropine. Phenyl-ethyl-barbituric acid in doses of 0.05 gram is a useful adjuvant.