Remarks

ON

THE ENDOCRINES AND SOME ASSOCIATED
PSYCHONEUROSES*

BY

W. LANGDON BROWN, M.A., M.D., F.R.C.P.
CONSULTING PHYSICIAN TO ST. BARTHOLOMEW'S HOSPITAL

I will begin with some rather dogmatic statements, because they are convenient pegs on which to hang recent observations, but I hope to be able to show that these pegs have a firm attachment to a wall of facts.

1. Endocrines are an elaboration of a survival of those chemical mechanisms to which animals responded before a central nervous system was developed.

2. When the central nervous system was developed it entered into an alliance with pre-existing chemical mechanisms, particularly through its lowest level, the visceral nervous system.

3. The visceral nervous system may be subdivided into (a) the sympathetic, and (b) the parasympathetic; each co-operates with its group of endocrines.

4. The sympathetic is largely katabolic in its activities, and is associated with the thyroid, pituitary, and adrenals.

5. The parasympathetic (or extended vagus) is largely anabolic in its activities, and is associated with the pancreas. The parathyroids co-operate with the internal secretion of the pancreas, but there is no direct evidence of their control by the vagus.

6. The gonads interact particularly with the sympathetic-endocrine group.

7. The pineal and thymus are not true endocrines, as they are not known to form any internal secretion. They can, however, through some agency not at present completely understood, influence the endocrine system, and usually do so by retarding its action; particularly do they retard the onset of sexual maturity in favour of somatic growth.

PROGRESS DURING THE LAST DECADE

Three entirely new hormones have been isolated—insulin, oestrin, and parathormone; the thyroid hormone, thyroxine, has been obtained in a crystalline form and synthetically prepared; pituitrin has been shown to contain two distinct substances—pitressin, which raises the blood pressure, and oxytocin, which contracts the uterus. On the purely biochemical side, therefore, great advances have been made. Clinically the discovery of insulin has revolutionized the prognosis and treatment of diabetes, has clarified our views on many of the endocrine interactions, and has proved a valuable help in the treatment of hyperthyroidism, hepatic toxæmias, and various wasting diseases. Parathormone has been of great practical service in the treatment of tetany, and has played an important part in the recognition of hyperparathyroidism. Oestrin has been of limited use clinically, and evidently technical difficulties have still to be overcome. Active extracts have been prepared from the anterior lobe of the pituitary and from the adrenal cortex, though these have not as yet proved capable of much clinical application.

The revival of iodine therapy in hyperthyroidism by Plummer in 1922 has been of great service, though many observers would limit its application to the periods before and after operation, regarding it as in no sense curative. Nevertheless, its early use, combined with other medical treatment, seems to have prevented a number of cases reaching the stage at which operation would have otherwise been inevitable. Operation for hyperthyroidism has grown greatly in esteem, but it must be emphasized that

the low mortality rates often quoted to-day are obtained only by those surgeons specially skilled in performing the operation, which in other hands still remains dangerous. It is interesting to observe that the operation has grown in favour, especially in cases in which cardiac decompensation, including auricular fibrillation, has developed—that is, in just those cases which were formerly regarded as outside the sphere of surgery. Here the results of operation are astonishingly good, and medical treatment alone cannot hope to stabilize such patients. The operation of election is subtotal thyroidectomy, although in highly toxic cases a preliminary ligation of the arteries to the gland is still practised. The method of anaesthetization of the patient is of great importance; G. L. Keynes recommends rectal avertin before the patient is moved from the bed, followed by local anaesthesia, and supplemented by gas and oxygen if necessary. The question of "toxic adenomata" has been much discussed, and it is generally agreed, following Dunhill, that they are not true new growths, but hyperthyroidic changes recurring in a previously damaged gland. It is better, therefore, to speak of such cases as secondary Graves's disease. The damaging effect of such a condition on the heart is explained by its occurrence in later life, when the cardiac reserve is not so great as in youth. It is certainly a striking fact that in earlier life a large, diffuse hypertrophy of the gland will injure the heart less than will a comparatively localized "adenoma" later on.

