served by fierce denunciation from the bench, by flogging with the cat, or by capital punishment. If all criminal conduct was deliberate and purposive then a case might be made out for such procedures, but in the majority of instances the criminal act is usually instinctive and emotionally determined, or else it is the result of the distorted reasoning of a mentally abnormal person. The difficulties, however, are very great, and as doctors it is our duty to assist the courts and not produce reports testifying how we think the law should be administered. It may, however, be respectfully and tentatively suggested that the plea of diminished responsibility could be extended to other criminal actions—for example, sexual crimes.

The whole matter is far from easy; it is much more complicated, as has been pointed out by Simpson (1948), than merely to base your decision on whether or not the accused would have committed his offence if a policeman had been at his elbow. If the answer is in the negative then drag him to the scaffold; if in the affirmative, make arrangements for him in a suitable State institution.

Conclusion

I apologize if I have wandered about a good deal in presenting some of the experience I have had in court work. I am impressed by the increasing co-operation between doctors and lawyers, and I have wondered how we might get even closer together. By the time we are fully qualified and have gained considerable experience we have become almost too set in our respective points of view. It has seemed to me that it might be a constructive suggestion if lawyers, doctors, the clergy, social workers, and even scientists, on whom intellectual and cultural progress largely depends, could have a common basic training, and then later branch off into their respective specialties. My basic training course would consist of an intensive programme whereby it might be possible to blend the pursuit of knowledge for its own sake, which we call disinterested intellectual curiosity, with a greater understanding of the fundamental facts of human nature, of which there is such abysmal ignorance. Technically this might entail a course of instruction in philosophy and psycho-biological principles, but perhaps if we took some of those with deep psychological insight and humanitarian instincts as our guides—men like William Shakespeare and Robert Burns—than we might learn to do greater justice to our common humanity.

But the final word would be with the Apostle Paul when, in the Epistle to the Romans vii. 1, he inquires: "Know ye not, brethren, (for I speak to them that know the law,) how that the law hath dominion over a man as long as he liveth?"

BIBLIOGRAPHY

- Davidson, H. A. (1947). *Arch. Neurol. Psychiat.* (Chicago), 57, 730
 — (1949). *Amer. J. Psychiat.*, 106, 424.
 Gibson, A. (1952). *Canad. med. Ass. J.*, 67, 477.
 Henderson, D. (1955). *Society and Criminal Conduct*. Roy. Coll. Phys. Ed.
 Kozol, H. L. (1948). *Amer. J. Psychiat.*, 104, 535.
 — (1949). *Ibid.*, 106, 420.
 Mullins, C. (1949). *J. ment. Sci.*, 95, 263.
 Simpson, T. B. (1948). *Edinb. med. J.*, 55, 577.
 Slater, J. K. (1948). *Edinb. med. J.*, 55, 581.

A forecast that the number of older men and women in the United Kingdom in 1971 will be over 37% more than in 1951 and the number of young people will be 6½% less is given in a report published by the Organization for European Economic Co-operation with the title *Demographic Trends in Western Europe* (H.M.S.O., 9s.). There will be 281 older men and women per 1,000 persons of working age in 1971 compared with 212 in 1951. The number of young people per 1,000 of the working population will change from 350 in 1951 to 359 in 1961 and 316 in 1971. The total population of this country is expected to increase from 50½ million in 1951 to nearly 53½ million in 1971, an increase of 6%, though this is reduced to 5% if allowance is made for a net rate of emigration of 25,000 a year. The report points out that in most of the fifteen member countries of O.E.E.C. the population will be higher in 1971 than in 1951.

SOME RECENT ADVANCES IN ENDOCRINOLOGY*

BY

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The increase in knowledge of the subject of endocrinology, like that of so many other branches of medicine, has been so rapid in the past decade or two that it is most difficult, even for one professedly engaged in the specialty, to keep abreast of all the advances made. How much more difficult, therefore, must it be for the general practitioner, not, of course, to keep really abreast of recent advances, for that is scarcely possible, but merely to have an awareness, and some appreciation, of the more important of these. This account attempts to review some of the recent advances in endocrinology which are likely to be of interest to practitioners—and, incidentally, which are of special interest to me.

The selection of material for inclusion in this review has not been easy. For example, an enormous literature on the thyroid gland has developed within the past few years, to summarize which is quite beyond my ability. To say nothing of advances in clinical knowledge, especially relating to diagnosis and treatment of thyroid disorders, there have been developments of fundamental importance in the physiology of thyroid function, outstanding among which is the work by Pitt-Rivers and by Gross leading to the discovery of 3:5:3-l-triiodothyronine, a part of the circulating thyroid hormone of much greater activity than thyroxine itself (see Gross and Pitt-Rivers, 1952). Another advance of great clinical importance has been the introduction a few years ago of the new insulins, but with this, as for example with recent progress in bone disease, in its endocrine context I am not well qualified to deal. It is proposed, therefore, to confine the following account to three main topics: some aspects of the adrenal cortex; pituitary insufficiency in the adult; and some recent developments in our knowledge of intersexuality.

The Adrenal Cortex

It is now generally agreed that the adrenal cortex produces three main groups of steroid hormones. These are often referred to as: glucocorticoids, mineralocorticoids, and sex steroids. It is probable that each of these groups contains more than one steroid, and that some contain several different steroids.

