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THOMAS ADDISON AND THE BACKGROUND TO CORTISONE*

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Naturally I was greatly honoured at the invitation to be the fifth Addison Memorial lecturer in this hospital, but the occupation of this distinguished position is a heavy responsibility for one who, like myself, is not a medical doctor. In fact, some might expect little in common between a biochemist and Thomas Addison, who, to quote Sir Henry Dale, was "second in that matchless succession of physicians and morbid anatomists—Richard Bright, Thomas Addison, William Gull, and Samuel Wilks—whose work at Guy's Hospital in the earlier and middle years of the nineteenth century raised to such heights the reputation of this school as a great centre of medical teaching and investigation, and contributed so much to the foundation of the great nineteenth-century tradition of advancing medical knowledge by the accurate study and differentiation of diseases in the clinic, closely linked with an equally thorough scrutiny of their results as seen after death." But it is a just tribute to the memory and the widespread influence of Thomas Addison that at the present time chemists and biochemists as well as physicians are still actively tending the development of that enormous oak which has grown from the acorn that Addison unobtrusively planted in Guy's Hospital in 1855.

Influence of Addison's Work

The isolation and synthesis of cortisone and the recognition of its widespread therapeutic value are but one example of this. It is perhaps no exaggeration to say that the whole of biological science has felt the influence of Addison's labours. But as we look back across the activities of nearly 100 years it is surprising to observe what little immediate effect, particularly in this country, arose from the publication of Addison's short monograph of 1855 entitled *On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules*. This monograph will doubtless be familiar to all those interested in Addison's life and work, but I may recall that in it he writes: "The leading and characteristic features of the morbid state to which I would direct attention are anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and peculiar change of the colour of the skin, occurring in connexion with a diseased condition of the suprarenal capsules." Undoubtedly

Addison's interest in and knowledge of dermatology played an important part in his investigation of what he describes as a "dingy or smoky appearance of the skin," which might also show "various tints or shades of deep amber or chestnut brown." Equally well his interest in pathology in general, and in morbid anatomy in particular, together with an acute ability to appreciate relationships which had previously escaped recognition, was an essential factor in his outstanding success.

Addison's monograph is mainly devoted to the reports of eleven cases, these being given in the language and style of their respective reporters. Subsequent comment has thrown doubt on the validity of the inclusion of some of the cases published by Addison—especially those in which only one adrenal was diseased—and Addison's own loyal friend and pupil, Sir Samuel Wilks, accepted only four of these eleven cases. Nevertheless Addison's acute observation and intuition were not at fault in his main contention, although we must agree that he proved nothing that would satisfy the critical comment of a modern statistician. I do not wish in any way to underrate the immense importance of statistical analysis in science, but I believe that the incautious and unjustified application of statistical methods to many discoveries of significance in the history of science and of medicine might have resulted in their immediate suppression.

Assessment of His Discovery

The world of biology, and particularly of medicine, rarely displays the mathematical regularity and platonic perfection that allows a statistician to assess the significance of the result of the small number of observations that alone are often possible. Addison based his discovery on eleven cases, some of which are doubtful. Pierre Marie in 1886 based his diagnosis of acromegaly on two cases of his own together with five previously reported under other names. In both instances the discoveries were completely confirmed and of the greatest importance despite their lack of statistically sound support. While, of course, we should co-operate with statisticians, and take advantage of the powerful tools which they have to offer when their application is appropriate, let us not be frightened into believing that observations which do not yield significant "standard errors" or "coefficients of correlation" are therefore useless. The importance of Addison's fundamental observations

*The fifth Addison Memorial Lecture, delivered at Guy's Hospital Medical School on July 5.

can always encourage our independence of thought in such matters.

But it was not statistics that caused Addison's contemporaries and successors to debate the question of Addison's disease (an eponym first applied by Trousseau in Paris in 1856) so vigorously and for so long. Addisonian anaemia and Addison's disease were somewhat entangled in people's minds, and in the notes which appeared in the reprinted collected papers of Thomas Addison, totalling 13 in all, published in 1868 under the editorship of Drs. Wilks and Daldy, the editors note that "anaemia and Addison's disease are not pathologically connected." They also write at this time, "Like most other great discoveries the full recognition of its [Addison's disease] importance has been slowly adopted, and the progressive investigation of its clinical nature languidly prosecuted . . . even now it does not find a place in the nosology of some writers."

