Diagnosis and Management of Hypopituitarism

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The term hypopituitarism implies deficiency of at least one pituitary hormone, which may be apparent clinically or demonstrated by an appropriate test. Partial degrees of hypopituitarism are much more common than the syndrome of panhypopituitarism. The possibility of a pituitary cause should be considered in all patients with hypothyroidism, hypogonadism, or hypoadrenalism although disease of the target organs is commoner than that of the pituitary itself.

AETIOLOGY

The major causes of hypopituitarism are shown in Table 1. Pituitary tumours, particularly chromophobe adenomas, are now the commonest cause of hypopituitarism. Basophil tumours are rarely large enough to cause expansion of

| Table 1. Major Causes of Hypopituitarism |
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| 1. Pituitary tumours: chromophobe, eosinophil, basophile or mixed. |
| 2. Tumours in the region of the hypothalamus and pituitary stalk: craniopharyngiomas, meningiomas, gliomas of the optic chiasm, pinealomas, secondary deposits (especially from breast and lung). |
| 3. Granulomas: sarcoidosis, syphilis, eosinophilic granuloma, Hand-Schüller-Christian disease. |
| 4. Vascular: post-partum necrosis, previous tuberculous meningitis, pituitary apoplexy, carotid aneurysm. |
| 5. Miscellaneous: post-traumatic, after surgery or radiotherapy to the pituitary or hypothalamus, drug-induced, e.g. corticosteroids suppressing ACTH release, oestrogens suppressing gonadotrophin release, isolated pituitary hormone deficiencies (probably due to releasing-hormone deficiency). |

the pituitary fossa. Eosinophilic tumours, recognised by their over-production of growth hormone, do not commonly cause hypopituitarism other than gonadotrophin deficiency. The commonest 'pituitary tumour' in childhood is
the craniopharyngioma, although no age group is exempt. Secondary tumours usually occur in patients with previously recognised malignant disease.

Granulomas are rare causes of hypopituitarism; bone or pulmonary lesions sometimes give a clue to their presence.

Post-partum pituitary necrosis was formerly a common cause of hypopituitarism but with the improvement of obstetric practice this cause is now much rarer in the UK. Pituitary apoplexy, often occurring in association with a pituitary tumour, may present as a neurosurgical emergency with severe headache, signs of meningeal irritation and visual failure.

Iatrogenic hypopituitarism is now common as a result of surgical hypophysectomy or radiation of the pituitary for pituitary tumours or in the treatment of breast carcinoma or diabetic retinopathy. A variety of drugs may interfere with pituitary hormone production, e.g. corticosteroids, phenothiazines and oral contraceptives. It is likely that most of these act at the hypothalamic level. Head injury, with or without fracture of the skull, may cause permanent deficiency of anterior pituitary hormones but the diabetes insipidus which follows head injury is almost invariably a transient phenomenon, remitting within a year. Isolated deficiencies of anterior lobe hormones are likely to result from genetically-determined hypothalamic abnormalities with deficiency of a particular releasing hormone. Selective failure of growth hormone release may occur on either a familial or a sporadic basis. Gonadotrophin deficiency is sometimes associated with anosmia or hyposmia (Kallman’s syndrome).

**CLINICAL DIAGNOSIS**

The clinical features of hypopituitarism depend on the pattern of deficiency of the various pituitary hormones and upon the nature of the local lesion in the pituitary. The age and sex of the patient and the rate of progression of the disease are obviously important. The anterior pituitary produces six types of hormone: growth hormone (GH), prolactin, gonadotrophins—follicle-stimulating hormone (FSH) and luteinizing hormone (LH)—thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), and melanocyte-stimulating hormone (MSH). The posterior pituitary releases arginine vasopressin (antidiuretic hormone, ADH) and oxytocin.

Overproduction of one pituitary hormone, e.g. GH or ACTH, may be associated with deficiency of other hormones as seen in acromegaly or Cushing’s syndrome respectively.