Glucocorticoids

These are so called because, *inter alia*, they influence carbohydrate metabolism, encouraging gluconeogenesis from protein and the deposition of glycogen in the liver. They therefore cause protein catabolism. Another important property, of which much clinical use is made, is their anti-inflammatory action. They reduce the number of circulating eosinophils in the blood. It is probable that the principal steroid of this group secreted by the adrenal cortex is hydrocortisone (compound F, 17-hydroxycorticosterone or cortisol), the actions of which are essentially the same as those of cortisone (compound E, 11-dehydro-17-hydroxycorticosterone). Kendall (1952) reviewed in synoptic form the research which led to the isolation and

* Based on a lecture to the Kingston Division of the British Medical Association delivered on February 14, 1956.

identification of the adrenocortical steroids and to the demonstration of the profound effects of cortisone and hydrocortisone. It is important to note that, remarkable as are the restorative effects of these two steroids in adrenal deficiency states, these substances are less well endowed with life-maintaining properties than are the mineralocorticoids. Actually, hydrocortisone and cortisone themselves have important effects on electrolyte and water metabolism, so that the differentiation into glucocorticoids and mineralocorticoids is to some extent arbitrary and not altogether sharply defined. For example, in Addison's disease there is an excessive loss of sodium in the urine and the kidney is unable to handle a water load efficiently; cortisone or hydrocortisone restores the ability to handle a water load as well as the electrolyte balance, but whereas the

steroids." This term was applied by Norymberski (1952) to those corticosteroids having the side-chain 17:20:21-triol, 17:21-diol-20-one, or 17:20-glycol, which, on treatment with sodium bismuthate, are converted into 17-ketosteroids and which can be estimated as such in the usual manner (a fairly straightforward chemical procedure). By measuring the 17-ketosteroids before and after sodium bismuthate treatment, the 17-ketogenic steroid figure is obtained by difference. By obviating the difficulties of hydrolysis and extraction of urinary corticosteroids inherent in other methods for their determination, this new procedure offers great practical advantages, and seems to be the most satisfactory for clinical use. The 24-hour excretion of 17-ketogenic steroids is 9.6–22 mg. for normal men, 4.6–18 mg. for normal women, and 2.3–3.8 mg. for normal children aged 6–11 (Norymberski *et al.*, 1953; Hubble, 1955; Diczfalussy *et al.*, 1955).

The measurement of adrenal corticosteroids in the blood originally depended upon bioassay (Vogt, 1943), but Nelson and Samuels (1952) were the first to devise a chemical procedure which has met with acceptance and, with various modifications, has been utilized by a number of workers (see review by Bongiovanni and Eberlein, 1955). It is too complicated, however, to have general clinical application.

Mineralocorticoids

The recently isolated substance *aldosterone* is without doubt the most important member of this group, and is considered in detail below.

Sex Steroids

These form a heterogeneous collection of steroid substances, including androgens, oestrogens, and progesterone, all of which, in varying amounts, are produced by the adrenal cortex. It is probably only in various pathological states that the cortical oestrogen and progesterone output has any clinical significance, but the adrenal androgens constitute the "N" hormone of Albright, so called because it has a nitrogen anabolic action, in contrast to the nitrogen catabolic action of the "S" hormone—the glucocorticoids. Determination of the now familiar urinary 17-ketosteroids gives a somewhat rough-and-ready measure of the output of adrenal androgens (augmented in the male by the testicular androgens).

An excellent general account of the adrenal steroids is given by Bishop (1954).

Aldosterone

As long ago as 1934 it was recognized that the amorphous fraction of adrenal extracts was particularly effective in maintaining life in adrenalectomized animals. Two decades elapsed before a specific crystalline component of this fraction, aldosterone, originally called electrocortin (in allusion to its electrolyte-regulating effects), was isolated and characterized. The final stages of this work were led by Simpson and Tait in England, and the chemical characterization was achieved by these authors, in collaboration with Reichstein, Wettstein, and their colleagues (Simpson *et al.*, 1954a, 1954b, 1954c)—a remarkable piece of co-operative work carried out at the Courtauld Institute of the Middlesex Hospital, the University of Basle, and the research laboratories of Ciba Ltd.

The three lines of study which have led to our present stage of knowledge, ably reviewed by Gaunt *et al.* (1955), were (1) that concerned with the nature and effects of the amorphous fraction; (2) investigations of the biological activity of deoxycortone (D.C.A.), synthesized by Steiger and Reichstein in 1937, and found to have marked electrolyte-regulating effects; and (3) that which arose from the demonstration, first by Luetscher and his colleagues in 1950, of the existence of a urinary sodium-retaining substance, particularly high titres of which were present in

latter is also restored by mineralocorticoids (see aldosterone, below), they cannot, apparently, restore the water-load-handling ability of the kidney.

Opinions are still divided on the mechanism by which cortisone enables the kidney to handle a water load. It may have a direct action on the renal tubule (Lewis, 1952); and in this connexion Burston and Garrod (1952) have shown that it raises the lowered glomerular filtration rate and renal plasma flow, and decreases the excessive tubular reabsorption found in adrenal insufficiency; but it is also possible that cortisone leads to an increased rate of removal from the blood of antidiuretic hormone (secreted by the posterior pituitary) and so causes diuresis of a water load (Slessor, 1952).

