ENDOCRINOLOGY IN CLINICAL PSYCHIATRY.

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INTRODUCTION.

THE range and precision of clinical endocrinology in recent years have been increased by the introduction of more and better purified hormones, and by the use of hormone analysis and physiological tests for endocrine function.

The importance of the anterior pituitary in many endocrine problems has been demonstrated, and it now appears that some disorders of other glands, such as the gonads, thyroid and adrenals, are secondary to disturbances of the control that it exerts on them through the medium of its special hormones. Among the modern reviews on the physiology and clinical pathology of the pituitary and adrenal glands, subjects outside the scope of this paper, those by Hildebrand and Rynearson (1943) and Kepler and Keating (1941), may be mentioned.

The complexity of endocrine inter-relationships introduces the difficulty of ascertaining to what extent symptoms are primary or secondary to a pituitary disorder, as for example in hyperthyroidism or myxoedema which can be of primary pituitary origin (Lerman and Stebbins, 1942), Cushing's syndrome and amenorrhoea. In psychiatry the difficulty is appreciably greater. Demonstration of undeniable endocrine disturbances does not authorize the claim that they have causal relationship with mental symptoms, and it is seldom possible to assess their relative importance. Nor is it certain in what way psychic events can influence endocrine function although, as in amenorrhoea following emotional upset, or hypopituitarism in anorexia nervosa, it is clear that it frequently does so. There is as yet no clear psychiatric illness due to endocrine causes entirely, or in great degree, and which can be cured by endocrine therapy. Recent work has shown that such conditions may yet be demonstrated, and if so are likely to be complex syndromes.

Most psychiatric hospitals and clinics lack the technical staff and facilities essential for biological assays and other special endocrine methods, so it is not surprising that the majority of papers published in recent years are concerned with treatment. Therapy in psychiatric cases has been mostly dictated by temporal and therefore presumably aetiological connections between physiological and mental events, notably the menopause, climacteric conditions and impotence. A substantial mass of evidence derived from this empirical method exists which shows that, although in some cases endocrine therapy can influence the course of mental events, in many others it is apparently without effect, in spite of the existence of endocrine disorders. There is a real need for objective methods to assess the nature and severity of endocrine factors and of their response to treatment.

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Endocrinological Methods in Psychiatry.

Among the means available for the objective study of endocrine function, i.e. biochemical, physiochemical, histological and hormone analyses, two—estimation of urinary excretion of 17-keto-steroids and the vaginal smear—have recently assumed considerable practical importance.

17-Keto-steroids.

Neutral 17-keto-steroids, the chief of the metabolic end-products of steroid metabolism, can be estimated colorimetrically, and expressed as milligrammes per 24 hours (Callow *et al.*, 1939, 1940). This amount is an index of the secretory activity of the adrenal cortex in females, and of the adrenal cortex and testes in males, and can be correlated with the output of androgens determined by biological assay. Normal ranges per 24 hours are 4·0 to 15·0 mgm. (Friedgood and Whidden, 1939); 3·5 to 14·6 mgm. for females, 9·4 to 20 mgm. for males (Patterson *et al.*, 1942). The daily output for each individual is fairly constant, although variations between individuals are wide, and increases from *nil* at birth to maximum at 18 years, maintained thereafter, with a sharp decline after middle age. Abnormally high values at any age are found in tumours and hyperplasia of the adrenal cortex, interstitial cell tumour of the testis, and sometimes in virilism and ovarian arrhenoblastoma (Talbot and Butler, 1942). Fraser *et al.* (1941) found that the normal range for men between 20 and 40 years was 8·1 to 20·6 mgm., for females 5·1 to 14·2 mgm., and considered that all urinary 17-keto-steroids are derived from the male gonads and adrenal cortex, approximately 5 and 9 mgm. respectively from each. Non-endocrine conditions, such as malnutrition, anaemia, gastro-intestinal disease, infections and especially liver disorders lower the level; they suggest that in uncomplicated cases the following values can be expected: Normal male, 14·0 mgm., female 9·0 mgm., female with Addison's disease 0·0 mgm., male with Addison's disease 5·0 mgm.; pan-hypopituitarism 0·0 mgm.; gonadectomized male 9·0 mgm., gonadectomized female 9·0 mgm.; hypothyroidism very low, sometimes no more than 0·5 mgm. per 24 hours. Thus this estimation has a considerable diagnostic value, and in females may be a definite indication of adrenal insufficiency. Electro-shock therapy and prefrontal leucotomy frequently effect a rise, presumably by interference with the cerebral control of the pituitary, as does injected corticotrophic hormone in hypopituitarism by stimulation of the adrenal cortex (Hemphill *et al.*, 1942; Hemphill and Reiss, 1942); chorionic gonadotrophin therapy stimulates the testis but not the adrenal cortex to increase production of 17-keto-steroids (Fraser *et al.*, 1941).

Vaginal Smear.

Changes in the type of cell and quantity of mucus seen in smears from the vaginal mucosa occur throughout the menstrual cycle and after the menopause (Papanicolaou and Shorr, 1935). Examination of the vaginal smear therefore furnishes important information on ovarian function. A simplified technique has been described by Geist and Salmon (1939), who classify smears from menopausal patients as follows:

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Reaction 1: Advanced oestrogen deficiency—absence of squamous cells, presence of leucocytes and small round or oval " atrophy " cells with darkly-staining nuclei.

Reaction 2: Moderate oestrogen deficiency—varying number of large epithelial cells with fairly large nuclei; a proportion of " atrophy " cells.

Reaction 3: Slight oestrogen deficiency—majority of cells are large epithelial, varying in shape and size, often seen in clumps; few or no " atrophy " cells.

Reaction 4: No oestrogen deficiency—large flat squamous cells with small well-staining nuclei rather smaller than in reaction 3. No atrophy cells, few leucocytes.

Adequate treatment with oestrogens transforms the type of smear according to the changes induced in the vaginal mucosa, and atrophic characters may be entirely removed (Papanicolaou and Shorr, 1936). The appropriate dosage of oestrogens and the duration of therapy can be largely judged on the vaginal smear response. Atypical vaginal smears are not uncommon, and considerable experience is required for their interpretation. These and other complications of the method have been described in detail by Mack (1943).

Endocrine Preparations.

Modern endocrine preparations in use may be considered as anterior pituitary hormones, gonadotrophic hormones, female and male sex hormones, adrenal cortical hormones. Corticotrophic and thyrotrophic hormones, by means of which the pituitary maintains the functional activity of the adrenal cortex and the thyroid and capable of restoring these glands when atrophied, are not available in large quantities. The former has already been used therapeutically in psychiatry, and the latter in hypothyroidism secondary to hypopituitarism. Gonadotrophic hormone is supplied in two forms—from the serum of pregnant mares and from pregnancy urine. The former causes ripening of ovarian follicles and stimulates spermatogenesis; the latter, which chiefly influences corpus luteum formation and the interstitial cells of the testis, has been extensively used in the treatment of male hypogonadism and undescended testis.

Probably none of these preparations are chemically pure and their actions are not simple; there may be several combinations of hormones secreted by the anterior pituitary with gonadotrophic actions, some of which are reproduced by hormones of pregnant mares' serum and pregnancy urine. The usual dose of each is 500 units, repeated two or more times weekly for a number of weeks according to the indications (Simpson, 1942).