The role of the parathyroids in the metabolism of calcium and phosphorus has been satisfactorily determined, and the clinical entities of hypo- and hyper-parathyroidism have been established.

Valuable additions to our knowledge of the pituitary body have been made. The work of P. E. Smith, and of Evans and Simpson, has clearly shown its influence on growth (through the eosinophilic cells in the anterior lobe), on sex (through the basophilic cells in the same lobe), and on fat metabolism (through the associated action of the posterior lobe and overlying diencephalon). Cushing has demonstrated the close connexion between this gland and that part of the nervous system concerned with emotion.

The association and interactions between the pituitary and the gonads has been the subject of much research. The work of Dixon and Marshall deserves special mention. They showed the stimulating effect of oestrin on the secretion of pituitrin, and the opposing influence of the luteal hormone on this until the onset of parturition, when the corpus luteum begins to degenerate, releasing the oestrin with a consequent flow of the oxytocic principle into the cerebro-spinal fluid. Taking this in conjunction with other work, we may say that an anterior pituitary hormone stimulates the production of oestrin, which increases the secretion of the post-pituitary hormone, which in its turn stimulates uterine contraction. The introduction of the vaginal-smear test in rats has provided a method for the detection of oestrin, and has shown how widely distributed this hormone is elsewhere than in the ovary—for example, in the placenta and urine of pregnancy.

The work of Stewart and Rogoff has led us to attribute a larger share to the adrenal cortex in the pathology of Addison's disease, while Achard, Thiers, and others have added to our knowledge of the similarity of the virilizing effects of tumours of the adrenal cortex and of basophilic adenomas of the anterior pituitary.

The evidence for the existence of status lymphaticus as a clinical entity has been seriously criticized, and a more critical attitude has been adopted towards the indiscriminate use of polyglandular extracts without due consideration of the physiological principles involved, and the pharmacological evidence.

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THE PITUITARY

Although nothing was known of the function of the pituitary until 1895, when Oliver and Schäfer extracted an active physiological substance from it, it is now seen to be the leader of the endocrine orchestra. The anatomists of the past, looking at the brain enclosed in bone and joined by a narrow stalk to this small body similarly enclosed, formed the conception of a brain in miniature, which, as it were, responded to, or repeated the actions of, the big brain above. Modern research has shown that there is more in this idea than was supposed in the nineteenth century. Harvey Cushing said:

"No other single structure of the body is so doubly protected, so centrally placed, so well hidden [as the pituitary]. Here, in this well-concealed spot, almost to be covered by a thumb nail, lies the very mainspring of primitive existence—vegetative, emotional, and reproductive—on which, with more or less success, man, chiefly, has come to superimpose a cortex of inhibitions. The symptoms arising from disturbance of this ancestral apparatus are beginning to stand out in their true significance. The diencephalon is an ancient part of the brain which remains essentially unaltered in all creatures that have a brain at all. Moreover, it proves to have direct connexions with the first of the organs of internal secretion to become recognizably differentiated, and on which the very perpetuation of the species depends. Such primitive instincts as hunger, thirst, and sleep also seem to be mediated through this region. Cyclicity, which may be diurnal, lunar, or seasonal, is a peculiarity of many physiological processes, such as oestrus, menstruation, hibernation, and, indeed, ordinary sleep. That these processes are somehow under the control of the diencephalo-pituitary apparatus seems most probable. Recent investigations serve closely to relate the diencephalon to metabolic processes, to the primary emotions, and, lastly, to the sympathetic nervous system."

The Anterior Lobe

It has been known for a good many years that the anterior lobe of the pituitary contains eosinophil and basophil cells; it has also been recognized, clinically and experimentally, that this lobe is concerned both with growth and with sexual development.

Simmonds of Hamburg pointed out the frequency with which the pituitary may be affected by embolic processes in the course of septic infections. The symptoms naturally vary with the age of onset. If such an infarct occurs in childhood, and involves only the anterior lobe, the patient may show an extraordinary premature senility, as first described by Jonathan Hutchinson and later more fully by Hastings Gilford, under the name of "progeria," signifying premature old age. The "enfeebled old dotard of five" of the *Bab Ballads* must surely have been an example of this. Similar cases due to a failure in development of the adrenal cortex have also been reported. This is not the only instance in which similar symptoms may result from anterior pituitary and cortical adrenal lesions.

