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THE ENDOCRINE ORCHESTRA*

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For we are members one of another.—Eph. iv. 25.

Sir Walter Langdon-Brown (1931) was the first to write that "the pituitary is the leader in the endocrine orchestra." This phrase has been frequently misquoted, and not infrequently criticized. You will observe that he referred to "the leader *in* the endocrine orchestra," having in mind the pituitary as the first fiddle and not as the conductor. If we wish we may still reserve the rostrum and the baton for the hypothalamus. He was careful not to carry his picturesque analogy too far, and we shall be wise to follow his example. Aphorisms and analogies do something to decorate the plain face of science, and if they make the lady more attractive to the neophyte, then they serve their turn.

The metaphor was apposite enough in 1931 when Langdon-Brown first employed it. Smith (1930) had recently reported that the removal of the pituitary in the rat resulted in dwarfism and sexual immaturity, but that normal growth and development was restored by pituitary transplants. Evans and Simpson (1928) had isolated a growth hormone from the eosinophil cells. Harvey Cushing (1930) had just delivered the Lister Memorial Lecture in which he provided a group of clinical pictures which illustrated these results of animal research.

Langdon-Brown came to this new knowledge with a mind long prepared. In a fragment of autobiography which he wrote for his wife in 1932 he tells of his undergraduate work at Cambridge:

"In the Easter vacation I applied for permission to stay up and work at embryology by myself. I incubated hens' eggs, stopping their growth at different stages and laboriously cutting microscopic sections of the embryo in long ribbons and then mounting them on slides. Day after day, the whole day, hardening in preservatives, staining, cutting, mounting and then drawing my sections. The quiet, glowing happiness of it all comes back as I write. Gradually to see the brain, the backbone, the eyes, the heart forming themselves before my eyes. I could hardly tear myself away from this self-imposed task. I can still recall the thrill as I saw—what had not then been described—the pituitary arising like a nephridium which, according to a theory I was already formulating, it ought to do. I remember drawing a diagram on the laboratory benches before a group of fellow students to illustrate the idea of the evolution of the ductless glands (whose functions were then quite unknown) which was surging in my brain."

Langdon-Brown's intellectual range, both inside and outside medicine, was unusually wide, but in the twin

fields of the autonomic nervous system and the endocrine system he maintained a constant interest. He was always fascinated by the influence of the emotions on these two systems, and in the last twenty years of his life he was very occupied with the importance of psychological factors in the production of physical ill-health. When I was asked to deliver this Langdon-Brown Lecture I was therefore naturally attracted by the subject of the influence of emotional factors on the control and function of the endocrine system. Experimentalists have, however, in this generation been mainly concerned with the hypothalamus, the pituitary, and the hormones themselves, and a relatively small amount of time has been given to the exploration of the extensive neural connexions of the hypothalamus with the cerebral cortex, the basal ganglia, and the thalamus. New analytical techniques are now being developed (Mason, 1959) which will eventually map out this enormous field, and, although the early results undoubtedly indicate that these higher centres have a profound effect in modifying hormonal output, I decided that it would be premature to try to review the relations of the nervous system with the endocrine system. I must hope that some successor of mine in the Langdon-Brown Lectureship will embrace an opportunity which no one would have seized more eagerly than Langdon-Brown himself.

There is, however, one area of the brain outside the hypothalamus in which hormonal control has been shown to be located, and this is the posterior diencephalon-pineal region. Gordon Farrell (1959, 1960) and his colleagues, by a series of comprehensive and brilliant researches, have established that this area secretes a hormone (first called "glomerulotrophin," but now named "adrenoglomerulotrophin" in response to the protests of sensitive nephrophils) which controls the secretion of aldosterone from the zona glomerulosa of the adrenal cortex. Destructive lesions in the mid-brain of cats show that a large area, lying inferior to the central grey substance and between the substantia nigra on both sides, is concerned with the regulation of aldosterone production. Experiments with extracts of beef brain have, however, demonstrated that the pineal gland produces the most potent extract in the production of aldosterone from the zona glomerulosa of the adrenal cortex. Further research is suggesting that there is also an inhibitory component in the pineal complex (Farrell, 1960). Langdon-Brown would have been fascinated by this new-found function for the pineal