Oestrogenic hormones are administered, preferably by injection or implantation, as oestrone, oestradiol, oestradiol benzoate in oily solution, or allied substances, the so-called natural oestrogens, the last named being the most potent, and stilboestrol and hexoestrol, synthetic oestrogens, highly effective by mouth but liable to produce toxic reactions. There is a wide latitude of dosage of natural oestrogens; a few hundred to 50,000 or more units have been advocated as a single dose. From 0·5 mgm. to 5·0 mgm. is about the range of stilboestrol. Hormones of the corpus luteum (progesterone) have not been

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used to any extent in psychiatry. An alternative to progesterone, which is only effective subcutaneously, is pregneninolon, active orally, administered in 20 to 50 mgm. doses (Zondek and Rozin, 1939).

For male sex hormone therapy the choice lies between testosterone propionate by injection, implantation, inunction, or in suppositories, and methyl testosterone orally (sublingually). The dose of the latter, which should be about three times the former, is from 10 to 50 mgm. or more per day (Dodds, 1942).

Extracts of adrenal cortex containing several hormones are used chiefly for substitution therapy in Addison's disease and in shock. One purified hormone, desoxycorticosterone (Doca), can be prepared synthetically. Its action is concerned with the transfer of sodium and potassium ions and regulation of water balance.

The function of the adrenal cortex is disturbed in acute infections and exhaustion, and therefore may play a part in the development of toxic exhaustive psychoses. It has been suggested that neurasthenic-like symptoms after acute infections respond well to adrenal cortical therapy, and may in this way be distinguished from functional neurasthenia (Greene, 1935). Adrenal cortical extracts and Doca are as yet in short supply.

Involutional Melancholia.

Mental changes at or after the menopause are common, and vary greatly in severity. Although predominantly affective reactions of depressive type there is often no history of previous mental illness.

Treatment with follicular hormone has been extensively used on the assumption that cessation of ovarian function with diminished production of oestrogens is causally related to mental change. The results claimed by different groups of workers often appear to be contradictory. These claims could be reconciled to some extent if a common classification of climacteric conditions were adopted, and if mild menopausal illnesses not requiring hospitalization were distinguished from the involution-melancholic psychosis. The latter has been divided into convenient clinical types as simple, paranoid, somatic and mixed according to the symptomatology (Eymon *et al.*, 1942); it is common experience that the prognosis is not equally good in all.

Menopausal symptoms may be both physical and mental, but are troublesome in only about 15 per cent. of normal women, of which a small proportion develop a severe psychosis. Nevertheless male and female involutional melancholia may rank about seventh in importance in mental hospital admissions (Palmer *et al.*, 1941).

The physical symptoms, apart from menstrual irregularities, are, for the most part, vaso-motor: hot flushes in head and trunk, sweats, attacks of aches in head and limbs, paraesthesiae, and neuralgic pains, chiefly in head and back of neck, intermittent breast swellings. Obesity is common, and when associated with low blood pressure is usually accompanied by mental changes (McDowell and Patterson, 1940).

Emotional instability, altered appetite and libido, impairment of concentration, lassitude, depression and vague neurasthenic manifestations are found

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in varying degree, and should be regarded as characteristic of the milder mental reactions. In severe involutional melancholia extreme depression, delusions of guilt and visceral malfunction, paranoid ideas, attempts at suicide, refusal of food, and agitated, resistive behaviour are prominent. Hot flushes and allied symptoms are not infrequently absent. This type of reaction may not be fully developed until a considerable time after the menopause. Detailed accounts of symptomatology are given by McDowell and Patterson (1940), and Hawkinson (1938), based on 1,000 cases.

The vaso-motor and milder neurasthenic symptoms can be observed in premature or atypical menopauses and after hysterectomy, although most markedly where there is a neurotic predisposition, and are to be regarded as largely of endocrine origin (Lewis and Jackson, 1940), but although it has been claimed notably by Ault *et al.* (1941) that involutional melancholia is an exaggeration of the climacteric symptom and curable by oestrogen, it is more generally held that the malignant symptoms depend on many interacting factors, of which the most important and prognostically unfavourable for hormone therapy is the pre-psychotic personality. Typically perfectionistic, penurious, over-conscientious, often lacking in humour and sexual drive, the keynote is " rigidity " (Postle *et al.*, 1941 ; Burlinghame and Patterson, 1941 ; Wittson, 1940). Eymon *et al.* (1942) failed to find any direct connection between the menopause, natural or surgical, and severe involutional melancholia, but noted a rigid pre-psychotic personality as the most important single aetiological factor.

It is believed that production of gonadotrophic and anterior pituitary hormones is balanced by the level of circulating oestrogen, being high when the latter is low ; with irregular ripening of ovarian follicles at menopause the oestrogen level falls and for a time there may be an excessive output of anterior pituitary hormones (Zondek, 1930). Increased urinary gonadotrophins have been observed as early as three days after oöphorectomy (Damm, 1936 ; Salmon *et al.*, 1940). It has been suggested that excessive production of anterior pituitary hormones is responsible for climacteric symptoms, especially vaso-motor disturbances, which do not occur when oestrogen level is low alone, but only if gonadotrophic hormone output is high (Nathanson *et al.*, 1940). Administration of oestrogen can reduce urinary gonadotrophins (Rowlands, Scharpey-Schafer, 1940), and it has been claimed that in this way symptoms are relieved by inhibition of the anterior pituitary, the urinary gonadotrophins' level being a guide to prognosis (Postle *et al.*, 1941 ; Lawrence *et al.*, 1941). Severinghaus (1941), on the other hand, asserts that increased output of gonadotrophins is seldom pathogenic, and that relief may be obtained by oestrogen therapy while it is still high ; Heller (1941) believes that there is no constant pattern for normal excretion of gonadotrophic hormones, assays having no clinical value except in extreme hypogonadism.

Involutional melancholia has been divided into types according to the prevailing endocrine picture (Hemphill and Reiss, 1940): (1) Pure hypo-ovarian ; menopausal symptoms prominent, usually considerable increase of fat. (2) Hypo-ovarian combined with hypo-thyroidism ; menopausal symptoms slight, degree of myxoedema, mental state usually severe agitated

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depression. (3) Hypo-ovarian combined with hyperthyroidism; mental and physical symptoms resemble type 1 with, in addition, obvious hyperthyroidism and some degree of anxiety. (4) Hypo-ovarian combined with hypo-adrenalism; marked loss of weight, asthenia, dry pigmented skin, loss of hair, delusions relating to alimentary disorders, anorexia, refusal of food and deep depression.

They believe that types 1 and 3, which are the more common milder climacteric changes, are related to over-activity of the anterior pituitary; in these types oestrogen therapy is indicated. On the other hand, types 2 and 4 seem to be related to hypo-function of thyroids, adrenals and gonads, secondary to pituitary insufficiency, and in these oestrogen therapy is more likely to be harmful. Types 2 and 4 are more commonly seen in the severe involutional melancholic psychosis, for which convulsive therapy is widely advocated.

Hormone Therapy.

For oestrogen therapy, natural oestrogens in the form of oestrone, oestradiol benzoate or similar products, orally, but more effectively by injection, are widely used.

The synthetic oestrogens stilboestrol and hexoestrol have the advantage of cheapness and greater potency when taken by mouth, but can produce toxic effects. Male sex hormones, testosterone propionate and methyl testosterone for oral and sublingual use have had some vogue. To obtain an equivalent effect, judged on the vaginal smear, after 11 days' treatment with oestrone 1 mgm. daily, alpha-oestradiol benzoate 0·42 mgm., diethyl-stilboestrol 0·5 mgm. respectively are required, somewhat contrary to the results of animal experiments (Stoddard and Metzger, 1942).

In general, menopausal patients excrete little oestrogen and excessive gonadotrophins. The vaginal smear is atrophic, mucus from cervical glands is scanty, viscid and cellular. After adequate treatment with oestrogen gonadotrophins are reduced, the vaginal mucosa is restored, and the cervical secretion becomes clear and acellular. Vaso-motor symptoms believed to be due to unopposed over-activity of the anterior pituitary usually disappear (Bennett, 1942). Dosage and duration of treatment should aim at accomplishing and maintaining these results.