The secretion of glucocorticoids is under the control of the anterior pituitary gland, being dependent upon the secretion by that gland of adrenocorticotrophic hormone (A.C.T.H., corticotrophin). They have the important property, not shared apparently by other adrenal steroids, of inhibiting, in sufficient dosage, the secretion of corticotrophin. The significance of this is considered later.

Of the role of the adrenal cortex in adaptation to stress and of the therapeutic uses of cortisone in non-endocrine conditions nothing will be said; to treat adequately of these matters would require a large volume in itself. However, some mention of the practical question of the clinical estimation of glucocorticoid hormones might well be made. The first attempts utilized the ability of these steroids to deposit glycogen in the liver of adrenalectomized animals, but such bioassay was of very limited applicability. Several chemical methods have been developed, measuring "reducing" steroids, "formaldehydogenic" steroids, and so on, depending upon the particular chemical property involved by which the estimation was made. These methods, however, have all been beset with difficulties in the complete hydrolysis and extraction of the hormones from urine and in the prevention of serious losses in the process.

The simplest (albeit still technically complicated) method, devised by Norymberski and his colleagues (1953), measures the output of glucocorticoid hormones as "17-ketogenic

diseases characterized by oedema. Eventually it was shown that this substance is aldosterone.

Details of the background of knowledge which led to the isolation and characterization of aldosterone will not be discussed here; they are summarized in the review of Gaunt *et al.* mentioned above. Suffice it to say that in 1954 Simpson *et al.* announced that electrocortin, as it had been called before the chemical structure was known, was 11- β -21-dihydroxy-3,20-diketo-4-pregnene-18-al, or the 18-aldehyde of corticosterone, and they therefore proposed the name "aldosterone." This structure is unique among the

hormonal steroids in two respects: (1) the presence of the 18-aldehyde group, and (2) the fact that in solution it exists largely in an isomeric form, the 11-hemiacetal. Biological work with aldosterone has been hampered by the fact that it is present only in minute amounts in adrenal extracts, and it is probable that the urine of nephrotic patients may be the best natural source. Not until an economic method of synthesis is discovered will the substance become available in quantity.

Aldosterone has been shown to maintain electrolyte balance and well-being in Addisonian patients. Its potency appears to be of the order of twenty to thirty times that of D.C.A., with the minimum dosage about 100 μ g. a day. Doses of the order of 1 mg. a day can cause some salt and water retention. Thorn *et al.* (mentioned by Gaunt *et al.*, 1955) believe that depression of the urinary Na/K ratio is the most sensitive indicator of aldosterone activity in man, and that it is most effectively administered either intravenously or by frequent injections in aqueous solution. More recent studies by Prunty and his colleagues (Hetzel *et al.*, 1956) have confirmed and extended these observations; they found the intramuscular route to give the most regular effect on sodium retention.

The influence of aldosterone on water excretion is complex, depending upon a number of factors. It resembles D.C.A. in its relative inability to repair the poor handling of a water load by Addisonian patients; in contrast, cortisone readily restores the ability to excrete a water load by such patients. In certain experimental conditions, however, aldosterone may have definite diuretic properties.

Aldosterone protects adrenal-deficient subjects against the effects of stress far better than D.C.A. It has relatively little effect on carbohydrate or protein metabolism, unlike cortisone. It appears to have little protective action against allergic manifestations. It has little if any action in inhibiting the secretion of corticotrophin by the pituitary. Unlike D.C.A., it does not appear to have hypertensive action, although it will maintain normal blood pressure in Addisonian patients.

Although it has been shown that aldosterone excretion is increased in a number of pathological states—in patients with oedema of cardiac and renal origin, in eclampsia, hepatic cirrhosis, in malignant hypertension, and post-operatively, during the period of potassium loss—it is important, as Luetscher (1952) has pointed out, to recognize that many of the changes in renal and endocrine function in these states are the result and not the cause of the several diseases.

A syndrome of *primary aldosteronism* was described by Conn (1955), and a case similar to that of Conn was reported by Mader and Iseri (1954). Subsequent surgery revealed the presence of adrenal tumours in both instances. A further case, also with an adrenal tumour, has now been reported from Wales by Chalmers *et al.* (1956). The principal features of the syndrome are high titres of aldosterone-like material in the urine, low plasma potassium and high sodium, alkalosis, polyuria, intermittent tetany, muscular weakness, and hypertension. There was no oedema. The excretion of 17-hydroxycorticoids was normal or only slightly raised. Mader and Iseri emphasized the marked lowering of plasma magnesium and the negative magnesium balance in their case, and they also noted adrenal atrophy, suggesting that pituitary-suppressing steroids were being elaborated. Conn suggests that other examples of "potassium-losing nephritis" may be instances of the same syndrome; and indeed it was this suggestion which led Chalmers and his colleagues to reinvestigate their patient, previously diagnosed as a case of "potassium-losing nephritis," with the subsequent discovery of the adrenal tumour by radiography after pre-sacral air insufflation. It is clearly of considerable interest that adrenal tumours may occur which secrete excess aldosterone—counterparts of those tumours which produce primarily 17-hydroxycorticoids and cause Cushing's syndrome, and those which produce androgens and cause the adrenogenital syndrome. These cases perhaps define true chronic aldosterone overdosage effects in a way not yet possible experimentally because of the scarcity of the hormone.