The pattern of hormone deficiency in patients with organic pituitary disease is important; gonadotrophins and GH secretion are lost early (Landon et al., 1966; Wilkinson et al., 1970), to be followed by ACTH, then TSH,
and finally ADH. Deficiency of ADH is rare in lesions confined to the pituitary fossa unless there has been surgical intervention; diabetes insipidus always suggests the presence of some suprasellar disease.

To establish a diagnosis of hypopituitarism the clinician must look for deficiencies of each of the pituitary hormones, both clinically and by laboratory tests and then must determine the underlying cause of the disorder. Ideally, the plasma level and production rate of each of the anterior and posterior pituitary hormones should be measured, but this is not yet possible. Tests based on deficiency of the hormones produced by the target organs must often suffice. If deficiency of a target organ hormone can be demonstrated as well as a normal response of the target organ to administration of the pituitary trophic hormone, deficiency of that trophic hormone can be inferred. It is now generally accepted that estimates of basal hormone production may be normal in patients with endocrine disease and that more information can be derived from dynamic tests that measure the reserve capacity of the gland. Such tests, using various physiological stimuli, are routinely applied to determine GH and ACTH production. With the advent of synthetic hypothalamic releasing hormones, the natural stimuli to pituitary hormone production, it is now possible to test the pituitary reserve of TSH, prolactin, FSH, and LH.

The local lesion is of importance in the case of tumours when the patient presents with headaches or visual defects. The type of headache is very variable but the pain is usually persistent and located in the frontal, temporal or vertical regions or behind the eyes. Patients with acromegaly commonly complain of pain in the occipital region and back of the neck, probably due to compression of cervical nerve roots from arthritis and bony overgrowth.

The presence of a local lesion in the region of the pituitary may be suspected by abnormalities of vision, particularly visual field defects or the presence of optic atrophy, though papilloedema is rare unless there is marked suprasellar extension of a pituitary tumour. The visual fields should be plotted carefully by an ophthalmologist in all patients with evidence of hypopituitarism. X-rays of the skull may show enlargement of the pituitary fossa or a double contour of its margins, indicating asymmetrical enlargement. Smallness of the sella is of little help in the diagnosis of hypopituitarism since a 'small sella' is not infrequently seen in the normal population. Enlargement or flattening of the sella can also result from suprasellar tumours or from raised intracranial pressure with a dilated third ventricle. Calcification above the diaphragm sellae will usually indicate the presence of a craniopharyngioma but it can also result from previous tuberculous meningitis. It must be distinguished from calcification in the carotid arteries.
Patients whose hypopituitarism results from damage to the hypothalamus may present with a variety of hypothalamic disturbances (Jenkins, 1972). The normal rhythm of sleep may be disturbed, with somnolence during the day and wakefulness at night. Initiative and motor activity may be reduced despite full restoration of hormonal deficiencies. Appetite and food intake are increased more often than decreased. It is usually assumed that most forms of psychogenic anorexia are mediated through the hypothalamus. Reduced thirst, a rare sequel of damage to the thirst centre in the anterior hypothalamus, may lead to inadequate water intake, a particularly dangerous complication in patients who already have diabetes insipidus. Libido may be reduced and this is usually resistant to hormone medication in women whereas androgens may help in men. Behaviour disorders are sometimes a problem, with pathological lying, stealing, or generally immature patterns of response. Temperature regulation defects can lead to hyperthermia but hypothermia is more common. In children, true precocious puberty may result from functional disturbance of the hypothalamus, relatively common in girls; in boys organic damage, often by tumour formation, is usually responsible.

GROWTH HORMONE DEFICIENCY
GH deficiency in the child is associated with shortness of stature (the word ‘dwarf’ should be avoided), an immature facies, plumpness and retardation of bone age. The features of isolated GH deficiency have been reviewed by Tanner et al. (1971). The syndrome is commoner in boys and half of those affected have an abnormally small penis and poorly-developed scrotum. Laron and Perzelan (1969) observed that about half of a group of children subsequently shown to be suffering from GH deficiency were significantly short at birth, implying that fetal linear growth is, at least in part, under the control of fetal GH.