It is claimed by some that with more prolonged and heavy therapy graver mental symptoms can be influenced, but this is much in dispute, and unsupported by physiological evidence.

The physiological action of oestrogen is probably complex, it may in part operate locally upon blood vessels. Reynolds *et al.* (1941) have shown experimentally that arteriole dilatation causes hot flushes; oestrogen prevents this effect by stabilizing the peripheral vascular tree, but may fail if psychogenic influences are outstanding. Although they found that oestrogen did fail in 10 out of 13 cases of induced menopause in the presence of strong psychic factors, they believe that flushing of the menopausal type cannot be produced by a neurosis alone if the ovaries are functioning normally. Oestrogen increases the blood content of the brain in experimental animals (Reiss and Golla, 1940); intense cerebral vascular dilatation may be the mechanism whereby it affects emotional and mental processes (Baruk and Racine, 1940).

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Individual requirements to produce a physiological result vary greatly: 10,000 to 20,000 units intra-muscularly every other day with a smaller maintenance dose thereafter (Ault *et al.*, 1941). 10,000 to 30,000 units every third day with 1,000 to 6,000 by mouth on intervening days until the vaginal smear is normal, with maintenance therapy for a further six months to one year (Hawkinson, 1938) have been found satisfactory.

Implantation of oestrone crystals to ensure a steady absorption of hormone for weeks or months has been advocated (Bennett and Linde, 1942; Salmon *et al.*, 1941; Bennett and Biskind, 1940). There is evidence that fibrous encapsulation sometimes interferes with absorption, and that over-dosage can occur (*vide* testosterone therapy).

Stilboestrol in doses of 1–5 mgm. by mouth is comparable to natural oestrogens in the relief of climacteric symptoms of surgical or natural menopause (Davis, 1940), and can keep the vaginal epithelium at the mid-menstrual form (Severinghaus, 1940), but may not impart the feeling of well-being customary to their use (Salmon *et al.*, 1940). Toxic symptoms, for the most part gastro-intestinal upset, vertigo, pruritus, oedema of the eyelids, fullness in vulva, are not uncommon with the doses of 1 mgm. daily (Rickles, 1941), and have been reported in 10 per cent. (Payne and Muckle, 1940), 64 per cent. (Salmon *et al.*, 1940), and erotic tendencies in a small proportion (Davidoff and Goodstone, 1942) of cases treated with stilboestrol.

A new oestrogenic preparation, oestrone sulphate, a mixture of conjugated oestrogens, has recently been introduced. It is effective by mouth, is less liable to cause toxic reactions than diethylstilboestrol and produces a greater feeling of well-being (Freed *et al.*, 1943). 1·25 mgm. are at least as potent as 2,000 international units of oestrogenic substance and may be more potent than 5,000 units (Sevringhaus and StJohn, 1943).

In order to minimize abnormal uterine bleeding, endometrial hyperplasia, anovulation, and other disadvantages of continuous oestrogen therapy, Palmer (1942) has recommended that diethylstilboestrol should be administered—0·1 to 0·5 mgm. daily by mouth for 21 days with no treatment for a further 5–10 days—in an attempt to simulate a normal cycle, the interval representing the menstrual period. Cyclical oestrogen therapy, although advocated for both, is more suited to younger patients than menopausal subjects where the object is continued relief of symptoms.

Menopausal hyperthyroidism due to over-production of thyrotrophic hormone can sometimes be controlled by oestrogen through the inhibitory effect it exerts on the anterior pituitary, thyroidectomy is ineffective (Goldman *et al.*, 1940).

Prolonged administration of oestrogen is not entirely harmless and can induce functional castration; great increase of eosinophilic cells in the pituitary has been noticed at autopsy after administration of 6,000,000 units in well-divided doses (Zondek, 1940); gross atrophy of adrenal cortex and medulla followed 750,000 units weekly for six months (Dynes, 1939), but there is no conclusive evidence that it has been responsible for uterine neoplasms. Increased sexual drive and pelvic discomfort occasionally aggravate psychic symptoms in mild cases (Heaver, 1940).

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Agitation is a common accompaniment of severe melancholia. On the assumption that it might be due to calcium deficiency, increasing neural activity, Palmer *et al.* (1941) and Strecker (1942) raised the blood-calcium level in a series of selected cases by administration of parathormone 50 to 100 units with ammonium chloride and calcium gluconate. They were unable to report any improvement. Calcium has been credited with augmenting the effect of oestrogen (Kuzrok *et al.*, 1938).

Testosterone has been used as an alternative to oestrogens to relieve climacteric symptoms. It can do so and seemingly inhibit pituitary activity without producing uterine bleeding, either alone or in combination with stilboestrol (Kurzrock and Rothbart, 1942), and with natural oestrogen (Wollner, 1941). The latter reported atypical growths in the cervical mucosa in two cases.

Implantation of testosterone pellets 25 mgm. may be a better alternative to testosterone 5–10 mgm. three times weekly (Silberman *et al.*, 1940). Careful control of dosage must be stressed, for masculinization has followed a six-months' course of testosterone 25 mgm. twice weekly (Hamblen, 1942), and a total amount of 850 mgm. (Greenhill and Freed, 1939).

There seems to be no justifiable indication for androgen in preference to oestrogen therapy in psychiatric disturbances of the female climacteric.

Results of Endocrine Therapy.

Marked improvement or cure in 80–90 per cent. of cases treated has been claimed by Ault *et al.* (1940 and 1941); considerably less optimistic were Hawkinson (1938), Notkin *et al.* (1940), Palmer *et al.* (1941) and others. The results depend on the selection of case material, the response to treatment being obviously very much better in early climacteric neuroses than in severe melancholic states.

The general conclusions that if all menopausal women suffering from various degrees of melancholia were treated with oestrogen the recovery-rate would be better, and the duration of the illnesses shortened than if all were untreated (Danziger *et al.*, 1942), but that only the simple type of illness is likely to be benefited, the severe psychotic picture being seldom altered (Davidoff *et al.*, 1943), are probably true.

Very many papers testify to the excellent results obtained in florid involutional melancholia by convulsive therapy and prefrontal leucotomy, and in such cases these would seem to be the methods of choice.

Hemphill and Reiss (1942) investigated and treated cases of involutional melancholia in which symptoms of hypoadrenalism, i.e. asthenia, " desiccated skin," cutaneous pigmentation, brittle hair, low blood pressure and very low excretion of 17-keto-steroids were combined with anorexia, delusions of alimentary disorder, and severe melancholic depression. They regarded the delusions as derived from adrenal insufficiency, secondary to hypo-pituitarism, with inadequate output of corticotrophic hormone. Treatment with a purified biologically active corticotrophic hormone brought about improvement in appetite and general physical condition with loss of the specific delusions of visceral illness. They suggested that these cases belonged to a group of

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involutional melancholics in which hypopituitarism following the menopause is a principal endocrine factor.

Prognosis.

The prognosis of involutional states depends less on endocrine than on constitutional and psychic factors. A strong affective element and absence of paranoid ideas with pliable pre-psychotic personality favour recovery (Burlingham and Patterson, 1941); attempts at suicide may therefore be of good portent (Brussell, 1940). Paranoid ideas, automatism, insufficiency of affect, continued gross somatic delusions, cerebral arterio-sclerosis and duration of illness of more than a year are of grave significance (Strecker, 1942).