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gland, for he often referred (1922) to Gaskell's conclusion that the pineal gland was all that remained in the higher vertebrates of the pair of median eyes in arthropods, one of which exists still in the larval lamprey, the immediate ancestor of the lowest vertebrates. How delighted, too, he would have been by Farrell's speculative comment in the discussion at the Laurentian Hormone Conference of 1958:

"The pineal organ has been regarded by some embryologists as a degenerate eye. I wonder if this organ is an electrolytic receptor of some kind? I think it would be a most intriguing study. Simple forms of aquatic life might have need for an 'eye' which can detect the sodium content of the water. You can imagine such an animal swimming along the shore and coming to a fresh-water stream in which he isn't prepared to live. An electrolyte-sensitive structure may detect the fresh water, and the animal goes the other way. On the other hand, if he wants to go into fresh water he'll know where to go. It would be a lot of fun to study this; it sounds as though it's worth a summer at Wood's Hole." (Farrell, 1959.)

Langdon-Brown continued throughout his life to relate his biological knowledge to the development of the endocrine system. He wrote on one occasion: "The mesomatic coxal glands of the arthropod ancestor gave rise to the thyroid, parathyroids and thymus . . . the thymus arising from the dorsal side of the gill slit, and the parathyroids from the ventral side" (Langdon-Brown, 1922). He would have been happy to read of the support which his nephew, Sir Geoffrey Keynes (1954), has given to the theory of an endocrine activity for the thymus.

I shall consider now what has been learnt of the control of the anterior pituitary hormones by the hypothalamus, mentioning first the portal system of the hypothalamus and the hypophysis.

Hypophysial Portal System

Harris (1955) has been foremost in maintaining that the hypophysial portal system carries humoral substances from the hypothalamus which regulate anterior pituitary activity. This hypothesis is now generally accepted. The anterior pituitary, like the liver, has not only an arterial blood supply and venous drainage but a portal system also. These portal vessels take origin in the median eminence of the hypothalamus as a primary plexus of capillaries which join together to form small trunks that run down the infundibular stalk to the anterior pituitary.

Sections of the pituitary stalk which divide the portal vessels result in atrophy of the target glands—gonads, thyroid, and adrenal cortex—and when the portal vessels regenerate there is a return of pituitary function.

Nikitovich-Winer and Everett (1958), working in Harris's laboratory, have made the crucial experiments. They transplanted the anterior pituitary under the capsule of the kidney, and then, after some weeks, placed it under the median eminence of the hypothalamus. When the transplant was again well vascularized by the portal vessels, activity was largely restored to the atrophied endocrine organs. When a similar graft was placed beneath the temporal lobe endocrine function was no better than it had been when the graft was in the kidney.

Hypothalamic Control of the Anterior Pituitary

The hypothalamic control of the anterior pituitary has been investigated in many animals by three

experimental techniques. In the first, the pituitary is transplanted, as we have seen, to other sites in the body, such as the eye and the kidney; in the second, destructive electrolytic lesions are selectively placed in different regions of the hypothalamus; and, in the third, various areas in the hypothalamus are stimulated by unipolar or bipolar electrodes left in position for several weeks. In all these experiments the results are usually assessed, not by direct measurement of the trophic hormones from the anterior pituitary, but indirectly by changes in the target organs.

The object of the transplanting experiments is to define the degree of dependency of the five trophic hormones—follicle-stimulating hormone (F.S.H.), luteinizing hormone (L.H.), prolactin (L.T.H.), thyrotrophic hormone (T.S.H.), and adrenocorticotrophic hormone (corticotrophin; A.C.T.H.)—on the hypothalamus. A complex pattern of hypothalamic control emerges. The secretion of L.T.H. by the pituitary is autonomous, and it proceeds in regular fashion when separated from the hypothalamus (Everett, 1954, 1956). The secretion of the two other sex trophic hormones, F.S.H. and L.H., is entirely dependent on hypothalamic regulation (Harris, 1955; Greer, 1957). Thyroid function is greatly reduced, but a little autonomous activity remains (Brown-Grant *et al.*, 1957). The adrenals atrophy, but they still respond to what have been called "metabolic" stresses, such as laparotomy or the injection of adrenaline (Greer, 1960). We can summarize this experimental evidence in this way. For the regular delivery of the trophic hormones, with the exception of L.T.H., some hypothalamic agency is required.