The mechanisms controlling the secretion of aldosterone are not yet known, but one important fact is certain: aldosterone is not under the complete and direct control of corticotrophin as are the other major corticoids. From the fact that life and electrolyte balance can be maintained after hypophysectomy, and that hypophysectomized animals die promptly after adrenalectomy, it has been clear that the adrenal can secrete an electrolyte-regulating material, independent of the pituitary. Patients with panhypopituitarism excrete normal amounts of aldosterone (Gordon *et al.*, 1954; Luetscher and Axelrad, 1954), although the secretion of other corticoids is greatly reduced. Aldosterone excretion is enhanced by a low-salt diet, and Laragh and Stoerk (1953) have provided strong evidence in the dog, supported by observations in man and the rat, that increase in the plasma potassium ion, or a decrease in the plasma Na/K ratio, may be the most potent stimulus to aldosterone secretion, though whether directly or indirectly is not known. It is possible, though less certain, that pituitary growth hormone may stimulate, and that other corticoids may suppress, the secretion of aldosterone. However, Farrell *et al.* (1956) have shown that the administration of 100 mg. of cortisone or hydrocortisone daily for five weeks to dogs does not reduce the amount of aldosterone in the adrenal venous blood, though the secretion of other corticosteroids is markedly reduced. The adrenals underwent atrophy as a result of this treatment, but the zona glomerulosa, the probable site of production of aldosterone, remained unaffected.

The observation that low-salt diets call forth a compensatory secretion of aldosterone means that the effectiveness of such diets is more or less self-limited. For this and for other reasons, the discovery of some practical means of inhibiting the secretion of aldosterone would be of considerable therapeutic value.

Some Aspects of Adrenal Hyperfunction

Hyperfunction of the adrenal cortex may affect any or all of its three groups of hormones, may be congenital or acquired, and may be due to hyperplasia or to tumour. A number of syndromes may thus arise, one of which, primary aldosteronism, has received some mention already. Two others of importance are Cushing's syndrome, in which overproduction of glucocorticoids is the essential feature; and the adrenogenital syndrome, in its various forms, in

which overproduction of adrenal androgens is responsible for the manifestations. I shall deal briefly with the present concepts of these diseases.

Cushing's Syndrome

This syndrome may be due to an adrenal tumour producing an excess of glucocorticoids or, more often, an excess of all adrenal steroids in varying proportions; or to adrenal hyperplasia. In the former condition, mixed patterns are most likely to be found, with virilization as well as the features more appropriate to Cushing's syndrome itself (obesity, essentially of the trunk; purple or red striae; hypertension; osteoporosis; decreased glucose tolerance; or actual diabetes mellitus), and the contralateral adrenal gland is usually atrophic—because the increased glucocorticoid output by the tumour inhibits the secretion by the pituitary of corticotrophin.

In Cushing's syndrome due to hyperplasia it seems that a defect exists in the mechanism by which hydrocortisone (or cortisone) normally inhibits the pituitary secretion of corticotrophin so that overactivity of the basophil cells (hence the older term pituitary basophilism) leads to excessive secretion of corticotrophin. Occasionally a basophil adenoma may be present, but the development of this could well be a consequence rather than the cause of the excessive pituitary function. Alternative possibilities are that the regulation of corticotrophin production takes place at a higher level of circulating hydrocortisone; and that the adrenal cortex is hyperreactive to corticotrophin. Certain it is that the already increased output of glucocorticoids, as measured either by the plasma corticosteroids or, for example, by the urinary 17-ketogenic steroids, is still further strikingly augmented by the administration of corticotrophin to patients with adrenal hyperplasia causing Cushing's syndrome. In contrast, corticotrophin has little effect on hormone production in patients with adrenal tumours, so that use may be made of the response to corticotrophin for differentiation between tumour and hyperplasia.

In all cases of Cushing's syndrome an elevated output of 17-ketogenic steroids would be expected. The 17-ketosteroid output, however, is usually normal when the syndrome is due to adrenal hyperplasia, but when due to tumour, an elevation, sometimes enormous, is to be expected.

Adrenogenital Syndrome

This takes various forms, depending upon whether it is congenital or acquired and whether it occurs in the male or female. In the female the congenital form give rise to female pseudohermaphroditism and the acquired form to sexual precocity or to virilism. In the male it produces macrogenitosomia praecox. In all these varieties the 17-ketosteroid excretion is greatly increased, especially so when due to adrenal tumour. The response of the 17-ketosteroids to cortisone aids in differentiation between tumour and hyperplasia, since this substance depresses the 17-ketosteroid output in the latter case, but has no effect in the former.

The very interesting theory regarding the pathogenesis of adrenal hyperplasia, put forward by Jailer (1953), is that the adrenal cortex in this condition is unable adequately to hydroxylate the 11 and 21 positions of C-21 steroids, leading to the production of an incomplete adrenal steroid, 17-hydroxyprogesterone, instead of the normal production of 17-hydroxycorticosterone (hydrocortisone). Because 17-hydroxyprogesterone is unable to inhibit the secretion of corticotrophin by the pituitary, the latter produces excessive amounts of that hormone, and the overstimulated adrenal cortex converts large quantities of steroid precursors into 17-hydroxyprogesterone. This, in turn, is metabolized to form substances excreted as 17-ketosteroids and also into pregnanetriol, the excretion of which has been detected in this disease (Dorfman and Ungar, 1953). Fitting in well with the above theory is the effectiveness in treatment of cortisone first introduced for this purpose by Lawson Wilkins and his colleagues (Wilkins *et al.*, 1952a, 1952b,

1952c, 1954; Wilkins and Cara, 1954); it depresses the excessive pituitary corticotrophin output and hence the adrenal overactivity, leading to a fall in 17-ketosteroid excretion to normal levels.