In conclusion, in simple menopausal reactions, symptoms of neurotic and neurasthenic nature are combined with the usual climacteric and vaso-motor disturbances varying greatly in severity in individual cases; hyperthyroidism and anxiety may complicate the picture. There is considerable evidence that functional hyperactivity of the anterior pituitary is here of causative importance. Treatment with stilboestrol 0·5–5 mgm. daily by mouth until the vaginal smear is non-atrophic, climacteric symptoms relieved, and urinary excretion of gonadotrophins is low, with a small maintenance dose thereafter, or oestradiol benzoate by injection and later orally, if stilboestrol is badly tolerated, should be successful in the majority of cases. The vaginal smear furnishes the best objective evidence that treatment has been adequate (Ripley *et al.*, 1940); over-dosage is easily achieved and should be avoided, especially in maintenance therapy and prolonged courses of treatment. For the severe melancholic psychosis in which hypothyroidism or hypo-adrenalism are sometimes present, oestrogen therapy is unlikely to be effective, and may by inhibiting pituitary activity be harmful. Convulsive therapy is to be recommended here. There may be a place for corticotrophic and possibly thyrotrophic hormones as an alternative or adjuvant to shock treatment, when they become available in quantity.

MALE CLIMACTERIC.

The incidence of involutional melancholia in males is about one-quarter of that in females, and the onset between 50 and 65 about ten years later (Strecker, 1942). The diagnosis is often unclear, the picture being sometimes complicated by arteriosclerosis and early senility. Important symptoms are: Vaso-motor disturbances, flushes, facial pallor, impotence, loss of sexual interest, prostatic difficulties, headaches, irritability, weakness, fatigability, failing concentration, and in more severe cases agitation, restlessness, insomnia, delusions of guilt and bodily illness, suicidal intentions (Palmer *et al.*, 1941; Werner, 1939), and angina-like pains (McGavock, 1943). A combination of several of these symptoms in a man of over middle age without evidence of dementia should suggest the diagnosis. The symptoms have been attributed to excessive production of gonadotrophic and anterior pituitary hormones and/or defective internal secretion of the testis (Hamilton, 1941). Testosterone propionate by injection, methyl testosterone by mouth and pellets of testosterone by implantation have

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been used to replace testis hormones and to inhibit the anterior pituitary; Catchpole *et al.* (1942) showed that hypogonads excreted excessive urinary gonadotrophins, which fell to normal after three months' treatment with 20 to 70 mgm. of testosterone daily.

Implantation of 300 to 450 mgm. by a special trocar in the posterior axillary line, after an initial course of injections to estimate the requirements and response, has been claimed to maintain a therapeutic effect from 2 to 6 months (Eidelberg and Ornstein, 1941), but there is evidence that pellets become encapsulated and useless by 11 weeks, and that as absorption is irregular the response is not in ratio to the dose, methyl testosterone by mouth being more effective and economical (Escamilla and Lisser, 1941). Androgen therapy has disadvantages. Doses of 5 mgm. can for a while increase, but of 25 mgm. cause reduction in spermatogenesis in normal men (Rubenstein and Kurland, 1939). Rashes, vaso-motor disturbances and headaches and erotism have been recorded (Davidoff and Goodstone, 1942). Minimum therapeutic requirements may be 10 to 25 mgm. two to five times weekly, which have been found sufficient to inhibit spermatogenesis (Pardoll and Belinson, 1941). The reported results of endocrine therapy are not promising; 65 per cent. of one series improved, but this included only mild and moderately severe cases (Davidoff and Goodstone, 1942). Improvement was noted in about half only of another selected series (Dantziger and Blask, 1942). Some improvement in insomnia, headache and motor instability has been recorded (Hill, 1940). Zeifert (1942), employing massive doses, 1,300 mgm. in 40 days, observed no toxic effects, but reported benefit in milder reactions only.

Testosterone may relieve symptoms due to peripheral vascular disease through its local action on blood vessels (Edwards *et al.*, 1939); others have been unable to confirm this (Beaser and Massell, 1942); in the hypogonad it alters pigmentation of the skin, as indicated by the Hardy spectro-photometer (Edwards *et al.*, 1941), and when effective in males usually produces some flushing. It has been shown by endurance tests to produce improvement in dynamic work in eunuchoids (Simonson *et al.*, 1941), but not in normal men (Samuels *et al.*, 1942).

As in female involutional melancholia the most satisfactory form of treatment is convulsive therapy or leucotomy, for in severe cases androgen therapy is probably ineffective. The bulk of the evidence goes to show that testosteron propionate, preferably methyl testosterone orally (suppositories are available), may occasionally produce dramatic results in male climacterics where neurasthenic and vaso-motor symptoms are prominent, and is indicated if urinary gonadotrophins are excessive. It can impart a feeling of well-being by diminishing muscular fatigue and improving circulation if there is a genuine hypogonad element. It may be of benefit in early cerebral arteriosclerosis, and should be given a trial if this condition contra-indicates shock treatment.

Anorexia Nervosa and Hypopituitarism.

Several hypotheses have been advanced to explain the origin of anorexia nervosa, the physical picture of which closely resembles Simmond's disease. Among the more important are: That its cause and development are entirely

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psychogenic; that, following an initial psychic upset, inadequate intake of food and undernutrition produce functional depression of the pituitary and secondary insufficiency of gonads, thyroid, and adrenals; that it is a special or mild form of pituitary cachexia; that it is "cerebral" hypopituitarism, due to alteration of the cerebral control of the pituitary. In spite of the large number of contributions and the considerable interest the subject has aroused, no one hypothesis is entirely satisfactory or generally accepted.

Reviewing 595 case-histories of Simmond's disease and relevant literature, Escamilla and Lisser (1942) give the following as cardinal symptoms: (1) Loss of weight, (2) loss of sexual function, (3) asthenia, (4) low basal metabolic rate (around minus 20). Pregnancy antedated symptoms in 42 per cent. of verified cases, the majority of which were adult females; in some the illness endured for as long as 40 years. Substitution therapy with various endocrine preparations was of value in 60 per cent.

The symptoms of Simmond's disease are due in part to secondary atrophy of gonads, thyroid, and adrenals, from failure of production of anterior pituitary hormones, frequently the result of necrosis of the pituitary following pregnancy. The term Simmond's disease is usually applied to post-partum hypo-pituitarism, but it is generally agreed that a pituitary cachexia can result from pituitary damage due to other causes. Male cases have been described, diagnosed by weight loss, debility, asthenia, loss of hair, skin changes, genital atrophy, hypotension, hypoglycaemic attacks, and reduced excretion of anterior pituitary hormones (Mogensen, 1940; Salomon and Lascano, 1942). Improvement after treatment with chorionic gonadotrophic hormone (Mogensen, 1940), with thyroid extract, testosterone and desoxycorticosterone (Williams and Whittenberger, 1942), with hypophyseal grafts (Marti, 1942; Rochat, 1942), have been recorded. Substitution therapy, however, is seldom of much value in anorexia nervosa (Richardson, 1939).

The clinical picture of a well-developed case of anorexia nervosa corresponds with that of pituitary cachexia in that emaciation is profound, basal metabolic rate usually low, sexual function depressed, but by contrast the subjects are commonly young unmarried women of neurotic obsessional personality, although males have been reported. An important point in the differential diagnosis of anorexia nervosa is that restless hyperactivity is common, as opposed to the weakness and comparative inactivity of Simmond's disease (Brosin, 1941).