Bone age is always retarded and muscle growth is also limited, whereas subcutaneous fat is increased. Fasting hypoglycaemia is rare but increased insulin sensitivity is common. In adults, GH deficiency is probably responsible for the high-pitched voice, the immature facies, the soft and finely wrinkled skin, and the increased body fat.

Varieties of GH deficiency. GH deficiency is commonly an isolated phenomenon due to impaired production of GH. Some cases are familial and the disease can be inherited as an autosomal recessive characteristic. The same clinical sequelae may also result from production of an immunologically active, but biologically inactive GH molecule, or from peripheral resistance to the action of normal GH. Laron (1967) observed that the insulin response to arginine infusion was less than normal in certain patients with shortness of
stature despite the presence of high circulating levels of immunoreactive GH. It was suggested that the impaired insulin response was an index of the lack of biological activity of the endogenous GH. It has since been shown that the serum level of sulphation factor is low in such patients and cannot be raised by administration of GH whereas the low level of sulphation factor in GH deficient children can be restored to normal by GH administration. Peripheral resistance to GH administration has also been demonstrated by Rimoin et al. (1967) and by Merimee et al. (1968) in the African pygmy.

Other causes of shortness of stature. Children with hypothyroidism are short in stature and show impaired skeletal maturation. In addition they have a decreased GH response to insulin-induced hypoglycaemia (Brauman and Corvilain, 1968), although this is largely due to relative insulin resistance. It is important to correct hypothyroidism before assessing GH output in such patients.

Children treated with large doses of corticosteroids also show reduction of linear growth. This effect is mainly due to a corticosteroid-induced antagonism to the effects of GH at the peripheral tissue level (Morris et al., 1968a, b).

Children with familial short stature or growth delay can usually be classified on the basis of a careful family history.

Psychosocial short stature due to emotional deprivation is usually associated with recognisable problems in the home environment. GH deficiency remits spontaneously in response to a change in environment.

Other varieties of shortness of stature include those resulting from 'low birth weight', malnutrition, serious diseases of major organs or systems, bone diseases and a wide variety of 'syndromes'.

Tests for growth hormone deficiency. In most major centres the level of circulating growth hormone can be measured by radioimmunoassay. Fasting levels of growth hormone are low in normal people and it is necessary to use tests that elevate growth hormone levels before growth hormone deficiency can be proved. Many agents have been employed to stimulate growth hormone release, e.g. insulin-induced hypoglycaemia, arginine or glucagon infusions, lysine vasopressin, physical exertion, and the administration of Bovril. Normal children show a marked rise in circulating GH levels 20 minutes after the end of 10 minutes hard physical exercise and this procedure is a useful screening test to exclude GH deficiency. Similarly, the rise in GH levels which occurs an hour or two after the onset of sleep can also be a helpful screening test. In children (and women), Bovril, being a safe and useful stimulus to growth hormone release, is now used to test patients suspected of growth hormone deficiency (Jackson et al., 1968). In adults suspected of hypopituitarism, the insulin hypoglycaemia test is usually carried out, though this must be done in
hospital with great care. After i.v. administration of soluble insulin 0.1 unit/kg body weight, specimens of blood are taken at half-hourly intervals for estimation of blood sugar, growth hormone and cortisol. Insulin-induced hypoglycaemia also stimulates ACTH output and, hence, increases the level of plasma cortisol, so ACTH deficiency can be looked for at the same time. In a normal person, the blood sugar falls to less than 50 per cent of the basal value, rising to a normal level after two hours. In patients with significant hypopituitarism the hypoglycaemia is more marked and the fasting level is not restored by two hours, though in patients with mild hypopituitarism the blood sugar changes may not differ from normal (Wilkinson et al., 1970).

Impaired GH and ACTH output can be demonstrated only if adequate hypoglycaemia is produced. Sufficient insulin must be given to lower the blood sugar to 40 mg/100 ml or less and to cause sweating. If hypoglycaemia is inadequate the test must be repeated with a larger dose of insulin. Patients with acromegaly, obesity and Cushing’s syndrome tend to be insulin resistant.