The Eosinophil Cells.—Evans and Simpson have been able to isolate from the eosinophil cells a hormone which is concerned with growth, and another from the basophil cells which is concerned with sexual development. Moreover, there is a definite antagonism between them, the growth hormone being capable of completely nullifying the other if both are simultaneously injected. That growth precedes sexual maturity is presumably due to the early predominance of the growth hormone. When the basophil cells are able to assert themselves over the eosinophil cells puberty occurs. The association between the eosinophil cells and growth is indicated by the coincidence of eosinophilous adenomas with gigantism or hemihypertrophy, if they develop before the epiphyses join up, and with acromegaly if they develop subsequently. Gigantism is sometimes quite partial—as in one finger. Beware of removing such local gigantisms; the operation has been followed by a gigantic growth of the whole limb. This has an interesting bearing on Susman's recent hypothesis as to the influence of over-activity of the anterior lobe in the causation of malignant disease.

The Basophil Cells.—The association between the basophil cells and sexual development is perhaps best illustrated clinically by certain cases of virilism in women. I have been particularly interested in the type described by Achard and Thiers as "diabetes of bearded women." There are six characteristics, of which only the first three are essential: (1) hirsuties on the face—masculine in type, with partial baldness of the frontal region; (2) obesity; (3) disturbed genital functions; (4) high blood pressure; (5) cutaneous striae; (6) glycosuria, or at least lowered carbohydrate tolerance. I have described cases presenting all these features, with increased basal metabolic rate in addition. In the cases collected and described by Achard and Thiers the necropsies, when obtained, generally showed adrenal or pituitary tumours. One such patient I saw had a basophilic adenoma of her anterior pituitary, another had a hypertrophy of both adrenal cortices. Here, again, we see the resemblance between the symptoms resulting from certain pituitary and adrenal lesions.

Evans found that a continuous administration of the sex hormone from the basophil pituitary cells leads to cessation of oestrus, as if it stimulated the ovary to the point of exhaustion. Rhythm is the essence of reproductive function; and this fact should be borne in mind in the clinical use of sex hormones.

Anterior Pituitary Hormones.—In a study of the anterior pituitary hormones carried out by Bugbee, Simond, and Grimes, it was found that of the eleven different properties ascribed to the secretion of this lobe, the property of growth could be clearly distinguished from the others and attributed to one hormone, while the chemical substances responsible for the remainder were closely similar in their general chemical properties. We shall not greatly err in regarding them as variants of one hormone. This clears the ground and enables us to say that the eosinophil cells produce the growth hormone, while the basophil cells produce a hormone which is responsible for the other activities of the lobe—the principal one being sex-activation.

The Chromophobe Cells.—But the anterior lobe also contains cells which resist staining—the so-called chromophobe cells. Their function is unknown; all we can say is that an adenoma composed of such cells actually diminishes pituitary function, but apparently only by direct pressure on the chromophil cells. The original cases of Fröhlich's syndrome were due to chromophobe adenomas. But a simple pituitary inadequacy can produce the syndrome, and, whether it is produced by a tumour or not, we shall see that more than the anterior lobe has to be involved. Many of the milder cases unassociated with a tumour show extraordinary improvement at puberty.

The Posterior Lobe

Of the two constituents of pituitrin—oxytocin and pitressin—the former stimulates contractions of the uterus, and can act under conditions which exclude nervous influences. As Dixon pointed out, it is remarkable that medical men in empirically using pituitary extract to stimulate uterine contractions should have adopted the method which Nature has employed from time immemorial. The secretion also seems necessary to involution of the uterus after parturition.

Vasomotor Effect of Pitressin.—Although this was the first pituitary function to be discovered, it has been rather overshadowed by that of adrenaline. Yet, of the two glands, the pressor effect of emotion would be more likely to be produced by the one so much nearer the emotional centres. Emotional explosion with an accompanying rise of blood pressure has recently been observed to occur in an animal whose cortical inhibitions have been removed by severing the nerve paths from the frontal cortex to the diencephalon.