Destructive lesions and electric stimuli have been used to discover the sites of hypothalamic control. Lesions in the median eminence, just above the infundibular stalk, cause gonadal atrophy, while in the anterior hypothalamus they produce an increased secretion of F.S.H. So that two areas for F.S.H. control are postulated, the one stimulating and the other inhibitory (Harris, 1960). Conversely, stimulating electrodes applied to the median eminence cause an increased secretion of L.H., while a destructive lesion in the anterior hypothalamus produces a diminished output of L.H. (Harris, 1960). For these reproductive trophic hormones, entirely dependent as they are on the hypothalamus for their release, there are then two centres—the one for braking, and the other for acceleration. This dual control has not yet been demonstrated for the other two trophic hormones, A.C.T.H. and T.S.H.

Let us assume that high levels of circulating oestrogen depress the stimulating centre, or excite the inhibitory centre, in the hypothalamus. What then passes down the portal vessels to the anterior pituitary to depress the release of F.S.H.? Is it a higher concentration of oestrogen than is already reaching the anterior hypophysis through the systemic arteries? Is the humoral agent an oestrogen, with some changed protein binding? Is there some other hormone secreted by the hypothalamus, specific for one trophic hormone, or common for several, such as vasopressin, which lies ready in the median eminence to play such a part? (For the hormones of the neurohypophysis, unlike those of the adenohypophysis, are actually produced in the hypothalamus.)

These questions which I have just posed for the gonadotrophins have been debated, too, for thyrotrophin. Harris and Woods (1958) have produced

evidence that vasopressin may act as the neurohumoral transmitter for thyrotrophin release, while Brown-Grant (1960) has suggested that the hypothalamus might act as a filter for thyroxine so that the anterior pituitary would receive blood of varying hormone content and respond by increasing or diminishing its output of T.S.H. This hypothesis has been adopted and extended by Purves (1960), who suggests that in the median eminence of the hypothalamus, or in the pituitary stalk, thyroxine is either destroyed or bound in a form which is relatively ineffective in releasing T.S.H. in the anterior pituitary.

It would have been pleasant to produce a less complex and better-defined account of the hypothalamic control of the anterior pituitary hormones. The brilliant experimental work outlined here has been done in the short space of ten years, and it is now possible to see that when the final picture emerges, although clarification will have been achieved, simplification is hardly possible. The experimentalist, engaged in constructing hypotheses and in devising experiments which may support or rebut them, must now and again be astonished that mechanisms so complicated are contained in an area so small as the hypothalamus.

The Ten Cerebral Hormones and Their Regulating Mechanisms

Most of us carry in our minds the simple notion of a servo feed-back mechanism which controls the relationship of the anterior pituitary and its target organs: "I ask for more, I get more; I need less and less is provided." More thyroxine is circulating and less thyrotrophin is secreted; less thyroxine is circulating and the output of thyrotrophin rises. This rigidity of homeostasis is well suited to the constantly changing needs of the body, but it appears to be easily overthrown. For example, emotional stress in the rabbit causes a decreased output of thyroxine, and prolonged exposure to cold an increased thyroid activity, and neither of these effects is corrected by an altered output of T.S.H. (Brown-Grant, 1960). A similar situation occurs in disease, when the feed-back mechanism is transcended and the increased output of target hormones in Cushing's disease, and in thyrotoxicosis, is uncontrolled by the trophic hormones.

The feed-back mechanism does, however, exist, and the experimentalists have set themselves to answer the question: Where and how does it operate? The answers are not simple. The methods used are the injection of the target hormone, or the grafting of a fragment of the target gland, in the anterior pituitary or in selected areas of the hypothalamus. Ovarian fragments placed in the region of the paraventricular nuclei (anterior hypothalamus) reduce uterine weight, but they have no effect when placed in the anterior pituitary (Flerkó and Szentágothai, 1957). Oestrogen, which depresses F.S.H. output, stimulates the release of L.H. No feed-back mechanism is known for L.T.H.

Thyroxine is equally effective in suppressing the output of T.S.H., both in the anterior hypothalamus and in the anterior pituitary. It is probable that cortisol, too, operates both in the hypothalamus and in the pituitary to regulate the secretion of A.C.T.H., though this is still uncertain.