Normal subjects show a peak value of GH in excess of 20 ng/ml (MRC Standard A, HGH) in response to adequate hypoglycaemia. When peak levels of <10 ng/ml occur, deficiency of growth hormone secretion is established. Values between 10–20 ng/ml in a child with the clinical features of GH deficiency may imply partial deficiency and some of these children will benefit from GH therapy.

Treatment of growth hormone deficiency. In adults no treatment is required. In children, where the problem is largely one of shortness of stature, the diagnosis should be established as soon as possible and treatment started. Significant shortness of stature is defined as a height below the third percentile on standard charts, and relative lack of growth should usually be documented for at least one year. GH deficiency must be confirmed by at least one of the stress tests described above. Any deficiencies of other pituitary hormones should be corrected, although the dose of hydrocortisone should be kept as low as possible to prevent interference with growth response. Prior to treatment it must, of course, be established that the bone age is low enough to give sufficient growth potential for long-term therapy.

Treatment with GH in a dose of 10 I.U. twice weekly by intramuscular injection is followed by a sharp fall in blood urea and by nitrogen retention. There is acceleration of linear growth and to a lesser degree of skeletal maturation with a decrease in adipose tissue and an increase in muscle mass. A striking feature is the increase in maturation of the features and body habitus. In some patients antibodies to GH develop and in a minority of these there is reduction or abolition of response to the hormone. Recent evidence suggests that antibodies are more likely to develop to some GH preparations than
to others, probably reflecting damage to the molecule during extraction and purification from human pituitaries.

PROLACTIN EXCESS AND DEFICIENCY
There is now no doubt that a separate prolactin molecule is synthesised by the human pituitary (Sherwood, 1971). The GH molecule itself has an intrinsic lactogenic action as indicated by the galactorrhoea of acromegaly. Sexual ateliotic dwarfs in whom there is clear evidence of HGH deficiency can undergo pregnancy followed by normal lactation (Rimoin et al., 1968).

Postpartum hypopituitarism is characterised by failure to initiate lactation and to resume menstruation; this is the only situation where prolactin deficiency has obvious clinical effects.

Overproduction of prolactin is sometimes associated with deficiency of other pituitary hormones when hypothalamic or pituitary lesions interfere with the synthesis, transport or action of prolactin-release inhibiting hormone (PRIH) by which the hypothalamus normally restrains prolactin release from the anterior pituitary. The commonest clinical presentation of prolactin overproduction is that of galactorrhoea associated with secondary amenorrhoea due to impaired gonadotrophin release. This follows pregnancy or the contraceptive pill.

Bioassays and immunoassays have demonstrated the existence of an independent prolactin in man and are beginning to yield valuable information on disorders of prolactin secretion.

Treatment of prolactin deficiency. Failure to initiate or maintain lactation is seldom of concern to most women. Prolactin is not available for clinical use.

GONADOTROPHIN DEFICIENCY
Gonadotrophin deficiency in the male causes impotence and loss of libido with oligospermia although, unlike patients with psychogenic impotence, those with hypopituitarism do not often complain of their disability. In women, oligomenorrhoea, irregular menstruation, or amenorrhoea result from lack of gonadotrophin production, and infertility is the rule. In both sexes, lack of the gonadal hormones, secondary to gonadotrophin deficiency, contributes to the characteristic fineness and excessive wrinkling of the skin.

While gonadotrophin deficiency occurs early in pituitary disease, organic disease is an uncommon cause of impaired gonadotrophin release. The commonest variety of secondary amenorrhoea is assumed to be of hypothalamic origin. It may follow weight loss from any cause (seen in its most obvious form in anorexia nervosa), weight gain in some women, and emotional
stress of any sort, particularly depressive illnesses. However, in many women there is no obvious precipitating factor; all tests may be normal and amenorrhea may persist or remit without obvious cause. Urinary gonadotrophin excretion is often normal in such patients and it is assumed that the fault lies in the particular hypothalamic centre responsible for the cyclical release of luteinizing-hormone releasing hormone (LRH) and, hence, of LH.