Addison himself appears first to have considered that the chain of symptoms observed depended not so much on the nature of the lesions of the suprarenal capsules as upon interference with the function of these glands, even though, as he frankly admits, their action and their influence on the general economy were almost or entirely unknown. But in this he was moving against the current of the times. It was the fashion to explain matters on the basis of reflex nervous action, and the heyday of the chemist, with his hormones and his humoral transmitters, had still to come. As the late Sir Frederick Gowland Hopkins (1938) wrote, "Up to near the end of the last century nearly every expert looked to the influence of the nervous system alone as concerned with the co-ordination of functions in the body; the conception of chemical regulation and co-ordination had achieved no place in the minds of the majority."

Addison himself was uncertain on these matters, and he is reported to have said in a discussion of the Royal Medical and Chirurgical Society in 1858: "We know that these organs [suprarenals] are situated in the direct vicinity and in contact with the solar plexus and semilunar ganglia, and receive from them a large supply of nerves, and who can tell what influence contact of these diseased organs might have on those great nerve centres and what share that secondary effect might have on the general health and in the production of the symptoms presented?" (Rolleston, 1936). Even as late as 1882 it was stated by J. F. Goodhart that Addison's disease was not due to any special morbid change in the adrenal glands alone, or to such changes *per se*, but to chronic inflammation spreading to and strangulating the abdominal sympathetic.

Growth of an Idea

The idea that health and even life depend upon the liberation of minute amounts of chemical substances into the blood stream by diminutive organs is now so widely accepted that it is perhaps difficult to put oneself in the position of those in the middle of last century to whom such an idea was not only novel but almost incredible. In order to trace the growth of this idea, leading as it does to cortisone and its congeners, we must first consider some aspects of the development of endocrinology before and during the last century.

Long before 1800 there were hints of the concept of internal secretions. Thus Richard Lower, in 1670, disagreeing with the ideas of Galen and of Vesalius that

the pituitary gland discharges pituitia (that is, phlegm or mucus—the waste material from the brain) through the infundibulum into the nasopharynx, wrote: "Whatever serum is separated into the ventricle of the brain and issues out of them through the infundibulum to the *glandula pituitaria*, distils not upon the palate but is poured into the blood and mixed with it." Théophile de Bordeu is often given the credit for the general concept of internal secretions, this ascription being based on the comment in his *Récherches sur les Maladies Chroniques* (1775) that each organ gives off emanations which are necessary and useful to the whole body. Bordeu's views, however, were not based on experimental or observational evidence, and had little general effect in his time.

Later, however, in 1836, T. Wilkinson King, of Guy's Hospital, in discussing the structure and function of the thyroid gland, clearly propounded the idea of an internal secretion; while George Gulliver wrote in 1840: "The adrenals pour into the blood a peculiar matter which has doubtless a special use, and is still an interesting and important subject for further inquiry"—a comment which is still true. He observed the presence of minute spheroidal bodies both in the adrenal glands and in their veins, and concluded that the adrenal veins are the excretory ducts of the adrenals, while Vulpian in 1856 found that both the medulla of the adrenals and the venous blood from these glands stained green with salts of iron, and believed that this must be significant with respect to the function of these organs.

The clearest early experimental indication of hormonal action comes from the observations of A. A. Berthold, in 1849, who found that the transplantation of a cock's testes to any other part of the body prevented the atrophy of the comb which usually follows castration in this species. He inferred from these observations that the testes exert an influence on the blood and so on the body as a whole, but this idea had little contemporary influence and was long forgotten.