Anti-diuretic Effect.—There was a tendency a few years ago to ascribe diabetes insipidus, not to the pituitary, but to the overlying diencephalon. While it is true that in some cases the diencephalon alone is damaged, and in others only the pituitary, it is highly improbable that corresponding effects should be produced by lesions in these two situations if there were no functional interaction between them. Many observations show that such interaction exists. Since the posterior pituitary produces an anti-diuretic hormone which will act on a denervated kidney, the logical conclusion would appear to be that, even when the diencephalon is responsible, it must act, not through a nervous, but through a chemical mechanism, and that this mechanism resides in the underlying pituitary.

Carbohydrate Metabolism.—Hyperpituitarism has long been known to be associated with a lowered carbohydrate tolerance, and not infrequently with glycosuria. Such glycosuria is usually intermittent, and during the intermission I have sometimes found the blood sugar curve completely normal, while during the glycosuric period it was distinctly raised. Here again the pituitary function shows a rhythmical variation.

Conversely, in hypopituitarism there is a raised carbohydrate tolerance. When insulin was discovered J. H. Burn soon showed that, as might be expected from these facts, it was antagonistic to pituitrin. Later, he showed that it was only the pitressin fraction which was involved; hence the lowered carbohydrate tolerance in hyperpituitarism.

Galactagogue Effect.—It is usually stated that this is merely due to a contraction of the muscles in the mammary ducts, but this would hardly account for three cases of pituitary tumour I have seen associated with lactation lasting seven, three, and two years respectively. I have seen this prolonged secretion cease promptly after the administration of corpus luteum.

The sharp bi-temporal headache sometimes suddenly experienced by a woman on putting the child to the breast appears to be due to the demand made upon the pituitary, and I have known it to be relieved by pituitary extract.

Fat Metabolism.—By the establishment of Fröhlich's syndrome attention was drawn to the association between pituitary lack and obesity. While it has recently been clearly proved that so-called pituitary obesity follows suprasellar damage (produced either by experiment or by diseases such as tumour or encephalitis), we cannot therefore exclude the secretion of the posterior pituitary from participation in this; far from it. Removal of the pituitary of a tadpole leads to a large and persistent fat organ. This fat persists, even after starvation, but is soon absorbed when pituitrin is injected. This accords with Coope's and Chamberlain's observation that pituitrin injections lead to an increase of fat in the liver (where it is metabolized), while the fat in the blood and peripheral tissues is diminished. From the close association between the gonads and the pituitary we can understand why castration or gonadal defects lead to obesity. But here again there is that blending of chemical and nervous mechanisms so characteristic of the pituitary. Although pituitrin injected into the cerebral ventricles is much more effective in promoting fat metabolism than when given subcutaneously, this action is abolished by severance of the nervous channels at any level between the pituitary and the liver, as well as by drugs which are supposed to paralyse the heat-regulating centres. It would also appear that fat metabolism in the liver, under the influence of pituitrin, has much to do with the maintenance of the body temperature. Raab is of opinion that any disturbance of the mechanism between the liver and the pituitary may lead to obesity.

THE DIENCEPHALO-PITUITARY APPARATUS AND THE EMOTIONS

That emotional expression springs mainly from the basal ganglia is well recognized. If cortical inhibition is removed, afferent impulses arriving here give rise to explosions of the "sham rage" described by Cannon and others. Clinically, we are only too familiar with the profound alterations in behaviour and emotional expression produced by lethargic encephalitis in this region.

The diencephalon is regarded by many as the head ganglion of the sympathetic nervous system; this renders intelligible the close association between emotional disturbances and an upset of the sympathetic nervous system. Again, the intimate ties between the basal ganglia and the leader of the endocrine glands through the diencephalon provides another association (this time of a chemical sort) between the emotions and the sympathetic-endocrine system. That endocrine disturbances and psychoneuroses should frequently coexist is therefore not surprising. It is not always easy, however, to determine which of the two is cause and which effect.