Tests for gonadotrophin deficiency. Radioimmunoassays of FSH and LH in plasma and urine are now widely available (Diczfalusy, 1969). Low levels of FSH and/or LH are found in some patients with hypopituitarism and in some with galactorrhoea. Raised LH values are indicative of primary gonadal failure but not all patients in this category have raised plasma or urinary LH levels and the results must be interpreted with caution. It has recently been shown that failure of the earlier stages of spermatogenesis, such as is seen in Klinefelter's syndrome, is associated with raised FSH levels. Animal experiments indicate that this is due to deficiency of a low molecular weight material produced during spermatogenesis. Hence the finding of raised FSH levels in a patient with hypogonadism implies tubular failure, whereas high LH levels suggest Leydig cell deficiency. Serial estimations of plasma LH which show a progressive rise may be useful in predicting the onset of puberty in boys with delayed development. Release of LH can be initiated by clomiphene and this has formed the basis of a dynamic test of gonadotrophin output (Marshall et al. 1970; Newton and Dixon, 1971). Bioassays based on the increase in mouse uterine weight produced by injection of a urinary extract measure both FSH and LH and give some idea of total gonadotrophin output. Total urinary gonadotrophin excretion values must be interpreted with care and occasional normal or high values in patients with secondary amenorrhea do not necessarily indicate ovarian failure and do not preclude a response to the administration of gonadotrophin in the treatment of infertility.

Treatment of gonadotrophin deficiency. In men, potency is easily restored by androgen medication in the majority of cases. An oral preparation, e.g. testosterone 10 mg four times a day sublingually, or mesterolone 25 mg four times daily, should be tried first. These preparations are preferred to methyl testosterone which sometimes causes dyspepsia or a cholestatic jaundice. Some patients respond better to i.m. injections of long-acting testosterone ester such as sustanon 250 mg intramuscularly in alternate weeks. Others prefer the subcutaneous implantation of testosterone pellets (400–600 mg) every 4 to 6 months. Rarely, fertility can be restored in men with hypopituitarism by administration of gonadotrophins.

In women, cyclical oestrogen-progesterone therapy allows withdrawal
bleeding. The regime recommended is: ethinyl oestradiol 0.01 mg twice a day for 24 days along with norethisterone 5 mg twice a day for the last 10 of these 24 days. After withdrawal of therapy, bleeding occurs within a few days and the course should be repeated at the end of menstruation. Some patients with gonadotrophin deficiency can be rendered fertile by administration of FSH and human chorionic gonadotrophin, the latter rupturing the ovarian follicle. Various regimes of FSH and HCG have been used and these are well summarised by Crooke (1970). Trial doses of FSH are usually given to determine sensitivity, and the response assessed directly by urinary oestrogen and progesterone assays or indirectly by the alteration in appearance of the cervix with increased secretion and viscosity of secretion (causing 'ferning') or by changes in vaginal cytology. Complications of gonadotrophin therapy include local reactions (of minor importance), multiple pregnancies, and the potentially hazardous hyper-stimulation syndrome.

In some women with secondary amenorrhoea usually associated with infrequent ovulation, clomiphene can be used to induce ovulation (Bishop, 1970). It acts on the hypothalamus to cause release of FSH and LH, so the patient’s pituitary must be capable of producing gonadotrophins for the drug to be effective. The response is monitored in the same way as that for gonadotrophin therapy. Adverse effects are similar to those occurring with gonadotrophin treatment but ovarian enlargement is less likely at current dose levels, multiple births occur less often, and other sequelae such as hot flushes, nausea and headaches are trivial and infrequent. It is usual to start treatment with 50 mg daily for five days and if there is no response to this dose, increase to 100 mg daily for five days for several cycles.

Luteinizing hormone-releasing hormone (LRH) has now been isolated and its structure determined. It is a decapeptide, and synthetic material has full biological activity. LRH releases both LH and FSH from the pituitary of men and women; however, its effect on LH release is much greater than that on FSH (Besser et al., 1972). It has been possible to induce ovulation in women using repeated injections or infusions of this material (Zarate et al., 1971) and it should prove of considerable value in the treatment of some of the commoner varieties of infertility.