The Influence of Claude Bernard

That material might be liberated direct into the blood stream, thereby becoming available for effect, in other parts of the body, was clearly demonstrated by Claude Bernard in his paper of 1850 entitled "Une nouvelle fonction du foie chez l'homme et chez les animaux," the substance of which was amplified in his thesis for the Doctorate in Science, published in 1853 under the title "Nouvelle fonction du foie." He had set out to determine in which organ sugar absorbed from the gut was burned, and in the hepatic veins of a sugar-fed dog he found an abundance of reducing carbohydrate, a result which seemed to indicate that sugar was not destroyed in the liver; nevertheless, in control animals, either fasting or fed on a carbohydrate-free diet, a similar amount of sugar was found in the blood of the hepatic veins while none could be detected in the blood of the portal vein. He concluded that "sugar is manufactured in the liver, which must therefore be considered as an organ which produces or *secretes* sugar" (Bernard, 1853, p. 54). These observations led to the discovery of glycogen, the isolation of which was described in 1857.

It is interesting to note that even Claude Bernard was not free from the obfuscating effects of the prevailing tendency to regard the nervous reflex as of immediate and dominating significance in physiological phenomena. He states in 1850 that the cutting of the vagi in the region

of the heart results in the complete disappearance of sugar from the liver. This erroneous finding led him to expect that electrical stimulation of the peripheral end of the cut vagus nerve would induce an exaggerated secretion of sugar in the liver, but in this he was disappointed.

In earlier experiments Bernard had found that irritation of the origin of the fifth nerve brought about the secretion of tears and saliva, so he now attempted to exaggerate the secretion of sugar by the liver by irritating the tenth nerve at its origin in the floor of the fourth ventricle. This was the basis of the discovery of his "piqûre" diabetes—a transitory glycosuria seen in well-fed animals. Since Bernard found that piqure was still effective after section of the vagi, and since the idea of reflex secretion was dominant, he was led to build up a wholly incorrect theory, according to which a nervous stimulus to the secretion of sugar by the liver originated in the lungs (Bernard, 1855: vol. 1, pp. 327 *et seq.*). Impulses from the lungs travelled up the vagi to a centre in the floor of the fourth ventricle, whence stimuli passed down the spinal cord through the splanchnic nerves to the liver. The idea that inspiration provides not only oxygen but also the stimulus for the hepatic secretion of sugar, which is thus made available for oxidation, is at least ingenious. I mention it now to illustrate by a typical example how directly dominating the nervous system was believed to be in 1855 and what little chance of general acceptance the idea of hormonal action, as an alternative to nervous control, could then have.

I should like at this stage to digress for a moment to speak of Frederick William Pavy, a distinguished Guy's physician, who died in 1911 at the age of 82. He received his medical education at Guy's, and after graduation in 1852 worked for a year in Bernard's laboratory in Paris, becoming lecturer in physiology at Guy's Hospital in 1853 (at the age of 24) and also assistant physician. Of his trenchant but just criticisms of Claude Bernard's earlier work I have written elsewhere (Young, 1936), but I should like to mention here that in his publications of 1854, 1860, and 1861 Pavy described experiments which were technically more satisfactory, both physiologically and chemically, than Bernard's, though the general conclusions Pavy drew from them, in contradiction of those of Claude Bernard, were in fact incorrect.

Bernard said at this time that the blood of the portal vein contained no sugar at all while that of the hepatic veins contained an abundance, and it may be inferred that Bernard found nearly 1% of sugar in the hepatic veins of his dead or dying animals. Pavy asserted, on the other hand, that the blood of the portal vein did indeed contain sugar, in amount indistinguishable from that in the other parts of the circulation of the living animal, and his figure for the sugar content of the blood of the right heart of the dog obtained by catheterization of the jugular vein of the living unanaesthetized animal is 0.047–0.073%—a remarkably accurate figure. His observation that the blood-sugar content rose rapidly as the result of restlessness or struggling of the animal was, I believe, the first observation of emotional hyperglycaemia. Since Addison did not retire from Guy's until 1860, while Pavy was appointed in 1854, it is probable that they met, though it is perhaps unlikely that they discussed the topical question of "internal secretion."

Although we do not regard the glucose liberated by the liver into the blood stream as a hormone, Bernard's clear demonstration that a substance can be secreted direct into the blood was of great importance in turning attention to such possibilities with respect to ductless glands in general.