It should be remembered, here, that the production of other hormones is subject to different methods of regulation. The output of vasopressin is probably

controlled both by the osmotic pressure of the plasma and by its volume (Van Dyke, 1960), while the stimuli for the production of adrenoglomerulotrophin, which regulates aldosterone excretion, include sodium depletion and a reduction in volume of body fluid (Bartter *et al.*, 1959). Growth hormone has not been included in this account, for we know nothing of its regulation.

I have summarized in Tables I and II what is known of the site of formation of these hormones—pituitary, hypothalamic, and pineal; the method of their regulation—nervous, chemical, or physical; and either their regulatory sites or their sites of action.

I have divided these hormones into two groups: in the first, those in which a feed-back mechanism from a target organ is established; and, in the second, those in which no feed-back mechanism has been established, and in which it may be assumed that the regulation of the rate of hormone production operates at the site of formation of the hormone. The unknown regulatory influences in the second group are nervous, chemical, and physical. Such additional mechanisms, as we have already seen, may operate also in the first group, and may indeed supersede the feed-back mechanism.

In Table I are included the trophic hormones with a feed-back mechanism, controlled by oestrogen, cortisol, or thyroxine, and all are formed in the anterior pituitary. The place of regulation is the hypothalamus in the case of the sex trophic hormones, and both the hypothalamus and the anterior pituitary in the case of T.S.H. and possibly also for A.C.T.H.

TABLE I.—*Cerebral Hormones With a Feed-back Mechanism*

Hormone	Site of Formation	Regulatory Mechanism	Site of Control
A.C.T.H.	Anterior pituitary	Cortisol	Anterior pituitary and (?) hypothalamus
F.S.H. L.H. (I.C.S.H.)	" "	Oestrogen, progesterone, androgen	Hypothalamus
T.S.H. "	" "	Thyroxine	Anterior pituitary and hypothalamus

TABLE II.—*Cerebral Hormones Without a Feed-back Mechanism*

Hormone	Site of Formation	Regulatory Mechanism	Site of Action
L.T.H. "	Anterior pituitary	Nervous	Breast, corpus luteum
Growth hormone	" "	?	All somatic cells
M.S.H. "	Pars intermedia	?	Skin
Oxytocin "	Hypothalamus	Nervous	Breast, uterus
Vasopressin "	" "	Plasma volume and osmotic pressure	Arterioles, renal tubules
A.G.T.H.	Pineal	Plasma sodium and volume	Adrenal cortex (zona glomerulosa)

In Table II are included the hormones without a controlling target hormone. Two, L.T.H. and the growth hormone, are formed in the anterior pituitary; one, the melanocyte-stimulating hormone (M.S.H.), is formed in the pars intermedia; two, vasopressin and oxytocin, are formed in the hypothalamus and stored in the posterior lobe of the pituitary; and one, adrenoglomerulotrophin (A.G.T.H.), is formed in the pineal gland. L.T.H. production appears to be controlled by nervous mechanisms, and its action is on the breast and the corpus luteum; the control of the growth hormone is as yet unknown, but is likely to be chemical, and its action is on somatic tissues; the control of M.S.H. is unknown, and its action is on the melanophores of the skin. The regulation of oxytocin

production is by nervous mechanisms, and its action is on the breast and the uterus. The regulation of vasopressin is by physical mechanisms, and its sites of action are the renal tubules and the arterioles. I have assumed that A.G.T.H. production is controlled by chemical and physical mechanisms, and not by the output of aldosterone which it stimulates, its site of action being the zona glomerulosa of the adrenal cortex.

There are, then, ten known cerebral hormones; in four of them a feed-back mechanism has been demonstrated; in four their rate of output appears to be regulated by nervous, chemical, and physical influences; and in two the regulatory mechanism is unknown.

Cellular Origin of the Anterior Pituitary Hormones

Six hormones are formed in the anterior pituitary, and one of the puzzles about the histology of that organ has been that, in the past, only three types of cells were identifiable—acidophil, basophil, and chromophobe—and the last of these was regarded as inert. The introduction of periodic-acid-Schiff (P.A.S.) stains, with several modifications, has gone some way to solve these difficulties. P.A.S. stains carbohydrate in fixed tissues. Growth hormone and L.T.H. are simple proteins, and might be expected to be formed in P.A.S.-negative cells—and these are still the acidophil cells of the old nomenclature. F.S.H., L.H., and T.S.H. are glycoproteins, and the cells which produce them might therefore be expected to be P.A.S.-positive. A.C.T.H. is a polypeptide, but, since by clinical correlations it appears to be derived from P.A.S.-positive cells, it is suggested that it may have a carbohydrate-containing complex, but I have not been able to discover any chemical evidence for this suggestion. These P.A.S.-positive cells are the basophil cells of the old nomenclature, and types are variously described by different authors which may be the source, again by deduction from their disappearance or hyperplasia in different clinical states, of the sex trophic hormones, and T.S.H. and A.C.T.H.