Fraser and Smith (1941) have sought to differentiate between organic pan-hypopituitarism and "functional" anorexia nervosa by estimation of 17-keto-steroids and an insulin tolerance test. In the organic disorder they found extremely low or no excretion of 17-keto-steroids, and after injection of insulin under controlled conditions, delay of blood sugar in returning to normal. 17-keto-steroid output was often low in anorexia nervosa, but in no case entirely absent. Although neither test is specific, they believe that the combination of both enables a diagnosis of pan-hypopituitarism to be made with fair accuracy. Their work does not exclude the possibility that so-called functional cases suffered from hypopituitarism, but in less degree than the organic, and it is noteworthy that they do not report conclusive cures by psychotherapy alone.

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A low output of 17-keto-steroids in women indicates adrenocortical insufficiency, which in its turn may be secondary to inability of the pituitary to produce adequate corticotrophic hormone. Weakness, skin and hair changes, hypotension and alimentary disturbances are included in the symptomatology of adrenal failure. Hemphill and Reiss (1942) have described cases of melancholia of both sexes in which these symptoms existed. Some of the females were unmarried; a proportion of the others had had previous pregnancies. In typical examples excretion of anterior pituitary hormones was *nil* and of 17-keto-steroids very low. Injected corticotrophic hormone caused improvement in appetite, nutrition and mental state; 17-keto-steroid output rose to normal level, attributable to trophic stimulation of the adrenal cortex. It appears that adrenal failure is a main factor in symptom production in hypopituitarism. In anorexia nervosa histo-pathological changes in the pituitary are not found at autopsy (Brosin and Apfelbach, 1941).

On the whole, the pathogenesis of anorexia nervosa suggested by Stephens (1941) seems to be the most acceptable. As a result of some mental disturbance appetite is lost and food intake is reduced. Atrophic and functional insufficiency of pituitary and other endocrines ensues primarily from gross under-nutrition. Depression of adrenals, thyroid and gonads occurs secondary to hypopituitarism, metabolism is affected and the typical physical picture is thus produced. Psychotherapy and adequate feeding may reverse these changes unless extreme; endocrine preparations may be unnecessary, but probably anterior pituitary hormones will assist (Doane *et al.*, 1939; Magendantz and Prager, 1940). Corticotrophic hormone is indicated if 17-keto-steroid output is low; when effective there should be an increase towards normal. It is improbable that deliberate starvation alone, unaccompanied by neuro-psychic irregularity, can produce the picture of typical anorexia nervosa. In hunger-striking prisoners, for example, weakness is often an earlier symptom than emaciation, and prohibits much effort and physical activity. Body cold, seemingly not experienced in anorexia nervosa, is keenly felt and complained of.

It is possible that an abnormal psychic state may, by interfering with the cerebral control of the pituitary, depress its function. One such case has been described (Reiss, 1943). Gross emaciation gave place to pathological obesity. He has proposed the designation "cerebral" pituitary cachexia for anorexia nervosa.

In conclusion the diagnosis of functional anorexia nervosa should not be made if excretion of anterior pituitary hormones and 17-keto-steroids is markedly subnormal. Motor hyperactivity out of proportion to the muscle bulk, apparent strength and the characteristic combination of the age, sex and personality type suggest the diagnosis. Where there is objective evidence of low hormone excretion anterior pituitary hormones should be administered coincidentally with other measures.

Substitution therapy offers the only hope in organic hypopituitarism.

Pregnancy and Puerperium.

Mental disturbances in pregnancy and the puerperium occur in 1 to 2 per cent. of cases; there is no characteristic psychotic reaction (Cruikshank, 1940;

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Wick, 1941; Kraines, 1941; Skottowe, 1942), and no evidence of a specific lactational psychosis. Schizophrenia and manic-depressive illnesses appear to account for about 60 per cent. of the total, but there is considerable disagreement between different authors, toxic-exhaustive reactions being cited at 3·6 per cent. (Smaldon, 1940) and 38 per cent. (Cruikshank, 1940). Boyd (1942) gives the following distribution: Manic-depressive 40 per cent., schizophrenic 20 per cent., delirium 28·5 per cent., psycho-neurosis 6 per cent., psychopathic personality 5 per cent., other conditions 0·5 per cent. Primiparae are most commonly affected (Imaz and Dubrowsky, 1939), but in Smaldon's (1940) series of 64 cases of dementia praecox, out of 220 pregnancy reactions multiparae predominated.

There is no case for terminating pregnancy as a prophylaxis, for repeated pregnancies do not necessarily cause subsequent psychotic recurrences (Howarth, 1939), and with the most complete family and personal history attacks cannot be predicted in more than 50 per cent. (Skottowe, 1942). A minority of reactions occur during gestation; the prognosis in ante-partum schizophrenia is very unfavourable (Cruikshank, 1940). Apart from constitutional make-up, severe emotional stress and malnutrition have been, it appears justifiably, cited by Howarth (1939) as important in the aetiology, and it is emphasized that adequate dietary control may prevent recurrences.

Although there is little evidence that any endocrine dysfunction has a specific influence, cases of puerperal schizophrenia have apparently cleared up after treatment with progesterone, possibly by correction of placental loss of luteal hormone which accentuated a psychotic reaction (Blomberg and Billig, 1942; Schmidt, 1943).

Treatment with luteal hormone, therefore, may be worth trying empirically in post-partum psychoses, and may even be indicated where there is a history of persistent premenstrual tension, or frequent anovulatory phases.

Mental Disturbances Related to the Menstrual Cycle.

Fluctuations in mental and emotional stability are observed in a fair proportion of women during the menstrual cycle. The incidence of fits in some epileptics bears a constant relationship to menstruation. Disturbances of water metabolism through the action of steroid hormones or hormonal imbalance may be of importance. Oedema seen in the premenstrual phase has been shown to be due to the water-retaining properties of steroid hormones (Thorn *et al.*, 1938). Relief of premenstrual discomfort may be obtained by administration of ammonium chloride in large doses, with the object of discharging sodium retention and thereby securing increased output of water (Greenhill and Freed, 1940), and may rationally have an application in the treatment of epilepsy, associated with water retention. Progesterone to replace insufficient production of corpus luteum hormone, a usual hormonal disbalance of anovulatory menstrual phases, has been advocated for the treatment of mental swings in the menstrual cycle (Israel, 1938; Schmidt, 1943). A more effective way of securing the same result is by injection of gonadotrophic hormone of pregnant mares' serum in the early part of the menstrual cycle to stimulate follicular ripening, ovulation and therefore formation of luteal hormone.

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Schizophrenia.

In no psychosis or group of psychoses can endocrine abnormalities be demonstrated as readily and with such a diversity of form as in schizophrenia. Nevertheless, apart from certain thyroid relationships, which have an importance with special forms of schizophrenia, no endocrine disorders have yet been described which consistently form part of the symptom picture of any schizophrenic reaction, and whose treatment has produced mental cure.

It has long been recognized that in schizophrenia the response to thyroid feeding is variable and sometimes unexpected, and occasionally mental improvement does take place (Hoskins and Sleeper, 1929; Angyal *et al.*, 1940). Cohen and Fierman (1938) found that in some schizophrenics daily administration of 15 to 18 gr. thyroid extract did not produce toxic or psychic effects, and that in spite of a great increase in oxygen consumption the pulse-rate fell after reaching a maximum of 110. It is not known why these anomalies are found nor what constitutes the form of schizophrenia in which they occur, but one clinical entity has been investigated in which fluctuations in mental state can be correlated with metabolic disturbances, susceptible to the influence of thyroid hormone.

Periodic Catatonia with Periodic Disturbances of Somatic Function.