The Adrenal Glands

In any case, the publication of Addison's monograph in 1855 did stimulate direct experimental investigation of the function of the adrenal glands, but it is perhaps unfortunate, though understandable, that it was the ebullient and somewhat unreliable French-American Brown-Séquard (1856) who was first in the field, finding that excision of both adrenal glands in numerous species of animal invariably proved rapidly fatal and concluding that these glands were indispensable to life. Philippeaux, who in 1857 found that rats survived the removal of both adrenal glands for many months, explained the fatalities in Brown-Séquard's experiments as the result of damage to adjacent tissues, and particularly the sympathetic. It is indeed likely that Brown-Séquard's fatalities resulted from traumatic shock and sepsis and that his conclusions were unjustified by his evidence. Nevertheless he later expanded his views on internal secretions in general terms, and in 1889 described his own rejuvenation by testicular extracts, an incident which certainly publicized the idea of internal secretions, although, as H. M. Evans has picturesquely expressed it, in this way "endocrinology suffered obstetric deformity at its very birth."

A new line of approach to the question of hormones opened in 1871 with the suggestion by Hilton Fagge, another Guy's man, that cretinism might occur in adults; and three years later Sir William Gull, yet another distinguished physician of Guy's Hospital, described a "cretinoid condition supervening in adult life in women," associated with atrophy of the thyroid gland, a condition to which Ord in 1877 gave the name myxoedema. The experimental investigation of myxoedema was complicated by the variable removal of parathyroid tissue with the thyroid gland, but by 1891 the effects of uncomplicated experimental thyroidectomy were well established. In this year Murray demonstrated clearly the corollary of these findings—namely, that the symptoms of myxoedema could be relieved by an extract of thyroid tissue. Endocrine therapy had thus begun. Nevertheless the adrenal gland did not yield its life-maintaining hormones for several decades, although the experiments of Oliver and Schäfer (1894), which led to the isolation of adrenaline, pointed the way.

The observations of Oliver and Schäfer at University College, London, were undertaken at the instance of Dr. George Oliver, a physician practising in the summer at Harrogate, who wrote chiefly on the pulse and on the measurement of blood pressure in man. It is said that Dr. Oliver, under the impression that a beneficial effect followed the administration of aqueous extracts of the adrenal glands to patients with hypotension, investigated the influence of the injection of such an extract on his own son. Believing that he had observed a contraction of the radial artery, he went up to London to tell his friend Professor E. A. Schäfer about it. Although incredulous, Schäfer gave some of the extract to an anaesthetized dog, previously used for

another experiment in which the blood pressure had been measured, and was amazed to see the mercury rise so high in the manometer that it almost overflowed. Realization quickly came that the active principle was manufactured in the adrenal medulla and not in the cortex, and that it was unable to relieve the symptoms which followed experimental removal of the adrenal glands. Later it was shown decisively by Houssay and Lewis (1923) and others that the adrenal cortex was essential for life but not the medulla.

Developments in Hormone Research

In the meantime the experiments of Bayliss and Starling (1902) at University College, London, on the chemical control of the secretion of pancreatic juice led to the development of the general concept of chemical messengers or hormones on a clearly defined experimental basis. But it was many years before a therapeutically important discovery, like that of the value of thyroid extract in myxoedema, was again made. Then, in 1922, Banting and Best announced the discovery of insulin, and the amazing efficacy of this hormone in the control of diabetes was quickly apparent. It was shortly after this that H. M. Evans succeeded in preparing crude extracts of anterior pituitary tissue which were hormonally active in stimulating growth and influencing the gonads, while later the extensive investigations of Houssay and his colleagues showed the striking influence of anterior pituitary extracts on carbohydrate metabolism.

Now up to this time all active endocrine extracts had been obtained by an initial aqueous extraction of the relevant tissue. Even Banting and Best's original preparation of insulin was a saline extract of the acinar-degenerated tissue from duct-tied pancreases. It seemed reasonable to argue in general that since a hormone is liberated into the blood stream it must be soluble in aqueous media and that therefore aqueous extraction of the glandular tissue should produce potent preparation of its contained hormone. Although in 1927 Rogoff and Stewart, and also Hartman and his colleagues, stated that they had prepared aqueous extracts of adrenal glands which were active in prolonging the life of adrenalectomized animals, the results were quite uncertain.