The diagram shows the tentative scheme produced by one group (Ezrin *et al.*, 1958, 1959; Swanson and Ezrin, 1960). The small chromophobe cell is the stem cell, the acidophil cell (alpha) is the source of L.T.H. and growth hormone; two P.A.S.-positive (the red beta and the blue-purple delta) cells are the source of

Normal anterior-pituitary-cell types stained by iron-P.A.S. technique. (From a diagram provided by Dr. Calvin Ezrin.)

A.C.T.H. and T.S.H. and of the sex trophic hormones respectively; and the large lightly staining chromophobe, the gamma cell (which is the amphophil cell in Russfield's nomenclature) (Russfield *et al.*, 1956), is now regarded as an actively secreting cell from which all hormones may be formed. The most interesting suggestion for clinicians which emerges from these investigations is that the chromophobe adenoma is not the inactive tumour which it was formerly thought to be, but an adenoma in a state of ineffective activity—a new hypothesis which correlates well with recent clinical observations.

The long-continued state of endocrine deficiency which often precedes the recognition of a chromophobe adenoma has puzzled clinicians. A woman patient of mine (Hubble, 1952) presented with impairment of visual fields at the age of 51, which was proved to be due to a large chromophobe adenoma. The endocrine associations of this tumour had been present for 40 years, for she had never menstruated and her height was 4 ft. 9 in. (145 cm.). Jefferson (1957) has suggested that these chromophobe adenomas develop because of an inability of the cells—what would be called to-day a defect in biosynthesis—to manufacture and appropriate trophic hormones. Van Wyk and Grumbach (1960) suggest that these chromophobe adenomas may develop in response to a failure of the target hormones. Either of these mechanisms may be operative, but where there has apparently been a very early failure of the growth and sex trophic hormones the Jeffersonian hypothesis provides an interesting and rational explanation, yet to be proved.

These modern descriptions, then, include five cell types, and, of these, three cells are each storing two hormones. It could be expected that two hormones derived from one cell might result in some overlap of function; or, alternatively, that when the cell was called upon to produce an excess of one of its trophic hormones the other might be deficiently formed. An example of the overlap in function is seen in the case of L.T.H. and the growth hormone, both of which are recognized in animals to have "mammogenic" and "galactopoietic" functions; and in man the not infrequent occurrence of galactorrhoea in association with acromegaly may be an illustration of this dual hormone effect.

There are several examples, too, both experimental and clinical, which may indicate a reversed relationship between the production of A.C.T.H. and T.S.H. This alternating production of T.S.H. and A.C.T.H. has been studied by Brown-Grant *et al.* (1957) in rabbits. The rabbit responds to experimental procedures known to increase the discharge of A.C.T.H. from the pituitary by decreasing thyroid activity. The thyroid response to stress is "thought to be due to a decrease in T.S.H. secretion coincident with the increased secretion of A.C.T.H. and perhaps consequent upon it" (Brown-Grant, 1960).

Interhormonal Relationships

There are many complex physiological relationships between the hormones, to which much attention has been given but with which I have not time to deal, such as the influence of the adrenal cortex on the sex hormones, the interaction of F.S.H. and L.H., and the synergistic effects of thyroxine and the growth hormone on growth.

Some hormones have overlapping actions, and these have recently been satisfactorily explained by the chemists. Oxytocin and vasopressin have long been known to have common pharmacological qualities, and it has now been shown that both are cyclic octapeptides whose only structural difference is in two amino-acids (Lerner *et al.*, 1960). The pigmentation which occurs in conditions in which excessive quantities of A.C.T.H. are secreted, such as Addison's disease and congenital virilizing adrenal hyperplasia, has now been proved to depend on the fact that melanocyte-stimulating activity is built into the corticotrophin molecule—there are 13 common amino-acids in the molecules of A.C.T.H. and M.S.H. (Li, 1957; Hudson, 1960).

