EDITORIAL

Endocrinology and psychiatry

When the late Richard Asher's famous paper on 'Myxoedematous madness' in 1949 alerted a generation of British doctors to the association between hypothyroidism and psychosis, he was amplifying what had been noted in some of the earliest descriptions of myxoedema. There has been little advance in our knowledge of the association in recent years. It is now clear that, where the psychosis is organic, whether a state of delirium or of apparent dementia, a good response to thyroxine is likely. Where the psychosis is of 'functional' type, thyroxine is much less likely to be effective alone and appropriate symptomatic treatment is often required as well (Tonks, 1964). None of this is very surprising, since hypothyroidism leads to disturbance in cerebral function gross enough to be detected by electroencephalography and by simple psychological tests. While psychiatrists must continue to be on the look out for hypothyroidism presenting with psychiatric symptoms, the association is by no means as frequent in psychiatric hospitals as some endocrinologists have suspected it might be (Clower *et al.*, 1969). Nor is further clinical study of the association, when it occurs, likely to throw any more light on the nature and causation of functional psychiatric disorders than a study of symptomatic psychoses generally.

Has the study of hyperthyroidism anything more to offer? It seems not. Again, there are important clinical aspects, since anxiety-like symptoms of hyperthyroidism are sometimes phenomenologically indistinguishable from those of neurotic anxiety. No doubt a few hyperthyroid patients are wrongly diagnosed as neurotic, although the mistake is much more often made in the opposite direction. There are descriptions of concomitant florid psychosis and thyrotoxicosis in the older literature, but in fact the association is probably not particularly common. A sudden reduction in the increased output of thyroid hormone has itself been reported to cause an acute psychosis, but this is very unusual and presumably merely symptomatic of a rapid change in cerebral function (Bewsher *et al.*, 1971).

Since so much has been written on the relationship between the thyroid and the psyche, and since so many examination questions are still set on this topic, it is only fair to mention one or two intriguing findings of recent years. First, several controlled trials have led their authors to conclude that physiological amounts of tri-iodothyronine potentiate the effect of tricyclic antidepressants, perhaps by enhancing the responsiveness of certain receptor sites in the brain (Whybrow *et al.*, 1972). Might subtle fluctuations in endogenous thyroid hormone production alter the responsivity of the same receptor sites to endogenous transmitters? This would involve, of course, the major assumption that receptors concerned in the action of antidepressant drugs are also implicated in the genesis of depressive illness. Then came the totally unexpected finding that administration of thyrotropin-releasing hormone (TRH), as well as causing the pituitary to secrete thyrotropin, also induced a rapid if transient elevation of mood in some depressed subjects, an effect which thyrotropin itself certainly does not exert (Prange *et al.*, 1972).

Several years ago Manfred Bleuler and his colleagues in Zurich carried out a series of careful clinical studies of unselected series of patients with various endocrine disorders. In general, there was no particularly frequent association with psychosis, except in the case of Cushing's syndrome. Rather, the so-called endocrine psychosyndrome was monotonously observed—a state of dysphoric tension, a mixture of features of depressive and anxiety neurosis, such as is found in many patients with chronic physical illness. All of which supports the notion that there is nothing specific about the psychiatric concomitants of endocrine disorders generally, although when endocrine disease gives rise to acute metabolic disturbance a delirious state may develop, as in Addisonian crisis, severe hyperparathyroidism, or spontaneous hypoglycaemia.

The main exception, according to both the Zurich school and to other investigators, would seem to be Cushing's syndrome, where the occurrence of functional psychosis has regularly been reported as unusually frequent, and where disturbance of mood is reported to be very common indeed. There is also general agreement that relief of the endocrine disorder regularly leads to relief of the psychological disturbance (Furger, 1961; Ross *et al.*, 1966). Observations on the effects of pharmacological doses of cortisone and of synthetic corticosteroids are also relevant here. But we still do not know which particular action of the steroid is responsible for the psychological changes. Nor is there any real evidence to suggest that variations in cortisol secretion within the physiological range have any psychological effect in man. The notion that a surge in cortisol secretion might decrease the synthesis of serotonin in the brain and so trigger an episode of depression still lacks any firm experimental support.

The search for endocrine causes of the major mental disorders was arduous yet fruitless and has long since been abandoned. But the study of endocrine concomitants of psychiatric disorders—especially of emotional disorders—has been rather more productive, even if the findings of different investigators differ greatly. Many hormones or hormone metabolites have been assayed in the various body fluids of large numbers of patients suffering from different psychiatric disorders. The investigators' endeavour has not always been matched by the reliability and specificity of their chemical methods, by their control of important variables, or by the strict comparability of their control groups. American investigators showed many years ago that any novel experience, including admission to hospital, can cause a sizeable if transient alteration in endocrine (and especially in adrenocortical) function. (Whereas a chronic situation of intense distress, such as afflicts the parents of children dying from leukaemia, is very often not associated with any persistent increase in adrenocortical activity, no doubt because most parents manage to make some sort of adjustment even to this grim situation.) Furthermore, psychotropic drugs may not only interfere with chemical assay methods but may directly affect neuroendocrine control mechanisms in the brain, as indeed may the withdrawal of previously administered drugs. Finally, there is no reason to assume that groups of subjects baldly labelled 'depressive' by different investigators are necessarily closely similar genetically, clinically, or in any other way.

All of this makes life very difficult for the research worker who wishes to study the neuroendocrinology of psychiatric disorder. How often does one see a drug-free depressed patient who is willing to enter hospital yet to forswear treatment until endocrine equilibrium has been established? Nevertheless, there have been important recent findings, again mostly in respect of adrenocortical activity in affective disorder. The literature on this topic has been reviewed tiresomely often. Suffice it to say that some investigators found significant increase in adrenocortical activity in a sizeable proportion of depressives, others in only very few. A number of investigations carried out under the aegis of Dr. John Mason—a most distinguished investigator in the field of animal neuroendocrinology—led to the suggestion that it is not mood state *per se* but rather the failure of psychological defence mechanisms that is associated with increased cortisol production.