An entirely different method of attack was opened by Swingle and Pfiffner (1929, 1930). These workers first extracted the adrenal tissue with alcohol, and after fractionation with various types of lipid solvent, including benzene, the material was injected in oil. The activity of the extract thus prepared in prolonging the life of adrenalectomized animals was quickly and independently confirmed, and extraction with lipid solvents has formed the basis for all subsequent developments. It is of interest to ask why Swingle and Pfiffner succeeded where so many others had failed.

I believe the answer to this question lies under four main headings: (1) Their facilities for biological tests were extensive. They record that they used over 350 cats in their preliminary experiments: certainly a worker in this country would be fortunate to have one-tenth of this number available. (2) They realized that aqueous extracts of adrenal cortical tissue, even if these latter were dissected as free as possible from medulla, were bound to contain adrenaline or related compounds which might exert a toxic effect in large doses. (3) They appreciated the fact that extraction and fractionation

with fat solvents of material from a gland which contains as much lipid as does the adrenal cortex might well be more effective than procedures employing aqueous solvents. Since it had been known for many years that blood contains substantial amounts of cholesterol, there was no basis for the view that a hormone could not be a lipid substance. (4) Finally, they were not afraid to administer what, in those days, appeared to be unphysiologically large doses of extract. As Dr. M. Vogt (1950) has recently pointed out, the normal rate of secretion of the adrenal gland of the dog would exhaust its stored extractable active material in 6 to 12 seconds, and it is now clear that the adrenal glands store little preformed hormone—at least in an extractable state.

In their later publications Swingle and Pfiffner describe means whereby the active material could be obtained in aqueous solution, and also an ingenious method for removing adrenaline and its basic degradation products by filtration through permutite, a very early application of ion-exchange materials to biological investigation.

The Steroids

In 1930 it was generally held that for one endocrine gland there was one hormone. True, the pituitary gland, both anterior and posterior lobes, proved a little obdurate, but casuists were able to surmount these difficulties in a number of different ways—at least to their own satisfaction. But from 1935 onwards at least three different groups of investigators, one led by Reichstein, in Switzerland, and others by Kendall and by Wintersteiner, in the U.S.A. respectively, announced the isolation of a number of different crystalline materials potent in the maintenance of the adrenalectomized animal in good condition, and it was difficult to decide whether any one of these could be regarded as the sole hormone.

After much discussion it is now agreed that 7 of the 28 crystalline steroids isolated from the adrenal glands are active in maintaining an adrenalectomized animal in good health (see Diagram), while the so-called amorphous fraction, the uncrystallizable residue remaining after the separating of the characterized steroids, is very highly active in this respect. Of the crystalline substances progesterone is the least active in the life maintenance test, and its inclusion among the adrenal-cortically active steroids is not universal.

When both Reichstein and, later, Kendall isolated corticosterone in 1937 it was generally considered that this might be the hormone of the adrenal cortex, since it was so much more active in life maintenance than

Physiological Activities of Adrenal Steroids (5=high activity; 1=slight activity)

	Life Maintenance (Rat)	Renal Function (Dog)	Electrolyte Balance (Rat, Dog)	E.D.* Test (Rat)	Muscle Work Test (Ingle) (Rat)	Liver Glycogen (Rat)	Diabetogenic Test (Rat)
Corticosterone ..	1-2	2	1-2	1-2	3	3	3-4
17-hydroxycorticosterone ..	2	1	?	2	5	5	5
11-dehydrocorticosterone ..	1-2	2	1-2	?	2	2	3-4
Cortisone ..	2	1	?	2	4	4	5
11-deoxycorticosterone ..	4	4	5	4	1	1	1
17-hydroxy-11-deoxycorticosterone ..	3	4	?	2	1	1	1
Amorphous fraction ..	5	5	?	3	1-2	1	Nil?