Since instinctive behaviour was originally directed by chemical tropisms, we can understand that the endocrine glands, which still manufacture chemical controls, will continue to influence such behaviour. We may consider the psychological changes associated with disturbances of the individual endocrine glands.

PSYCHONEUROSES AND THE THYROID

The necessity for thyroxine in the due maintenance of mental activity is well recognized. It has been one of the triumphs of thyroid medication that it has rescued many from mental hebetude, or worse, to a life of normal mental activity. The cretin is dwarfed in body and mind, but is curiously placid and adaptable, just as the sufferer from an excess of thyroid is irritable and intransigent.

Myxoedema.—The adult sufferer from thyroid defect—that is, myxoedema—is more likely to be conscious of failing powers, and is therefore apt to be morose and suspicious, referring internal difficulties to external causes, as we are all apt to do. More usually the mental attitude is one of resigned melancholy. Sometimes there are hallucinations of sight and hearing. But the patient with myxoedema may occasionally become acutely maniacal. On several occasions I saw a patient with myxoedema, and he improved very much on thyroid treatment. Then I lost sight of him, and I thought that, as he had now found the appropriate dose of thyroid extract, he was treating himself. But I found later that he had abandoned medical treatment to take up Christian Science. Perhaps this was the first sign of impaired mental balance, but at any rate he became violently maniacal, and was removed to an asylum. Here it was recognized that he was myxoedematous, but in view of his mania they did not venture to give him thyroid. However, as he did not improve at all in three weeks, they put him on thyroid, with immediate benefit. He soon became sane and able to give his medical history, and the superintendent communicated with me. He remained quite sane, dying some years later after an operation for gall-stones. I have heard of other similar cases.

But children and adults whose hypothyroidism falls short of cretinism or myxoedema may also have their mental state greatly improved by thyroid treatment. In daily life one so often meets people whose condition does not amount to actual disease, but proclaims aloud their need for thyroid.

The thyroid has been called "the gland of creation." Just as thyroid secretion is essential to reproductive activity, so it is needed for every kind of creative activity, mental or artistic. Some time ago Crichton-Miller asked if anyone had ever heard of a myxoedematous artist. Tredgold

replied by citing a cretin who was an artist of some repute at Zürich in the eighteenth century. But possibly he was really only an achondroplastic. Crichton-Miller has returned to his point, and has asked for cases of subthyroidic creators—be it of works of art or of children. It is of course true that a subthyroidic woman may have children after she has had thyroid treatment. He further maintains that child-bearing and artistic creation are mutually exclusive, the storehouse of creative energy being unable to cope with both kinds of creation. And I think that, though we find apparent exceptions to this rule, it is very rare for both kinds of creation to be simultaneously possible.

Hyperthyroidism.—Crile says: "I have never known a case of Graves's disease to be caused by success or happiness alone, or by hard physical labour unattended by psychic strain, or to be the result of energy voluntarily discharged." Sufferers from this condition are always irritable, and tend to be explosive. Thoroughly unreasonable, they regard themselves as the only righteous persons in a wicked and froward world. "O cursed spite, that ever I was born to set it right," is the burden of their lament. We have been reminded that Shelley had a hyperthyroid face. He certainly represented the hyperthyroidic temperament at its best. Of his creative genius there is no doubt, but in practical matters he beat his wings ineffectually against the bars of his cage. Indeed, his friend Hogg compared him with an albatross—magnificent in flight, but merely grotesque in captivity.

The sufferer from hyperthyroidism always experiences difficulty with her environment, which not only makes her "gey ill to live with," but which may precipitate her into actual insanity, with suicidal tendencies. The thyroid gland is apt to enlarge in nerve storms, while in the manic-depressive psychoses I have seen the excited phase accompanied by signs of an overactive thyroid, to be replaced by signs of underaction as the phase of depression comes on.