That the above is not necessarily the whole story is to be deduced from the occurrence of varieties of congenital hyperplasia complicated by salt-losing tendencies or by hypertension. In the former type the increased loss of sodium in the urine leads to low plasma sodium levels accompanied by high—sometimes extraordinarily high—plasma potassium levels, and these electrolyte derangements are not correctable by cortisone therapy alone. Evidently the adrenal cortex in these cases is unable to produce adequate amounts of mineralocorticoids, as well as glucocorticoids, and the addition to the therapeutic regime of D.C.A., sometimes in large quantity, becomes necessary. Presumably aldosterone would be the ideal agent for the purpose; limited experience with 9- α -fluorohydrocortisone suggests that this substance, not yet available in quantity, is very effective not only for depressing the excessive adrenal androgen production but also in controlling the electrolyte balance. Three cases of congenital adrenal hyperfunction with hypertension were reported by Wilkins *et al.* (1954); one had macrogenitosomia praecox and the other two were female pseudohermaphrodites. Cortisone controlled the hypertension, though in the first patient overdosage actually made it worse. The mechanism involved in these cases is unknown.

Hypopituitarism

The following remarks are confined mainly to pituitary insufficiency in the adult, and are not concerned with pituitary dwarfism and infantilism.

The first description of the pathological lesions and the clinical syndrome of severe long-standing hypopituitarism was given as long ago as 1914 by Simmonds, whose name thereafter became applied eponymously to the condition. Until recent years, however, much vagueness and confusion has persisted, chiefly because of Simmonds's own introduction of the term "pituitary cachexia" in respect of his second and third patients who had pituitary tumours and had lost much weight (Simmonds, 1916), and because he emphasized the progeria shown by his sixth patient (Simmonds, 1918). Not until 1939, when Sheehan described the hypopituitarism arising from post-partum necrosis of the anterior lobe of the pituitary gland, was cachexia, as a cardinal sign of the syndrome, shown to be mythical. In spite of Sheehan's classical paper, the differentiation of panhypopituitarism from anorexia nervosa continued to prove difficult to many clinicians until very recent years. Even in 1942, for instance, Escamilla and Lisser, having reviewed the literature, laid down four cardinal characteristics of the disease, of which one was loss of weight; but the more critical study of Sheehan and Summers (1949), based on 95 cases in which at necropsy destruction of all, or nearly all, of the pituitary gland, without hypothalamic damage, had been proved, showed once again the conspicuous absence of loss of weight, and indeed some patients with this disease may even be obese.

The true picture of Simmonds's disease has now become well recognized. Invariable findings are paleness of the skin, lack of body hair and of axillary sweating, weakness, and sensitivity to cold. Indeed, as Sheehan and Summers stated, "A confident diagnosis of complete hypopituitarism can usually be made easily from a short clinical examination. The special tests are chiefly of value for confirmation of the diagnosis, for assessment of the severity of the disease, and for academic study." Unfortunately, all too often the diagnosis is missed, even when the history may be typical—for example, severe post-partum haemorrhage followed by failure of lactation, superinvolution of the uterus, and amenorrhoea—and the findings clear to any who can properly interpret them. Such cases may for years be labelled "anaemia"—which fails to respond to iron but does so readily to cortisone

(Summers, 1952)—or “myxoedema”—which responds only poorly to thyroid alone. Now that the great benefits of cortisone for these patients are well known, it is most important that the proper diagnosis should be made.

The tests for pituitary function, recently reviewed by Crooke (1955), are mostly tests for the function of the other endocrine glands subject to pituitary trophic influence—thyroid, adrenal cortex, and gonads. Many publications have appeared dealing with the results of these tests, and a number of authors have reached the conclusion that the degree of impairment of function is not necessarily related to the extent of pituitary damage, and that the secretion of the various hormones need not be impaired to the same degree. This leads to different clinical pictures in which there may be various combinations of hypothyroid, hypoadrenocortical, and hypogonadal manifestations. Even the activities of the adrenal cortex could apparently be impaired differentially and to different degrees (Paschkis and Cantarow, 1951; Oelbaum, 1952).

In discussing the course of anterior hypopituitarism, Hubble (1952) also cited evidence for the differential impairment of the various functions of the gland. He mentioned cases of genetic deficiency of growth and gonadotrophic hormones in the absence of any other abnormalities; and of partial pituitary insufficiency due to abnormal psychic states and to malnutrition. He concluded that the production of gonadotrophins is one of the most easily affected of anterior pituitary functions, and that clinical evidence of failure of the thyroid or adrenal cortex may never appear, or do so as late as twenty years after the failure of the gonads. In four male patients described by Maddock *et al.* (1953) there was evidence of failure of production of gonadotrophins and corticotrophin, but thyrotrophic hormone was secreted in normal amounts, again illustrating the possibilities of differential pituitary failure.