* Everse-De Fremery work test.

cortisone (or compound E, as it was then known), isolated by Kendall in the previous year. But in time it became clear that the different steroids possess different physiological effects according to, for example, whether or not they carry an oxygen atom or a hydroxyl group at position 11, or whether they possessed a hydroxyl group or a hydrogen atom, in addition to the side-chain, at position 17. Classifications such as that given in the Table are often put forward, but they must not be interpreted too rigidly, nor must the results be considered to apply to conditions other than those under which they were obtained. Thus in acute experiments on the rat and the dog (not adrenalectomized animals) Thorn, Engel, and Lewis (1941) and Ingle and Thorn (1941) found that cortisone and 17-hydroxy-corticosterone both cause an increase in the urinary excretion of sodium, chloride, and potassium ions. It was indeed strange to find that the administration of adrenal hormones should promote the loss of sodium and chloride ions, since it is a negative balance with respect to these very ions that contributes to the fatal outcome of adrenalectomy. Subsequently it was found by Ingle, Sheppard, Oberle, and Kuizenga (1946) that the increase in the excretion of

sodium and chloride ions is only temporary, lasting for one to three days, and that a normal balance is then maintained with respect to sodium and chloride, though the increased excretion of potassium ions is maintained for longer periods of time. Moreover, it appears that the negative balance of sodium and chloride ions characteristic of the adrenalectomized animal can be corrected by both cortisone and 17-hydroxy-corticosterone (see Ingle, 1950). Thus the influence of these active steroids is seen to vary greatly with the state of the animal to which they are administered.

Corticosterone and 17-hydroxy-corticosterone together probably constitute most of the active material secreted by the adrenal cortex. The elegant experiments of Pincus and his colleagues with the isolated perfused gland show that the adrenal tissues possess a powerful enzyme system catalysing the introduction of a hydroxyl group into position 11 of the steroid nucleus. They suggest the possibility that 11-deoxycorticosterone is an intermediate on the pathway of formation of corticosterone from cholesterol.

The chemical and physiological characterization of these steroids has been accompanied by clear evidence

CORTICOSTERONE

(Δ^4 -Pregnene-11(β):21 diol-3:20 dione)

17-HYDROXY-CORTICOSTERONE (KENDALL'S COMPOUND F)

(Δ^4 -Pregnene-11(β):17(β):21 triol-3:20 dione)

11-DEHYDRO-CORTICOSTERONE

(Δ^4 -Pregnene-21ol-3:11:20 trione)

CORTISONE (17 HYDROXY:11-DEHYDRO-CORTICOSTERONE)

(Δ^4 -Pregnene-17(β):21 diol-3:11:20 trione)

11-DEOXY-CORTICOSTERONE

(Δ^4 -Pregnene-21ol-3:20 dione)

17-HYDROXY:11-DEOXY-CORTICOSTERONE

(Δ^4 -Pregnene-17(β):21 diol-3:20 dione)

PROGESTERONE

(Δ^4 -Pregnene-3:20 dione)

The adrenal steroids active in maintaining adrenalectomized animals in good health.

of the control of their liberation by the nervous system acting indirectly but nevertheless effectively. According to G. W. Harris (1948) the stimulation of centres in the hypothalamus leads to the liberation of humoral transmitters from the infundibulum, and these substances are carried by the hypophysis-portal system to the anterior lobe of the pituitary gland, where the liberation of adrenocorticotrophic hormone (A.C.T.H.) is stimulated. A.C.T.H. is then carried in the blood stream to the adrenal cortex, where it promotes the production and secretion of two or more of the active steroids. Adrenaline secreted from the adrenal medulla can also stimulate the secretion of adrenal steroids from the adrenal cortex, but, as has emerged from the experiments of Dr. Vogt and of Professor C. N. H. Long and his colleagues, adrenaline acts, either directly or indirectly via centres in the hypothalamus, on the anterior pituitary lobe to stimulate the liberation of A.C.T.H. In this way the old views concerning the importance of nervous reflexes and the newer ones emphasizing the significance of chemical co-ordination have been reconciled.