It fell to a former colleague of Mason, Dr. E. Sachar, to espouse this view and to look for evidence to support it by investigating depressed patients with methods of the greatest elegance and refinement. A study of cortisol secretion rate by isotope dilution (with irreproachable radiochemical methods) showed no increase in secretion rate in 'apathetic' depressives, a modest increase in depressed patients with considerable subjective anxiety, and a marked increase in patients undergoing what he called psychotic disorganization—namely, the failure of defence mechanism and the development of delusional thinking (Sachar *et al.*, 1970). These findings certainly seemed to support the hypothesis that the quality of the emotional reaction, the intensity of the subjective distress, was the deciding factor, rather than the depressive disorder itself. Later work by Sachar, however, showed that increased cortisol secretion occurs in some 'apathetic' depressives, leading him to suggest that in some cases of depressive illness both anxiety and endocrine disturbance might reflect a central limbic system dysfunction.

In recent years, major advances in human neuroendocrinology have resulted from the use of

tests of the integrity and sensitivity of neuroendocrine control mechanisms and from the development of precise methods of hormone assay that require only small samples of blood, so that repeated sampling can be carried out over a 24 hour period.

In the normal subject, blood sampling every 20 minutes has shown that the adrenal secretes cortisol in only seven to nine bursts each day, with no secretory activity in the two hours or so before and after bedtime. In some unipolar depressives, Sachar and his colleagues (1973c) have found that the normal pattern is disrupted, with an increase in the number of secretory episodes, with active secretion during the normal non-secretory period, and with elevation of all peaks and troughs of plasma cortisol level throughout the 24 hours. The pattern returned to normal after the patients recovered. Australian workers had previously tested the integrity of some of the control mechanisms of cortisol secretion in depressives. As is now well known, they found that the effects of dexamethasone and of insulin-induced hypoglycaemia on cortisol secretion were much reduced in many of their patients (Carroll, 1969). They postulated 'an abnormal drive from other limbic areas', a concept very similar to Sachar's 'central limbic dysfunction'. The latter author has more recently shown that the growth hormone response to both insulin and L-dopa was reduced or absent in many of his unipolar depressed patients, although oral L-dopa continued to inhibit prolactin secretion in these subjects. The growth hormone response to L-dopa was normal in his bipolar patients (Sachar *et al.*, 1973a).

As Sachar points out, this type of investigation, combining neuropharmacological and endocrine techniques, may enable us to tease out disturbed hypothalamic functions in man. This prospect is the most exciting development in the endocrine study of depression. There is evidence that both noradrenergic and serotonergic neurones inhibit the secretion of corticotropin releasing factor (and therefore of both ACTH and cortisol) in animals. The increased cortisol secretion in some depressives would be consistent with a functional deficiency of either or both transmitters. Prolactin secretion is inhibited by dopaminergic neurones and there is good evidence that noradrenergic neurones are concerned in the secretion of growth hormone. The preserved prolactin response and the absent growth hormone response to L-dopa therefore suggest some defect in noradrenergic neurones, at least in unipolar depressives.

It is now possible to measure testosterone in small quantities of blood. Serial sampling has shown that this steroid is secreted in bursts (as are several pituitary hormones) and that the secretory pattern is closely related to the sleep–wake cycle. Because the sleep–wake cycle is so often disturbed in depressives, studies of the testosterone secretion pattern should prove valuable. So far, it has been reported that urinary testosterone excretion is reduced at times of emotional distress, but that plasma testosterone levels do not differ before and after recovery from depression. The latter study, however, was based on the estimation of only two plasma levels per patient (Sachar *et al.*, 1973b).

Methods for estimating gonadotropins (FSH and LH) in human blood are now available and they have been applied to the study of amenorrhoea in anorexia nervosa. For example, a recent paper in this journal showed how measurement of plasma LH and oestrogens, together with the use of clomiphene, helps to elucidate the relationship between weight gain and return of menstruation in this disorder (Beumont *et al.*, 1973).

In the last few years a series of brilliant investigations by Richard Michael has greatly increased our understanding of the neuroendocrinology of sexual behaviour in the rhesus monkey (Michael *et al.*, 1972). He has shown how hormonal changes in the female alter the sexual behaviour of both partners, in part through the agency of a pheromone, which is present in human as well as monkey vaginal secretions. Michael's work is likely soon to increase our knowledge of the extent to which human sexual behaviour is hormone-dependent. There are already hints that hormones are more important than we used to think. For example, the pattern of frequency of coitus during the menstrual cycle was remarkably similar in Michael's monkeys and in Udry and Morris's admittedly unsophisticated human subjects (Udry and Morris, 1968). Similarly, Goy and Resko's (1972) findings on modes of play shown by immature female rhesus monkeys exposed to an excess of androgenic hormone *in utero* are paralleled by Money's finding of boyish rather than girlish

behaviour in human female children similarly affected in fetal life by the adrenogenital syndrome (Ehrhardt *et al.*, 1968).

But what of this last example? Is not the adrenogenital syndrome an endocrine disease, and was not Money's study essentially clinical, or at least clinicopsychological? The answer is yes on both counts. But the endocrine disease occurs during a critical phase of development and reproduces in man many of the effects of laboratory experiment in animals. It is surely in the study of such special types of endocrine disorder, rather than of endocrine disease generally, that the clinical approach (which itself requires highly specialized methods) still has something to offer.

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