The coma of hypopituitarism, which has always been a rather puzzling feature of the disease, has been the subject of several publications in recent years—for example, Allott and Simmons (1951), Caughey *et al.* (1952), Sheehan and Summers (1952), etc. In a discussion at the Royal Society of Medicine, Caughey and Garrod (1955) pointed out the risk of coma from pituitary surgery in the presence of severe endocrine failure, and the value of cortisone in reducing that risk. Surgery in the neighbourhood of the pituitary gland and haemorrhage into a cystic pituitary adenoma are additionally dangerous because of the possibility of mechanical effects on the hypothalamus and other vital centres. Other precipitating causes of hypopituitary coma can also affect consciousness in patients without endocrine failure, provided the stimulus be intense enough. The difference in severe hypopituitarism is that the threshold of consciousness is set at a much lower level than normal, so that coma sometimes occurs with very slight provocation. The principal factors are hypoglycaemia, infections, water intoxication (because of the failure to excrete water at a normal rate owing to the secondary adrenal insufficiency), sodium depletion (apparently a rare cause), postural hypotension, and hypothermia (due apparently mainly to the secondary myxoedema). Caughey and Garrod show an ingenious diagram correlating, so far as possible, these various factors and indicating the appropriate counter-measures.

Some Recent Advances in Problems of Intersexuality

The recognition and differentiation of various forms of human intersexuality has gained a good deal of ground in recent years, and considerable impetus has been given to the advance of knowledge in this field by the development of a new and potent research tool—namely, chromosomal sex differentiation. Although it had been known to entomologists for some twenty years that morphological differences in the nuclei of somatic cells could be detected in the males and females of many species of insects, it is only since the work of Barr and his colleagues (Barr and Bertram, 1949; Barr *et al.*, 1950; Moore and Barr, 1953; Moore *et al.*,

1953), dating back a mere six years, that similar differences have been shown to exist in mammals, including humans. These workers have introduced the skin-biopsy technique for sex differentiation, and have reported that the cells in buccal scrapings can also be employed for the purpose (Moore and Barr, 1955). Davidson and Robertson Smith (1954) demonstrated that the nuclei of polymorphonuclear leucocytes in blood films may show sexual dimorphism—confirmed by Riis (1955), by Romatowski *et al.* (1955), and by Sun and Rakoff (1956)—and it seems probable that use of the blood film is in fact the simplest method of all.

The first accession to knowledge of problems of human intersexuality coming through the use of these new techniques relates to the question of sex in Turner's syndrome (sometimes called Bonnevie-Ullrich-Turner syndrome). The subject of this disorder usually appears to be a somewhat stunted, infantilistic girl, who may show various congenital anomalies, of which webbing of the neck and cubitus valgus are perhaps the commonest, and who has primary amenorrhoea with a high output of urinary gonadotrophins (primary hypogonadism).

The fact that male examples of this syndrome are very rare, together with the further curious fact that, while coarctation of the aorta is a common anomaly in girls with Turner's syndrome, it is otherwise decidedly commoner in males than in females, led Polani *et al.* (1954) to suspect that some at least of the apparent female cases of Turner's syndrome might be completely intersexualized genetic males. They therefore determined the chromosomal sex in three “female” patients with Turner's syndrome associated with coarctation of the aorta, using skin biopsies, and found them all to have the male chromosomal pattern. Soon afterwards Wilkins *et al.* (1954) reported on eight patients, all apparent females, with this syndrome, and found six to have male and two female epidermal nuclei. Wilkins and his colleagues (Grumbach *et al.*, 1955) have now increased the “score” to 20 out of 22 of these patients showing male chromatin. The earlier experimental work of Jost (1947) and of Raynaud and Frilley (1947) should be mentioned, since it, together with the discoveries described above, helps a great deal to explain the situation in Turner's syndrome and in some other related forms of intersexuality.

The work referred to demonstrated that removal or destruction of the gonads of embryos in mice and rabbits in the sexually indeterminate stage leads to the development of foetuses, all of which are apparently female, the males having undergone intersexualization. It is now generally supposed that in Turner's syndrome there is a failure of migration from the yolk sac endoderm of the primordial germ cells, the sex of which is determined genetically at the time of fertilization, or of their penetration into the cortex of the primitive ridge; in consequence of this, further differentiation of the gonad does not occur, leading to the “gonadal agenesis” which is an essential part of the syndrome. The embryo is thereby left in the same state as those in the experiments of Jost and of Raynaud and Frilley mentioned above, and if genetically male it develops into an intersexualized “female.” Evidently the normal foetal male gonad secretes a hormone necessary for the differentiation of the male genital tract.