I am more and more impressed with the influence of emotion in the causation of Graves's disease, which is readily comprehensible in view of the sympathetic innervation of the thyroid gland. This is particularly likely to happen if the distressing emotion has a matrimonial origin, while it often adds considerably to the difficulty in detecting the cause, as this is not usually a matter of advertisement. Fear is another emotion which has a marked effect in exciting hyperthyroidism, as was well shown during the air raids on London. Russell Brain has recently shown that exophthalmos is due to an affection of the upper part of the mid-brain, and that no hard-and-fast line can be drawn between the exophthalmos of Graves's disease and that of a central nervous lesion. This adds one more link to the connexion between the emotional nervous system and the endocrines.

PSYCHONEUROSES AND THE PITUITARY

It is curious that many of the psychological accompaniments of pituitary disease are the same whether associated with excess or with defect of pituitary activity. In fact, usually we can only speak of the psychological effects of *dyspituitarism*. It is true that a well-developed anterior lobe is often associated with an imaginative force, which can be controlled and brought to the service of an active brain; the fortunate possessor is also often musical and, in short, a practical visionary. It is also true that sufferers from a minor degree of hypopituitarism compensate for it by persistent conscientious effort, often in excess of their physical strength. But both the pituitary giant and the Fröhlich tend to lack inhibitions. They may lie, steal, and commit offences in a foolish, pointless way; often it would seem, merely to attract attention. They try to compensate for their feeling of inferiority by a craving

for the limelight, and if they cannot achieve this with their social equals they seek for it from their social inferiors. They are very prone to fantasy-thinking, seeking a dream world in which to escape from this feeling of inferiority. In two of my recent cases (one in a girl of 17), the craving for a child led to fantasies of pregnancy. Another girl stole a gold watch from a schoolfellow, and on her return home for the holidays told her mother it had been given her as a prize for good conduct!

It has been pointed out to me that these symptoms are not uncommon in psychoneurotics without pituitary disease. From the close association between the glandular and nervous structures in this particular region it does not surprise me that pituitary disease should excite such typical reactions.

PSYCHONEUROSES AND THE ADRENALS

The adrenal medulla, from its activating effect on the sympathetic, is a fighting gland. And as the adrenal cortex tends to virilism, the owner of a well-developed pair of adrenals is a pugnacious and masculine type, with plenty of drive, not to say aggression. If the adrenals are defective, we see a weakening of all these characteristics, with a tendency for the vagus to get the upper hand, which may precipitate such things as asthma. If the adrenals are overactive, we find a liability to anxiety neurosis, and to phobias of all kinds. In such an individual the dominant emotion is *fear*.

I have recorded an extraordinary case in which a woman became terror-stricken, deploring a mysterious calamity which had fallen upon her. At last she confided to me that she felt as if she were turning into a man. This led me to look for an adrenal tumour, which was found and removed. Her case is of especial interest because the psychological changes were recognizable before the physical. Her terror I refer to the concomitant irritation of the adrenal medulla by the tumour.

These are but a few examples from a field of great interest, which offers opportunities for further research. For, as Pottenger says, "Between the vegetative and psychical systems a vicious circle is established, and each harmful stimulus in the one influences the other. Every disease-process of a serious nature, therefore, must have a psychical side to it."

BLADDER HEALING AFTER SUPRAPUBIC CYSTOTOMY ESPECIALLY IN PROSTATECTOMY*

BY

JAMES B. MACALPINE, F.R.C.S.

HONORARY SURGEON AND SURGEON IN CHARGE OF THE GENITO-
URINARY DEPARTMENT, SALFORD ROYAL HOSPITAL,
MANCHESTER

In spite of many methods and fancies, the post-operative healing of bladder wounds remains unsatisfactory, as is shown by the slow recovery from sepsis and the formation of sloughs, for whose separation much time may be required. As the only particular in which the suprapubic wound differs from any other surgical wound is contamination with urine, and as I hold that to overcome this is the key to improvement, may I inflict on you some personal views, believing that they present advantages sufficient to justify me in bringing them to your notice?

I propose to consider (a) the methods of wound treatment which are responsible for this soakage, (b) the results of urinary extravasation, and (c) to suggest improved methods. As the bladder is more frequently opened for transvesical prostatectomy than for other

* Based on a paper read before the Manchester Surgical Society in opening a discussion on the technique of prostatectomy.