There are, however, many pluriglandular syndromes occurring in man which cannot be explained by the near-chemical identity of pituitary hormones. Examples of these syndromes are the coexistence of thyrotoxicosis and diabetes, of thyrotoxicosis with Addison's disease, of acromegaly with thyroid and adrenal enlargement and galactorrhoea, of hypogonadism with thyrotoxicosis, of puberty in boys with gynaecomastia, of Klinefelter's syndrome with thyroid and adrenal adenomas, and of hypothyroidism in girls with precocious puberty and galactorrhoea. Considerable interest has also been aroused recently by syndromes in which multiple endocrine adenomas are present. The pituitary adenomas which develop after ablation of the adrenals may give rise to pluriglandular syndromes.

It is possible to speculate concerning the mechanisms involved, but we cannot hope, for example, to explain with certainty the not infrequent occurrence of thyrotoxicosis with Addison's disease until we understand the aetiology of both these disorders, and until routine assays of thyrotrophin and corticotrophin are generally available. As we have seen, Brown-Grant postulates in experimental animals an inverse ratio in the output of A.C.T.H. and T.S.H. which could be held to explain these phenomena in man. Of 538 patients seen at the Mayo Clinic (McConahey *et al.*, 1960) during 1913–58 suffering from Addison's disease, 16 (3%) had Graves's disease either before, during, or after the onset of Addison's disease. In 12 of the 16 patients Graves's disease appeared some time before the Addison's disease was apparent.

Van Wyk and Grumbach (1960) invoked the explanation of a "pituitary overlap" to account for the presence of precocious menstruation, galactorrhoea, absence of pubic hair, and enlargement of the sella turcica in three hypothyroid children aged 7, 8, and 12 years. All these abnormal signs disappeared with thyroid therapy, and the size of the sella turcica gradually reverted towards normal. The authors suggest that hyperplasia, and possibly adenoma, of the anterior pituitary existed in their patients, and associated with the presumed high output of T.S.H. there was an overlapping secretion of gonadotrophins and mammatrophic hormones. In a patient of mine—a cretin aged 25—there was overdevelopment of the penis, testes, and scrotum, again without any growth of pubic hair (Hubble, 1955).

This pituitary overlap could be explained by the non-specificity of the neurohumoral mediator coming down the portal vessels from the hypothalamus so that more than one anterior pituitary cell is stimulated to activity, a true hyperpituitarism (Hubble, 1955). In some of

these syndromes the explanation may lie in the hyperplasia of the large gamma or amphophil cells which both Russfield and Ezrin believe to be capable of producing all the anterior pituitary hormones.

It might be expected that when the hormones which have a universal effect on cellular metabolism and growth—such as thyroxine and the growth hormone—are present, in deficiency or in excess, some evidence of this would be discovered in the function of other endocrine glands. This is becoming increasingly apparent.

For example, in hypothyroidism there is sometimes defective adrenocortical function as tested by urinary output of 17-OHCS and by A.C.T.H. stimulation (Hubble, 1955). Although conflicting reports have been published concerning the effect of thyroxine lack on the adrenal cortex, recent evidence establishes it beyond doubt (Felber *et al.*, 1959). Thyroxine deficiency may also affect pituitary function—myxoedema of the pituitary. The secretion of A.C.T.H. is reduced or deranged (Felber *et al.*, 1959), and the output of T.S.H. has occasionally been reported to be low and to be restored to normal or high levels by thyroxine therapy (Gilliland and Strudwick, 1956; Di George *et al.*, 1957). In the male cretin to whom I have already referred there was no gonadotrophin output in the urine when he was admitted to hospital, but with thyroxine therapy the output increased slowly to 6, 16, and, finally, to 18 mouse units/24 hours.

A more specific effect of growth hormone on the endocrine system will be no more than hypothetical until assays of growth hormone and treatment with human growth hormone are more readily available. Judging by the effects of acromegaly on the endocrine organs it is reasonable to suppose that the growth hormone has some effect on the parathyroids, the pancreas, the thyroid, the ovary, and the adrenal cortex. Harrison and Russell Fraser (1960) have advanced the theory (and given their reasons for believing it) that multiple endocrine adenoma syndrome (pituitary, parathyroid, and pancreas) is caused by an increased secretion of growth hormone. Dwarfs who are assumed to have a deficiency of growth and sex hormones—congenital hypopituitary dwarfism—may ultimately develop mild signs of hypothyroidism and hypoadrenocorticism (Hubble, 1957; Martin and Wilkins, 1958). I think this partial defect of the thyroid and the adrenal cortex may not be directly due to a defective production of T.S.H. and A.C.T.H., but may result from a lack of stimulation of these glands by the absent growth hormone.