Another fascinating form of completely intersexualized male is a variety of male pseudohermaphroditism, first recognized as such by Goldberg and Maxwell (1948), and subsequently receiving attention from several other writers (Schneider *et al.*, 1952; Williams, 1952; Beatty *et al.*, 1953; Armstrong, 1955). This variety is referred to by Williams as “intersex males with purely feminine external genitalia and body habitus.” Such individuals appear as essentially normal females, who commonly present on account of the primary amenorrhoea. Breast development is normal, though the nipples and areolae tend to be small. The external genitalia are normal, but the labia are small. There is a short vaginal pouch which ends blindly, the cervix being absent; and the uterus is absent or rudimentary. Axillary hair is absent and pubic hair scanty or absent. The

gonad is usually intra-abdominal, most often in the position of the ovary, but not infrequently it is in the inguinal canal, when it may be associated with a hernia. Histological examination of a gonadal biopsy shows it to be a testis. The vaginal smear shows a degree of cornification such as would not be found in primary amenorrhoea due to hypogonadism; the source of the oestrogens is the testes. The paper by Grumbach *et al.* (1955) is an important contribution to the further understanding of the relationship between the various types of male pseudohermaphroditism and the gonadal dysgenesis syndrome.

A further, related variety of male pseudohermaphroditism was described by me (Swyer, 1955). By means of chromosomal sex determination techniques, I concluded that two patients presenting with primary amenorrhoea were apparently of male sex. Unfortunately, the opportunity of doing gonadal biopsies on these patients has not arisen, but it would seem that little doubt of their genetic sex need be entertained, since Greenblatt and Carmona (1955) described a very similar case of what they called a "eunuchoid female," whose chromosomal sex was male and on whom laparotomy revealed rudimentary gonads, histological examination of which showed a cortex composed of stroma without follicles and a medulla and hilus containing many "Leydig cells." These patients differ from the "classical" type of pseudohermaphrodite described above; they appear as eunuchoidal "females" with primary amenorrhoea, having normal pubic and axillary hair, little or no mammary development, and normal external genitalia except for marked enlargement of the clitoris in one of my patients and in that of Greenblatt and Carmona. The cervix is nearly normal, the uterus hypoplastic, the vaginal smear hypo-oestrogenic. Strangely enough, the oestrogen levels seemed to be definitely higher than those found in other cases of primary amenorrhoea. Both my patients responded to oestrogen treatment by producing uterine bleedings on withdrawal. The possible significance of these findings and the differential diagnosis of primary amenorrhoea of endocrine origin have already been discussed (Swyer, 1955).

It is clear that when confronted with a patient complaining of primary amenorrhoea the possibility of intersexualization must be borne in mind. It goes without saying that if such a diagnosis is established neither the patient nor her relatives should be given any grounds for suspicion that an anomaly of sexual differentiation exists. To explain that there is some degree of abnormal development of the genital organs which would prevent conception but not normal marriage (apart from child-bearing) should be quite sufficient.

REFERENCES

- Allott, E. N., and Simmons, J. H. (1951). *British Medical Journal*, **2**, 568.
 Armstrong, C. N. (1955). *Ibid.*, **1**, 1173.
 Barr, M. L., and Bertram, E. G. (1949). *Nature (Lond.)*, **163**, 676.
 — Bertram, L. F., and Lindsay, H. A. (1950). *Anal. Rec.*, **107**, 283.
 Beatty, D. C., Champ, C. J., and Swyer, G. I. M. (1953). *British Medical Journal*, **1**, 1369.
 Bishop, P. M. F. (1954). *Recent Advances in Endocrinology*, Churchill, London.
 Bongiovanni, A. M., and Eberlein, W. R. (1955). *J. clin. Endocr.*, **15**, 1524.
 Burston, R. A., and Garrod, O. (1952). *Proc. roy. Soc. Med.*, **45**, 70.
 Caughey, J. E., James, A., and Macleod, E. K. (1952). *British Medical Journal*, **1**, 1216.
 Chalmers, T. M., Fitzgerald, M. G., James, A. H., and Scarborough, H. (1956). *Lancet*, **1**, 127.
 Conn, J. (1955). *J. Lab. clin. Med.*, **45**, 3.
 Crooke, A. C. (1955). *Lancet*, **2**, 1045.
 Davidson, W. M., and Smith, D. (1954). *British Medical Journal*, **2**, 6.
 Deming, O. B., and Luetscher, J. A. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, **73**, 171.
 Diezfelussy, E., Plantin, L.-O., Birke, G., and Westman, A. (1955). *Acta endocr. (Kbh.)*, **18**, 356.
 Dorfman, R. I., and Ungar, F. (1953). *Metabolism of Steroid Hormones*. Burgess, Minneapolis.
 Escanilla, R., and Lissner, H. (1942). *J. clin. Endocr.*, **2**, 65.
 Farrell, G. L., Banks, R. C., and Kolestsky, S. (1956). *Endocrinology*, **58**, 104.
 Gaunt, R., Renzi, A. A., and Chart, J. J. (1955). *J. clin. Endocr.*, **15**, 621.
 Goldberg, M. B., and Maxwell, A. F. (1948). *Ibid.*, **8**, 367.
 Gordon, E. S., Chart, J. J., Hagedorn, D., and Shipley, E. G. (1954). *Obstet. and Gynec.*, **4**, 39.
 Greenblatt, R. B., and Carmona, N. (1955). *J. clin. Endocr.*, **15**, 877.
 Gross, J., and Pitt-Rivers, R. (1952). *Brit. med. Bull.*, **8**, 136.
 Grumbach, M. M., Van Wyk, J. J., and Wilkins, L. (1955). *J. clin. Endocr.*, **15**, 1161.
 Hetzel, B. S., McSwiney, R. R., Mills, I. H., and Prunty, F. T. G. (1956). *J. Endocr.*, **13**, 112.
 Hubble, D. (1952). *Lancet*, **1**, 1123.
 — (1955). *Ibid.*, **1**, 1.