CORTICOTROPHIN DEFICIENCY

It is vital to recognise the features of ACTH deficiency since the resultant cortisol deficiency can prove fatal. Symptoms are non-specific and usually require a high index of suspicion in the appropriate clinical context, e.g. a patient with acromegaly who has undergone an yttrium implant may complains solely of severe headache when he is deficient in cortisol. Lack of
strength, energy and general well-being, nausea, vomiting, abdominal pain, or arthralgia may also indicate cortisol deficiency. Signs are lacking in the early stages; later the patient may look unduly pale, have a tachycardia with a weak pulse and hypotension. It should be noted that, in patients with organic pituitary disease, ACTH deficiency rarely occurs in the absence of gonadotrophin and GH deficiency.

Probably the commonest cause of ACTH deficiency at present is long-term corticosteroid therapy which causes suppression of the pituitary-hypothalamic ACTH-release mechanism and consequently adrenal atrophy. A practical problem is the safe withdrawal of steroid therapy. Patients receiving less than 15 mg of prednisone daily (or its equivalent) for less than a year rarely cause any problems, especially if withdrawal is gradual, though, of course, recurrence of the original disease may necessitate reinstitution of steroid treatment. A standard regime for attempted steroid withdrawal is as follows:

1. Stop previous steroid medication and replace by dexamethasone 0.5 mg twice a day.

2. Administer Tetracosactrin-depot 1 mg intramuscularly at 9 a.m. each day for three days, measuring plasma 11-hydroxycorticosteroids 4 to 6 hours later to confirm reversal of adrenal atrophy. Failure to reverse adrenal atrophy is very rare, but if plasma cortisol levels do not exceed 20 µg/100 ml by the third day the course of ACTH can be continued for a week.

3. On day 4, all medication is withdrawn and the patient’s subsequent clinical condition is observed carefully, checking pulse and blood pressure readings several times each day. Plasma cortisol levels are estimated at 9 a.m. each day and if the patient’s own hypothalamic-pituitary ACTH mechanism is intact this level should exceed 8 µg/100 ml by the third day after ACTH withdrawal.

Tests for ACTH deficiency. Measurement of ACTH by radioimmunoassay is a difficult procedure (Yalow and Berson, 1969) but, fortunately, plasma cortisol levels, usually measured as 11-hydroxycorticosteroids, mirror ACTH levels very closely and can be used instead. Dynamic tests for ACTH release are of more value than basal cortisol or ACTH estimations.

Plasma ACTH and, hence, cortisol release can be stimulated by many factors, e.g. insulin-induced hypoglycaemia, pyrogen, lysine vasopressin, and metyrapone (Jenkins and Else, 1968). Adrenal responsiveness should always be confirmed or restored prior to these tests by administration of ACTH. The most convenient routine test for the integrity of the pituitary-adrenal axis is the standard insulin-sensitivity test administering 0.1 units of soluble insulin per kg body weight intravenously and measuring blood sugar and plasma cortisol levels before and half-hourly afterwards for two hours.
Patients with hypopituitarism are best recognised on the basis of the maximum plasma cortisol achieved during the test rather than on the increment of cortisol, probably because of difficulty in obtaining truly basal levels in patients about to be tested (Wilkinson et al., 1970). All tests should be performed using an indwelling venous catheter to prevent the stress of repeated venepunctures. Insulin sensitivity tests should be carried out only in hospital, with careful medical supervision. Adequate hypoglycaemia must be achieved as mentioned previously.

Indirect evidence of ACTH and, hence, cortisol deficiency can be obtained by failure to excrete a standard water load and by flattening of T waves and lowered R-wave amplitude on the ECG. Correction of these non-specific abnormalities by cortisol administration suggests that the abnormalities were due to cortisol deficiency.

Lowering of plasma sodium and chloride levels is not uncommon in hypopituitarism and is usually due to water retention, correctable by cortisol administration.