The amounts of the hormones which are secreted each day under normal conditions are surprisingly large. Miss Vogt (1943, 1947) calculates that in the dog it may total more than 5 mg./kg./day (that is, for man, on a weight basis, about 350 mg./day), while evidence is accumulating to suggest that under conditions of stress the rate of secretion may rise tenfold or more.

Cortisone

I shall not attempt to discuss the bewildering array of clinical conditions in which treatment with cortisone and A.C.T.H. has proved to be beneficial during the time that has elapsed since the publication of Hench's dramatic results in the relief of rheumatoid arthritis with cortisone (see Hench, 1950). But I think one conclusion may be tentatively drawn from the welter of available evidence. It seems that cortisone does not in general influence directly a toxin or a noxious stimulus, but depresses the reaction of the cells of the body to the stimulus. This, it seems to me, is a point of fundamental importance. Claude Bernard wrote of the "constancy of the internal environment of the body" as being of the greatest importance in the maintenance of function in complex organisms, and this idea has held sway for nearly 100 years. But now we must, I believe, admit a new factor in the maintenance of function of which Bernard could not have been clearly aware. I refer to the ability conferred on a cell, by the action of adrenal steroids such as cortisone, to withstand abnormality in the internal environment. It is probable that we shall have to modify and extend Bernard's dictum to make clear that the constancy of conditions within the cell is more important in the preservation of function than is the constancy of the internal environment, although, of course, the control of conditions within the cell must depend to a very large extent upon the regulation of the internal environment.

It is perhaps significant that the endocrine system as a whole has evolved from tissues forming part of the barrier between the external and internal environments of the organism and is concerned with the regulation of the passage (both ingress and egress) of constituents of the primitive external environment between the external and internal environments. Such constituents of the

external environment include sodium, chlorine, potassium, iodine, calcium, phosphate, glucose (formed in the lumen of the gut), and even gametes. We know little as yet about the control of the translocation of material across the barrier between the internal environment and the interior of the cell, but again hormones appear to be involved, and particularly those of the adrenal cortex. Perhaps in the hypothalamus, with its centres controlling and co-ordinating endocrine activity, we have tissues in which the interior of the cell is exposed directly to the internal environment. The regulating responsiveness of such tissues to variations in the composition of the surrounding fluid might play an important part in the protection of the interior of the cells of other tissues against the undesirable results of changes in the internal environment in general. One day we may admit the danger of attempting to assess conditions within the cell by examining the composition of that part of the internal environment most easily accessible to analysis—namely, the blood.

It may well be that the protection of the heart muscle by cortisone during rheumatic fever is an example of the general process of control of the conditions in the interior of the cell in the presence of serious alternations in the constitution of internal environment. This is not merely an academic point, since our attitude to the whole question of acclimatization or adaptation may be influenced thereby. For instance, if we accept the Bernardian view that constancy of the internal environment is the desirable state in a complex organism then we shall assume that an organism in which a given stimulus induces a greater rise in temperature, in blood-sugar level, or in blood concentration is less well adapted and less biologically efficient than one in which the similar changes are smaller. Nevertheless, may it not be that the organism in which the greater change in internal environment can be tolerated without a relative diminution in function is in fact better adapted than that in which the processes of close control of the internal environment are needed to maintain function? I believe that our growing experience with cortisone and related substances, together with the current development of our ideas on adaptation—a subject first discussed by Selye from an endocrinological point of view—are in the process of effecting substantial changes in biological outlook in general. Although one may not agree with Selye in detail, it is clear that his ideas have been of great importance in fostering the present significance accorded to the adrenal glands in the processes of adaptation.

Conclusion

Advances in the field of hormones must depend on the availability of large amounts of purified material for experimental investigation, and it is a matter for regret that we in this country have been dependent for so long on our friends overseas for supplies of crystalline adrenal hormones. Research and industrial development must be mutually dependent, and in the U.S.A. the magnificent achievement of the large-scale artificial production of cortisone has provided benefits in both directions. Let us hope that in the advances undoubtedly to come in the hormone field research in our own country will not be hampered by a lack of enterprise in the large-scale production of substances of, initially, only academic importance.