- Jailer, J. W. (1953). *Bull. N.Y. Acad. Med.*, **29**, 377.
 Jost, A. (1947). *C.R. Soc. Biol. (Paris)*, **141**, 126.
 Kendall, E. C. (1952). *Edinb. med. J.*, **59**, 1.
 Laragh, J. H., and Stoerk, H. C. (1955). Quoted by Gaunt *et al.* (1955).
 Lewis, A. G. (1952). *Proc. roy. Soc. Med.*, **45**, 63.
 Luetscher, J. A. (1952). *Ann. Rev. Med.*, **3**, 75.
 — and Axelrad, B. J. (1954). *J. clin. Endocr.*, **14**, 1086.
 Maddock, W. O., Leach, R. B., Klein, S. P., and Myers, G. B. (1953). *Amer. J. med. Sci.*, **226**, 509.
 Mader, I. J., and Iseri, L. T. (1954). *J. Lab. clin. Med.*, **44**, 895.
 Moore, K. L., and Barr, M. L. (1953). *J. comp. Neurol.*, **98**, 213.
 — (1955). *Lancet*, **2**, 57.
 — Graham, M. A., and Barr, M. L. (1953). *Swg. Gynec. Obstet.*, **96**, 641.
 Nelson, D. H., and Samuels, L. T. (1952). *J. clin. Endocr.*, **12**, 519.
 Norymberski, J. K. (1952). *Nature (Lond.)*, **170**, 1074.
 — Stubbs, R. D., and West, H. F. (1953). *Lancet*, **1**, 1276.
 Oelbaum, M. H. (1952). *British Medical Journal*, **2**, 110.
 Paschkis, K. E., and Cantarow, A. (1951). *Ann. intern. Med.*, **34**, 669.
 Polani, P. E., Hunter, W. F., and Lennox, B. (1954). *Lancet*, **2**, 120.
 Raynaud, A., and Frilley, M. (1947). *Ann. Endocr. (Paris)*, **8**, 400.
 Riis, P. (1955). *Dan. med. Bull.*, **2**, 190.
 Romatowski, H., Tolksdorf, M., and Wiedemann, H. R. (1955). *Klin. Wschr.*, **33**, 911.
 Schneider, R. W., Van Ommen, R. A., and Hoerr, S. O. (1952). *J. clin. Endocr.*, **12**, 423.
 Sheehan, H. L. (1939). *Quart. J. Med.*, **8**, 277.
 — and Summers, V. K. (1949). *Ibid.*, **18**, 319.
 — (1952). *British Medical Journal*, **1**, 1214.
 Simmonds, M. (1914). *Dtsch. med. Wschr.*, **40**, 322.
 — (1916). *Ibid.*, **42**, 190.
 — (1918). *Ibid.*, **44**, 852.
 Simpson, S. A., Tait, J. F., Wettstein, A., Neher, R., von Ew. J., Schindler, O., and Reichstein, T. (1954a). *Experientia (Basel)*, **10**, 132.
 — (1954b). *Helv. chim. acta*, **37**, 1163.
 — (1954c). *Ibid.*, **37**, 1200.
 Slessor, A. (1952). *Proc. roy. Soc. Med.*, **45**, 67.
 Steiger, M., and Reichstein, T. (1937). *Helv. chim. acta*, **20**, 1164.
 Summers, V. K. (1952). *British Medical Journal*, **1**, 787.
 Sun, L. C. Y., and Rakoff, A. E. (1956). *J. clin. Endocr.*, **16**, 55.
 Swyer, G. I. M. (1955). *British Medical Journal*, **2**, 709.
 Vogt, M. (1943). *J. Physiol.*, **102**, 341.
 Wilkins, L., and Cara, J. (1954). *J. clin. Endocr.*, **14**, 287.
 — Crigler, J. F., Silverman, S. H., Gardner, L. I., and Migeon, C. J. (1952a). *Ibid.*, **12**, 277.
 — (1952b). *Ibid.*, **12**, 1015.
 — (1952c). *Ibid.*, **12**, 257.
 — Grumbach, M. M., and Van Wyk, J. J. (1954). *Ibid.*, **14**, 1270.
 Williams, D. I. (1952). *British Medical Journal*, **1**, 1264.

CEREBRAL ANGIOGRAPHY IN A NEUROSURGICAL SERVICE

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Carotid angiography has become the main auxiliary method in the diagnosis of intracranial lesions, and systematic accounts of its technique as well as the radiological appearances have been given by many authors (Engeset, 1944; Wickbom, 1948; Bull, 1949; Lima, 1950; Dowling, 1950; Curtis, 1951). The procedure has become so standardized that its performance is not beyond the skill and facilities of many x-ray departments—quite apart from specialized neuroradiological departments working close to a neurosurgical unit. For this reason alone some account of its place in diagnosis is desirable. Furthermore, the development and elaboration of methods of isotope localization (Sweet and Brownell, 1955) make it essential that a careful assessment be made of the value of angiography in a large series of cases presenting as neurosurgical problems.

The investigation has been limited to a consecutive four-year series, so that the figures in no way represent our total experience in any pathological group. In the