Under this heading Gjessing (1938, 1939) described a small group of schizophrenics, perhaps not more than 3 per cent. of all cases, in whom catatonic phases coincided with abnormal retention or excretion of nitrogen. He demonstrated that if the nitrogen retention was depleted by administration of thyroid hormone, in the positive storage type, the patient emerged from catatonia and could be kept well thereafter by a maintenance dose. Complete estimations of nitrogen balance are beyond the resources of most mental hospitals, but thyroid extract should be tried empirically in periodic or recurring catatonia. Hardwick and Stokes (1941) investigated nitrogen metabolism in cases believed to belong to Gjessing's group, and others as controls. They give the following criteria by which patients suitable for thyroid treatment may be recognized without preliminary biochemical studies: (1) Rhythmic illness of periodic catatonic type; (2) phases of illness always associated with increase of temperature, pulse and basal metabolic rate; (3) good tolerance of thyroid; (4) gain of weight during treatment.

Hyperthyrotic Catatonia.

A small group of female schizophrenics in which thyrotoxicosis was associated with catatonic phases, sometimes amounting to stupor, visual hallucinations, and disturbance of the body image, has been described by Hemphill (1942). Spontaneous recovery occurred in all cases; in some there had been previous attacks and remissions. There was no evidence of thyrotoxicosis, nor of goitre, associated with schizophrenia of any other form in a large series of mental patients. Relevant literature shows that schizophrenic reactions are by far the rarest mental complications of hyper-thyroidism, and tends to confirm the suggestion that when they occur, they have this special form in

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which the ultimate result is remission irrespective of the severity of the psychotic symptoms. The extreme rarity of goitre, in spite of the similarity in age-incidence, is a further illustration of endocrine hypoplasia in schizophrenia of early life.

Gonadal Function in Schizophrenia.

Testicular biopsy has been used by Hemphill *et al.* (1943) to demonstrate atrophic and degenerative changes in the testis in schizophrenia. The histological appearances were similar to those described by Mott (1919), and were not in proportion to the age, physical state of the patient, or to the duration of the psychosis. The testis appeared to be damaged most severely where symptoms had developed soon after puberty and in the rapidly dementing and deteriorated chronics, least where the onset dated to the late twenties and in the paranoid and mild chronic types. The pathological picture of severe testicular damage resembled in certain respects the secondary atrophy produced by hypophysectomy in animals. The analogy suggests an original pituitary disorder in schizophrenia antedating the histological and presumably mental pathology, and may provide a basis for treatment with anterior pituitary hormones.

Attempts to correct apparent gonadal disorder in schizophrenia with testosterone have been made by Helman (1939), Hoskins and Sutherland (1942), and with desoxycorticosterone by Haynes and Carhill (1941), who claim to have produced improvement but no definite cure. On the case-material and results it cannot be fairly asserted that these preparations in the dosage employed have any therapeutic value in schizophrenia.

Rosenweig and Frieman (1942) administered thyroid extract, testosterone and anterior pituitary gonadotrophin simultaneously to selected cases. They have reported that their patients responded by showing an increase of sexual interest, as measured by an instrument of their own devising, the "photoscope." Their work goes no further than to show that some psychological alteration, and possibly increase of psychic libido, can be stimulated in certain examples of schizophrenia by administration of hormones. It cannot be construed to indicate that hypogonadism is a common clinical symptom requiring specific treatment. Inadequate secondary sexual characteristics and homosexual tendencies were treated with testosterone in seven young cases of schizophrenia (Barahall, 1940). There was improvement in the somatic symptoms and increased growth of hair; mental state was unaffected.

Among other reports of endocrine irregularities, hypercreatinuria in 14 out of 20 cases, some without regression of secondary sexual characteristics (Stora and Tchernikowsky, 1938), and failure to respond in a normal way to injected pitressin by intestinal cramp and raised blood pressure (Finkelman and Simon, 1939) have been recorded.

Chemical studies of the level of adreno-cortical substances in blood during hypoglycaemic and shock treatment of schizophrenia were made by Tietz and Birnbaum (1942). They found, in 29 cases, that recovery was accompanied by a rising adreno-cortical substance level, after coma and electro-convulsive therapy. Failures showed low values and a great susceptibility to shock.

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In conclusion, there is a large body of scattered evidence indicating endocrine disturbances in schizophrenia, sufficient to prompt the suggestion of Hoskins (1943) that an abnormal sensitivity to sex hormones may be a major causative factor. But it is as yet too indefinite and incomplete to be a guide to therapy. This in the present state of knowledge should serve to discourage the indiscriminate use of potent hormone preparations.

Thyroid extract is worth a trial in cases of recurring or periodic schizophrenia that conform to the criteria given above. Spontaneous recovery is probable in schizophrenic reactions associated with thyrotoxicosis.

Mental States Associated with Disorders of the Thyroid.

(1) *Thyrotoxicosis.*—Mental reactions are uncommon in toxic goitre. Newton (1938) reported 4, confusion or depression, in 450 consecutive cases ; 3 survived operation ; their mental symptoms were not relieved. Howard and Ziegler (1942) investigated 70 thyroidectomized patients from the psychiatric angle. Prevailing disorders were depression, elation, or psychoneuroses ; delirium was infrequent and slight ; schizophrenia was not seen. They found no evidence that emotional states could cause hyperthyroidism. In the differential diagnosis between anxiety and hyperthyroidism, Beck (1939) maintains that apart from severe bodily illness in the latter there is no single symptom or combination of symptoms that have not been observed in both. The history alone furnishes a clue. It has been claimed that measurement of the impedance angle, an electrical property of the body, which has been used to assess degrees of hyperthyroidism (Brazier, 1933), could provide this distinction, but the value of this test has been seriously questioned on theoretical and clinical grounds by various workers. Hyperthyroidism is sometimes a complication of the menopause. It is then usually associated with depression and should be treated with oestrogens ; operation is ineffective (Wohl and Pastor, 1941).

Myxoedema.—Psychotic reactions in myxoedema are rare. Crowley (1940) observed 2 out of 4,500 mental admissions in 14 years. In both there was a paranoid state occurring after the menopause, probably a form of involutional melancholia, with special somatic delusions that the face was changed and visceral functions altered. Treated with thyroid extract both recovered. Wolfson (1940) has described two cases of myxoedema with restless confusion in the seventh decade which improved with thyroid treatment.

Therefore, apart from the references made in the section on schizophrenia, recent work has shown no specific relations between disorders of the thyroid and mental illness, and it appears that mental reactions are probably incidental. Thyroidectomy can in no case be advocated for the relief of mental symptoms.

Psychoses in Hypo-parathyroidism.

There is no psychosis characteristic of hypo-parathyroidism, but psychotic symptoms in 5 out of 18 cases of this uncommon condition have been described (Green and Swanson, 1941). Anxiety and a sense of impending disaster were common general symptoms, usually followed by toxic delirium during the first four months ; delusions of persecution, sexual hallucinations, and attempts at

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suicide were also observed. The prognosis is good. After adequate treatment for tetany the mental symptoms cleared up.

Deficiency Diseases.

Some evidence that anterior pituitary activity influences utilization of the vitamin B group has been provided by Sutton (1942). Great improvement was reported after treatment with anterior pituitary extract in severe pellagra, which had failed to respond adequately to vitamin B complex. Equivalent results were obtained with gonadotrophic hormone, and its use is recommended in alcoholic polyneuritis as well as pellagra. A further paper by Ashworth and Sutton (1942) provides supporting evidence. Administration of oestrogens in their cases of subclinical vitamin B complex deficiency produced polyneuritis, pellagra and cheilosis; the early symptoms were tenderness and pain in the nasal mucosa. They suggest that this deficiency is due to additional strain on the liver, but as it is now accepted that oestrogens can inhibit the anterior pituitary, it is more likely that disturbance of the anterior pituitary-vitamin B relationship is more important. There is much evidence from experimentally produced vitamin deficiencies in animals that spermatogenesis can be revived by administration either of additional vitamins or alternatively of a gonadotrophic hormone. Whether a disturbance of the pituitary is responsible for failure to utilize vitamin B, or is itself secondary to this vitamin lack in humans, is not known, but it is clearly of value to treat intractable polyneuritis and pellagra with gonadotrophic hormone or potent anterior pituitary extracts as well as vitamin B complex, and to ensure complete vitamin requirements during oestrogen therapy. This is of special importance in melancholic patients who are under-nourished and refuse food.