Thomas Addison's monograph of 1855 opens with the words: "It will hardly be disputed that at the present moment the functions of the suprarenal capsules, and the functions they exercise in the general economy, are almost or altogether unknown." Like so much of his writing, these words are still true. We have accumulated a mass of facts, but we still can say little about the influence of adrenal hormones in the general economy of the organism. Perhaps we must await the appearance of a second Thomas Addison to unlock a new door through which fresh ideas may flow. Let us hope that he will be recognized as readily as the genius of Thomas Addison was appreciated when, in 1824, he was appointed assistant physician to Guy's Hospital and began his long and fruitful career.

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The National Association for Mental Health is often asked by parents to arrange for institutional care for young mentally defective children, frequently mongols (*Mental Health*, Winter, 1951, p. 21). Sometimes these applications are received from maternity hospitals on behalf of almost newborn infants. In many cases, however, the association is not in favour of this early removal because of the very distressing effect such an act frequently has upon the parents, who are often told the child is mentally defective and advised to send him away from home without any preparation or explanation being given. Sometimes, too, it may take months before accommodation can be found; such vacancies as exist should be reserved for really urgent cases. They point out that in cases showing no pronounced stigmata of mental defect it is almost impossible to arrive at a reliable prognosis at an early age, and the risk of mistaken decision, which may have serious consequences for the child, should not be overlooked. Most medical schools pay too little attention to the subject of mental deficiency—particularly in its ethical and social aspects—and the association wishes to stress this and the fact that there are few postgraduate openings in this field. Another urgent need is for mental deficiency clinics in outpatient departments. It has also been suggested that mentally deficient children under school age should be reported to local health authorities. The editor of *Mental Health* invites readers' opinions on these views—at Maurice Craig House, 39, Queen Anne Street, London, W.1.

PLASMA INSULIN IN HUMAN DIABETES MELLITUS

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This paper summarizes our investigations on human diabetics, made by estimating the available insulin in their plasma. This is arrived at from the hypoglycaemic effect produced when their plasma is injected into specially prepared rats very sensitive to insulin. Our earlier publications (Bornstein, 1950; Bornstein and Trehwella, 1950, 1951; Bornstein and Lawrence, 1951) have aroused enough interest both in the technique and in the results to merit this further description. The plasma insulin results of 37 diabetics and 14 normal controls are now reported in tables, with comments and discussion.

Experimental Methods and Techniques

The method evolved by one of us (J. B.) (Bornstein, 1950; Bornstein and Trehwella, 1950) has been used throughout. Available plasma insulin is measured by injecting 1 ml. of plasma into special rats and observing for one hour the change in their blood sugar. These adults rats (called ADHA rats) are first made diabetic by an appropriate dose of alloxan. Then the hypophysis and both adrenals are removed, so that the animals become very sensitive to insulin and show a clear hypoglycaemic effect after even 1/20,000 of a unit, or 0.05 milliunit, the term used in this paper. It is obvious that such a rat presents difficulties in its preparation, its maintenance, and its standardization for the actual hour's blood-sugar test.

Standardization before Tests

(a) It is first essential to determine the conditions under which the blood-sugar concentrations of the ADHA rats are constant enough for the period of one hour necessary for an insulin assay. We should point out that different strains of rats vary considerably, and that temperature and diet control have to be closely investigated to obtain stable blood-sugar conditions. In all recorded experiments the rat environment temperature has been 27° C. In our experience bread soaked in milk—that is, readily assimilable carbohydrate—is the best standardizing diet. These rats were therefore freshly fed for one and a half hours in the morning with bread soaked in milk, and this food was then removed for one and a half hours before the start of the test. Tables I–IV show a satisfactory stability from the third to the fifth hour after the feeding procedure, and insulin assays were made from the third to the fourth hour.

(b) Next, after the injection of 0.5 and 1 ml. of saline, a series of *mock assays* were undertaken to test the stability of blood sugar and the absence of a spontaneous fall. These are shown in Tables II, III, and IV. Rats showing instability were rejected.

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