Previous methods of assessing pituitary-adrenal function by estimation of urinary 17-hydroxycorticosteroids or 17-oxosteroids are largely outmoded since there are so many alternative causes of lowered excretion of these metabolites, and patients with minor degrees of ACTH deficiency may have values within the normal range.

Treatment of ACTH deficiency. This is compensated for by administration of hydrocortisone 20 mg each morning and 10 mg each evening to mimic the normal diurnal rhythm of ACTH production. It is not necessary to give a mineralocorticoid since aldosterone production is largely independent of ACTH. Hypoadrenalism is often involved in the development of hypopituitary coma and higher initial doses of cortisol are required. Since the plasma cortisol levels and the clinical response to cortisol varies from patient to patient it is advisable to check the plasma cortisol levels when the patient is taking his usual substitution therapy (Besser, 1972).

MELANOCYTE-STIMULATING HORMONE DEFICIENCY
The human pituitary contains both $\alpha$- and $\beta$-MSH, the former representing only about 2 per cent of the total MSH as estimated by bioassay (Abe et al., 1967). Control of MSH release from the pituitary is mediated by melanocyte-stimulating hormone release-inhibiting hormone (MRIH). This has been shown to be a tripeptide, with a structure identical to the three C-terminal amino acids of oxytocin from which it may be derived. Deficiency of MSH is
responsible for the lack of pigmentation of the skin seen in patients with hypopituitarism. Pallor of the nipples may also be apparent.

β-MSH can now be measured either by immunoassay or bioassay. In normal subjects plasma β-MSH levels range from 20 to 110 pg/ml (Abe et al., 1969). Measurements of MSH levels have not so far found any place in the diagnosis of pituitary deficiency. No treatment is required for MSH deficiency since it has no other obvious clinical effects than pallor of the skin.

**Thyroid-Stimulating Hormone Deficiency**

Pituitary TSH deficiency rarely causes the swelling of cutaneous and subcutaneous tissues so characteristic of the myxoedema of primary thyroid disease. Minor degrees of hypothyroidism may be particularly difficult to diagnose, the patient complaining only of lack of energy and cold sensitivity.

*Tests of TSH deficiency.* Mild hypothyroidism due to TSH deficiency is often associated with only minor changes in thyroid function tests; in fact, all of these may be within the conventional normal range, yet the patient may benefit from replacement treatment.

Measurements of serum TSH levels by radioimmunoassay are now becoming more widely available (Hall et al., 1971, 1972). Unfortunately, TSH concentrations in normal serum are so low that it is not possible as yet to diagnose TSH deficiency by this method.

A variety of stresses have been applied in an effort to develop a dynamic test of pituitary TSH reserve: these include cold, pyrogen, hypoglycaemia, lysine vasopressin and antithyroid drugs. All have failed to release TSH consistently. The synthesis of thyrotrophin-releasing hormone (TRH), a tripeptide, has allowed this agent to be used as a test of TSH release. Hall et al. (1970) and Ormston et al. (1971) have demonstrated a rise in serum TSH in response to intravenous administration of this material in normal subjects. Patients with hypopituitarism show an impaired response of TSH to TRH whereas those with hypothalamic disease respond to TRH but show a characteristic prolonged response (Hall et al., 1972). A normal rise in TSH in response to TRH in a patient with pituitary disease virtually excludes hypothyroidism whereas an impaired response indicates a risk of hypothyroidism but is not in itself an indication for thyroxine medication.

*Treatment of TSH deficiency.* Human TSH is not available for clinical use and would in any case require to be given intramuscularly. Bovine TSH, although active in man, is antigenic and also unsuitable for clinical use. Replacement with thyroid hormone is given as in the treatment of primary thyroid failure. A dose of 0·1 to 0·2 mg of 1-thyroxine by mouth usually suffices and there is
no justification for the use of thyroid extract or tablets combining thyroxine and triiodothyronine.