Confusional Insanity.

The value of cortical suprarenal extract in certain types of acute confusion has been reported by Hoff and Straby (1940). Five cases of confusion in typhoid fever and four due to post-partum haemorrhage treated with suprarenal extract (cortigen, 2 c.c. intravenously daily) cleared up quickly. No response was obtained in other types of confusion. Indications for this treatment are low blood pressure, asthenia and pale yellow complexion. It is probable that where there has been severe loss of fluid and alteration of the sodium-potassium balance, suprarenal cortical extract by its specific action on electrolytes and body fluid has therapeutic value.

Epilepsy.

Although there is so far no direct evidence of an endocrine origin for epilepsy, disturbances of water balance can produce seizures in predisposed individuals. This fact has been used to differentiate between idiopathic epilepsy and hysterical fits. The test aims at inhibiting diuresis and increasing body hydration, by administration of pitressin and large quantities of water. A modified technique has been described by Blyth (1943) as follows: The bowels and bladder cleared, the patient is weighed and confined to bed. Sedatives are

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discontinued, ordinary diet maintained, and a copious intake of fluids ordered. The amount ingested and urinary output are measured and charted daily and the patient weighed morning and evening. An increase of 2 per cent. in body weight, with ingestion showing an increase over excretion, is evidence that a positive water balance has been established. This is attained on the average in 48 hours. ·25 c.c. of pitressin intramuscularly and 300 c.c. of water orally are then administered, followed thereafter by ·5 c.c. of pitressin and 300 c.c. of water every two hours up to ten doses, unless a fit results before. In susceptible cases fits usually occur by the fifth or sixth injection. Blyth claims that an accurate diagnosis was obtained in 87 unselected cases of average adult age. Fits were not produced in hysterical and non-epileptic subjects. Contra-indications to the use of pitressin are diabetes, nephritis, hypertension and cardio-vascular degeneration. Although this test will not necessarily demonstrate the existence of epilepsy in every epileptic subject, a positive result excludes certain non-epileptic conditions, e.g. hysteria, in epileptic suspects after as short a period as 72 hours' observation and hospitalization. The usually disagreeable nature of the test and limited information it affords should restrict its application to where a potential economy in time is of paramount importance.

Manic-Depressive Psychoses.

Apart from observations on affective reactions occurring after the menopause, a proportion of which are of the manic-depressive group, very little has been published about the endocrinology of this subject. Cahane and Cahane (1939) described hyperpituitarism in 50 per cent. of a series of manic-depressive psychotics (some in each phase). They base their statement on hypertrophy of the thyroid, excess of thyrotropin, and positive melanophore reaction in urine. Apparently their work has not been followed up, nor provided any basis for endocrine therapy in the manic-depressive psychosis.

Abnormal Sexuality.

Homosexuality.

Allen *et al.* (1938) have discussed at length endocrine and psychological causes of homosexuality. They have produced evidence that both may provide a basis for the aberration, and have reported cases where more heterosexual behaviour was noticed after unilateral adrenalectomy. Their investigations do not exclude homosexuality occurring in a normal endocrine constitution.

Histological studies of testes from what was described as a pathologically bi-sexual individual, failed to provide evidence of a pathological condition responsible for the psychic abnormality (Bogliolo, 1937).

In an attempt to find endocrinological co-relationships, estimations of androgens and oestrogens were made in 200 physically normal subjects; in 25 out of the 29 included clinical homosexuals androgen output was significantly less than oestrogen (Neustadt and Meyerson, 1941). On the results of hormone analyses in 17 male homosexuals and 31 controls Wright (1941) concluded that when the androgen-oestrogen ration is less than ten, homosexuality is to be

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expected. His paper gives few clinical details, but his conclusions agree with those of Glass *et al.* (1940). There is therefore striking evidence that an endocrine abnormality exists in some forms of homosexuality, and investigation in this field offers prospects for further study. There is no known endocrine treatment.

Hyper-sexuality.

Precocious boys and male sexual criminals were treated with stilboestrol, 5 mgm. daily, for 75 to 135 days (Dunn, 1941). Hyper-sexual tendencies were reduced and there was an accompanying pathological degeneration of seminiferous tubules. On cessation of treatment the tubules regenerated to some extent and abnormal behaviour was again evident within two months.

Castration has been advocated in unstable mental defectives and potential sex criminals (Hawke, 1941). He has claimed emotional and character stabilization and general mental improvement in 80 per cent. of 229 so treated. Vasectomy was not satisfactory. There was no change in voice or weight when castration was performed after puberty.

Cases subjected to legal castration for habitual or criminal sex offences have been examined by Rossle (1935), Koopman (1936), Sand and Okkels (1936, 1937). In the majority improved conduct resulted, but histological investigations of the removed testes seldom showed any signs of hyperactivity, atrophy was more commonly observed. On the whole there was little significant difference between testes of sex criminals and controls of comparable age and health. Koopman (1936) considered that if the testes had been available for histological examination before castration (as by biopsy) the operation could not have been justified in a single case. The social benefit of the operation must not be ascribed to the immediate endocrine effect, nor can it be held that hypersexuality is the result of abnormal or hyperactive testicular function.

Five cases of nymphomania were treated with 25 mgm. of testosterone at intervals with the object of inhibiting gonadal activity (Rubenstein *et al.*, 1940). Sustained cure was noticed in all. The authors warn that small doses of 5 mgm. may excite libido—an effect noted by Greenblatt *et al.* (1941); large doses are essential. Reports from other sources suggest that in frigid or physically normal women androgen therapy even in reasonably large doses may provoke rather than inhibit erotic tendencies.

Hypo-sexuality.

It is of importance that hypo-gonadism and cryptorchidism in young psychiatric cases should be treated. In the latter gonadotrophic hormone is usually employed and treatment preferably started before puberty. Among the many papers which might be cited, that of Thompson and Heckel (1941) is representative. They employed chorionic gonadotrophic hormone, 100 to 500 units three to six times per week. Testosterone orally, 10 to 40 mgm. daily, has been used in hypogonadism. Improvement in genital growth, increase of weight and libido, with improved sense of general health, have been commonly reported (Pratt, 1942). Tager (1942) claims that treatment has little effect in maturity; Eidelsberg and Ornstein (1940) point out that in true hypo-

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gonads treatment must be continued, the patient being unable to do without maintenance therapy. They have noticed no ill effects in such cases, even after a course of as much as 2,700 mgm. of testosterone propionate, and advocate implantation of 200 mgm. to cover a period of eight to sixteen weeks. Testosterone propionate is of low activity when administered orally. Methyl testosterone, sub-lingually, has about one-quarter of the potency of injected testosterone; it is therefore suitable for maintenance therapy (Spence, 1942). It seems probable that reduction in fatigability characteristic of the eunuchoid and improvement in libido and genital growth are reflected by loss of neurotic feelings and of the sense of being a social misfit.

That retarded growth and hypogonadism are important factors in youthful behaviour problems has been stressed by Rubenstein (1942), who treated a series of hypogonad boys with testosterone, 25 mgm. two to three times weekly. He believed that the improvement in growth and sexual development which resulted rendered the subjects more open to suggestion and psycho-therapy, and reported that all became much more socialized. He points out that it is thus possible to counteract a dysplastic tendency by endocrine therapy.