I have suggested explanations for these pluriglandular syndromes, some now proved, others hypothetical. It will not be long, so concentrated is the work of endocrinologists and the chemists, before we have explanations for all of them based on fact.

The Parallel and the Model

It could be claimed that, while the organization of the endocrine system is more complex than that of the other systems (with the single exception of cerebral organization, of which we know comparatively little), our understanding of its working, though very incomplete, is yet more advanced than our knowledge of many somatic functions. Even such a cursory review as I have been able to make of the control and balance of endocrine mechanisms has given some idea of their

complexity. It may seem derisory, then, to return to Langdon-Brown's parallel of the orchestra as a model for the endocrine system. As a biological analogy, however, it has some meaning for us. An orchestra is a group of individuals harmoniously loyal to their higher control and playing with a common purpose towards a common end—the best possible interpretation of the piece of music in front of them. In the endocrine system is a group of individual organs, with much more complicated relationships and with controls which, although complex, are yet unified, working with a common purpose towards a common end—the maintenance of homeostasis in the body.

I have looked in human affairs for a more appropriate analogy than the orchestra, but I have failed to find one. Man's social, political, and industrial organization, though a growth of many thousands of years, is but an embryo in biological evolution in comparison with the endocrine system. We may conclude, then, that, far from any of man's affairs providing an exact parallel for the endocrine system, the mechanisms of the endocrine system provide a model for man.

Langdon-Brown in his Maudsley Lecture delivered in 1936, and reprinted in his fine book of essays entitled *Thus We Are Men* (1938), discussed the biology of social life. He defined three phases of man's social evolution. In the first, individuality is at a discount and the community is held together by taboo and fertility rites. In the second phase, individualities develop and religious belief is towards individual salvation and personal immortality. We have not yet emerged into the third phase, in which the community works consciously, not instinctively as do the bees and the ants, and not without purpose aforethought as does the endocrine system, towards a common good. Langdon-Brown would have seen it as ironical, and yet not without hope for mankind, that the first hint of this conscious co-operation should have been, not for a common good, but for the avoidance of a common evil—the total destruction of man itself.

We would salute Langdon-Brown across the years as a devoted servant of this College, a fine physician, and in his time a pioneer of medical thought—and I part from him with this valedictory sentence which he chose for himself, "The life to which I belong uses me, and will pass beyond me, and I am content."

I am grateful to those who, by their discussions, have given me help in the preparation of this lecture. They include Dr. K. Brown-Grant, Dr. Calvin Ezrin, Dr. Melvin Grumbach, Professor G. W. Harris, Dr. R. L. Holmes, and Dr. Anita Mandl.

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MENTAL HOSPITAL INS AND OUTS

A SURVEY OF PATIENTS ADMITTED TO A MENTAL HOSPITAL IN THE PAST 30 YEARS

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In 1957 Brill and Patton reported that between March, 1955, and March, 1956, there had been a fall of 452 in the population of the New York State mental hospitals. Since a steady rise of 2,000 patients a year had been expected to continue, this fall excited much interest. In 1959 the same authors showed that the decline had continued in the next three years by 453, 1,218, and 1,988 patients respectively, out of a total mental hospital population of 90,000. Kramer and Pollack (1958) were able to confirm that the decrease in 1956 was not confined to New York and that it was common to 39 of the 48 States. In that year there was a total drop of 7,400 in the mental hospital population of the United States. By the end of 1957 a further fall of 3,200 had been recorded.

Experience has been similar in England and Wales. The Annual Abstract of Statistics (1960) shows that the decline also began in 1955 and that by the end of 1959 there were about 15,000 fewer patients in mental hospitals than at the end of 1954, when a peak of 148,600 was reached. This fall had occurred despite a rising number of admissions. The decline has upset the calculations of the more gloomy prophets—for example, Norris (1959), who expected the mental hospital population to rise to 159,000 by 1960.