ARGININE VASOPRESSIN DEFICIENCY

Deficiency of ADH is rare in patients with pituitary tumours unless there has been surgical interference or yttrium implantation or the tumour has extended beyond the confines of the pituitary fossa. Polyuria and polydipsia may be masked by concomitant cortisol deficiency. Other causes of polyuria must always be considered, e.g. psychogenic polydipsia, diabetes mellitus, hypercalcaemia, potassium depletion, and renal failure. A patient who is able to sleep through the night without having to pass urine does not suffer from a significant degree of diabetes insipidus. Hypothalamic disease commonly presents with diabetes insipidus, either alone or associated with hypogonadism. If hypothalamic disease is progressive, e.g. from secondary carcinoma, extension of the lesion to the thirst centre may prevent the usual self-correction of the polyuria, and intense water depletion with hypernatraemia can result.

Tests for ADH deficiency. ADH measurement by immunoassay or bioassay is very difficult and most clinicians must rely on indirect tests.

Twenty-four-hour urine volumes in excess of two litres are usually recorded with a low specific gravity. Dynamic tests, albeit indirect, of ADH output, are readily applied. The most useful is the 6½-hour fluid deprivation test described by Dashe et al. (1963). Here, urine and plasma osmolalities are measured before and 6½ hours after fluid deprivation. The test is safe, unlike the 24-hour fluid deprivation procedure which often has to be terminated because of intolerable thirst. Normally, the plasma osmolality remains in the region of 285 mosm/kg, whereas the urine osmolality rises to exceed the plasma values by at least twofold. In patients with diabetes insipidus who are unable to retain water the plasma value rises, often exceeding 300 mosm/kg, whereas the urine concentration remains low and little different from the plasma value.

Treatment of ADH deficiency. Posterior pituitary snuff should not now be used because of the high incidence of adverse effects. Most patients develop rhinitis, bronchospasm, bronchitis or pulmonary infiltration, and antibodies to posterior pituitary can be detected in their serum, though this does not necessarily interfere with the therapeutic effect (Pepys et al., 1966).

A lysine vasopressin (LVP) nasal spray is better tolerated and is often effective in mild cases. It should be used every time the patient passes urine, a technique that avoids overdosage. Pitressin tannate in oil given intramuscularly (2.5 I.U. daily or on alternate days) is very effective but careful
technique is required. The vials need to be warmed in water for several minutes and thoroughly shaken before injection. Injections should be given in the evening to ensure good control during the night, and the injection site should be varied.

Thiazide diuretics, e.g. chlorothiazide, cause a reduction in urine flow in patients with diabetes insipidus and are the only treatment of value in the nephrogenic form of the disease where vasopressin is ineffective.

Chlorpropamide has been shown to reduce urine flow in diabetes insipidus (Arduino et al., 1966) and is of value in patients who do not get adequate control with the LVP nasal spray. No effect is obtained in patients with nephrogenic diabetes insipidus and, similarly, some patients with pituitary-hypothalamic disease, probably those with the most severe ADH deficiency, are resistant to chlorpropamide.

It is usual to begin therapy with 100 mg of chlorpropamide daily, increasing the dose at intervals of several days up to a total dose of 350 mg. Hypoglycaemia is the main hazard of treatment, particularly in children, where the dose should rarely exceed 150 mg. The patient should be advised to take food prior to retiring and immediately on waking, care should be taken not to miss meals, and the relatives and the home doctor should be warned to look out for evidence of hypoglycaemia. In patients with too little endogenous vasopressin to respond to chlorpropamide, the LVP spray can be used as a supplement.

CONCLUSIONS
Clinical and laboratory assessment should allow deficiency of any particular pituitary hormone to be recognised. It is important to be aware of the pattern of deficiency of the pituitary hormones. With careful replacement therapy patients with hypopituitarism should be able to live a fully normal life and it is mandatory that the physician makes sure that hormone deficiencies are adequately treated. Treatment of impotence is often neglected, and this can have untold effects on domestic harmony. Life-long follow-up is required but need not be at intervals more frequent than every six months. All patients receiving cortisol replacement therapy should be educated in the hazards of cortisol depletion and be given a steroid card. Whenever possible the underlying disease should be treated. All patients with hypopituitarism of unknown aetiology should be followed up to allow early detection of a pituitary tumour.

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