Impotence.

The literature on this subject allows two conclusions to be drawn: (1) That castrates are not necessarily impotent, and that (2) impotence is not primarily an endocrine problem. The effects of castration have been dealt with by Tauber (1940) in an extensive review. Lange (1934) found that of 220 men castrated by war wounds 165 had married subsequently, and that good sexual drive was still present in the majority. Miller *et al.* (1938) described four surgical castrates, and two " psychic " impotents, as " broken in spirit "; hot flushes, irritability, uncontrollable moods, fatigability were present in the organic cases. Only the latter responded well to testosterone, 20 mgm. thrice weekly, lost the special symptoms and regained erectile capacity. Pulten *et al.* (1942) have stressed the importance of the psychic element in androgenic failure; there is no relationship between potency alone and androgen output (Wolbard, 1941).

Spence (1940) found that testosterone, 50 to 100 mgm. thrice weekly, sufficient to cause prolonged erection in eunuchs, was without effect in six cases of functional impotence.

Impotence is to be regarded as a psycho-therapeutic problem. Testosterone is of value only where there is definite objective evidence of hypogonadism; if there is only a slight neurotic element its stimulation may help, but it may, by increasing anxiety, aggravate the neurosis. Genito-urinary abnormalities are less important than psychic and emotional events; injected inert oil has frequently been found as effective as testosterone (Carmichael *et al.*, 1941). Testosterone is sometimes helpful in impotence of the male climacteric (Reed and McMillen, 1941).

Neurotics as well as hypogonads have a tendency to become dependent on testosterone, and once instituted it may not be easily dispensed with. This possibility is worth considering in each case before embarking on androgen therapy.

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Adreno-genital Syndrome.

Allen *et al.* (1938 and 1939) and Broster (1942) have described as a clinical syndrome in young women after puberty the association of an irregular growth of hair of male distribution, increased output of androgens, and frequently mental changes. The usual mental symptoms have been of paranoid type, with jealousy, shyness, ideas of reference and auditory hallucinations. The intensity of the mental reaction is no doubt, at least in part, due to the sense of inferiority and oddness induced by the cosmetic and social handicaps. The syndrome is attributed to pathological hyper-activity of the adrenal cortex. In some cases adrenal tumours have been found; in others hyperplasia of the cortex of the removed gland has been demonstrated histologically by a positive ponceau fuchsin reaction. Loss of hirsutism, reduction in excretion of androgens and in some cases disappearance of psychotic symptoms have followed unilateral adrenalectomy.

The condition may be suspected and operation contemplated in young female mental patients showing increasing virilism and an abnormally raised androgen output. Operation is valueless in menopausal hirsutism (Broster, 1942).

Cushing's Syndrome.

This disease, usually due to a basophil adenoma of the anterior pituitary, has as characteristic symptoms truncal obesity, moon face, purple linea atrophica and osteoporosis. Mental disorders occur with some frequency, and are usually depressions of reactive type, with agitation and sometimes ideas of jealousy in the later stages (Maclay and Stokes, 1938; Schlesinger and Horwitz, 1940; Lintz, 1941). Additional symptoms are lumbo-sacral pain, headache, dizziness, muscular weakness, polyuria, abdominal pains, loose motions, tendency to hypertension, hyperglycaemia and poor sugar tolerance, insomnia, restlessness, hirsutism and male pubic hair (Lintz and Tiner, 1941), sexual dystrophy, polyphagia, polydipsia, ecchymoses (Maclay and Stokes, 1938), relatively low output of urinary androgens (Broster, 1940).

The combination of a depressive illness with some of these symptoms, especially those first mentioned, should suggest Cushing's syndrome. The diagnosis from the adrenogenital syndrome may not be easy. A very high output of androgens points to the latter; pathological obesity is more suggestive of the former (Broster, 1940). Irradiation of the pituitary has been found effective (Lintz, 1941).

Calvarial Hyperostosis.

Localized hyperostoses of the inner table of skull are not uncommonly found at autopsy or by skiagram. Morgagni (1765) observed that this condition was sometimes associated with obesity and virilism, but his observation remained neglected until recent years. Following the accounts of Stewart (1928) and Morel (1931), hyperostosis frontalis interna has been regarded, but not universally recognized, as a distinct disease sometimes called "Morgagni's syndrome." Moore (1935) found radiological evidence of cranial hyperostosis in 72 out of 6,000 non-mental cases, and in 14 out of 33 psychotic females.

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Eldridge *et al.* (1940), in their study of 50 undoubted examples from a series of 200 psychotics, drew attention to the great preponderance of mental patients with cranial hyperostosis. They were unable to agree that Morel's triad of symptoms, i.e. obesity, visual defect and neurological disorder, was typical, and could find no case that conformed exactly with Morel's syndrome. Hyperostosis was present before the 40th year in 26 cases; obesity was prominent in 8 only; there was no endocrine condition common to many. They regarded calvarial hyperostosis as due to a general metabolic disorder seen in various mental illnesses, probably about 20 times as frequently as in the non-mental population.

Included in the extensive review of Roth (1942) are 8 personally investigated cases, all females. The extremes of age were 26 to 72. There was no characteristic mental illness; the youngest suffered from reactive depression. Facial hirsutism and truncal obesity were common, and in a few, abnormal sugar tolerance and other signs suggestive of pituitary involvement were seen. Cerebral arteriosclerosis and hypertension complicated some of the older cases. Such neuro-psychiatric signs as existed could not be attributed to the hyperostosis.

Relevant theories as to causation are discussed by Williams (1941); no satisfactory conclusion is advanced. He describes the commoner radiological forms of hyperostosis as frontal, nebular, diffuse, fronto-parietal; the terms are self-explanatory. In all his cases the coronal suture was effaced. This may be an early radiological sign. The extremes of age of his 19 cases were 41 and 79 years respectively; the period of hospitalization varied between 2 months and 48 years. Maximum heights and weights were respectively 66 in. and 59 in., and 285 lb. and 167 lb. The types of mental illness represented were: Dementia praecox 8, paranoid states 4, mental deficiency 4, cerebral arteriosclerosis, manic-depressive psychosis, cerebral syphilis one each.

Among female cases described by Hemphill and Stengel (1940) were three members of a family in which calvarial hyperostosis and a paranoid psychosis seemed to be inherited. Advanced bony changes were present in the skull of the youngest, aged 10, at a time when no endocrine nor neuropsychiatric could be detected. Meningeal irritability attributed to pathological changes in the meninges was observed in two, one not of the family. Blood calcium was within normal limits. No aetiological causes were ascertained.

At autopsy on the eldest, aged 65, there were degenerative changes in the frontal and parietal cortex and nuclei supraoptici. A small eosinophil adenoma of the pituitary, adrenal cortical hyperplasia, and evidence of parathyroid hyperfunction were found. Sclerosis of the anterior pituitary had been described previously (Stewart, 1928).

In conclusion, hyperostosis frontalis interna is found in a wide range of mental illnesses, almost exclusively in females, upwards of twenty times as frequently as in the non-mental population. Although in the majority of cases it is discovered accidentally and does not give rise to symptoms, in a few there are neuro-psychiatric and endocrine abnormalities sufficient to justify the recognition of a syndrome. Pathological studies in some cases have pointed to a complex endocrine disorder involving the anterior pituitary, suggesting

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an earlier hyperactivity. Although the arteriographic investigations of Moniz (1938) have indicated an increase of intracranial pressure in some patients, no operative or other form of treatment has been found of value. The belief that this condition is one of adult or old age is obviously unfounded, as there is nothing to show, in the great majority of cases, how long intracranial hyperostosis had existed before detection, and juvenile examples do occur.

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