FOURTH EDITION

Fundamentals of Clinical Endocrinology

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Preface

This book does not aim to be comprehensive. It contains what the authors believe are the essentials of endocrinology. We make no apologies for the absence of photographs of patients suffering from gross acromegaly or myxoedema which have decorated endocrinology texts from time immemorial. Modern endocrinology is based on the diagnosis of early endocrine disease leading to the institution of effective treatment before permanent or crippling sequelae develop.

The text is aimed at senior medical students and postgraduates working for higher examinations both in medicine and surgery. We do not accept any clear distinction between the undergraduate and postgraduate phases of education, merely a shift in emphasis and, hence, this textbook is aimed at a broad medical audience. We have retained many chapters in conventional arrangement dealing with anterior pituitary, posterior pituitary, and thyroid but have tried at all stages to stress the interrelationships within the endocrine system. A number of chapters are included dealing with endocrine topics we think of special importance such as pregnancy, disorders of growth, and hormonal syndromes associated with neoplasms not derived from endocrine glands.

Diagnosis in clinical endocrinology has made great advances in recent years, particularly with the advent of radioimmunoassays of hormones, techniques that are replacing many of the indirect tests of endocrine function and the laborious and often imprecise bioassays. We have tried to provide sufficient detail in the text or appendix to help in the diagnosis of most endocrine syndromes. We have avoided the use of frequent references in the text, giving merely a few key articles and listing useful reviews.

Wherever possible we have tried to describe values in a meaningful way, the mean and standard deviation always being given where appropriate and when available. For many assays, however, such values have not only not been published, but they might well vary with the particular laboratory performing the estimation. Wherever possible the somewhat old-fashioned and not very informative method of giving a 'range' of values has been avoided. Readers are advised to find out for themselves the precise parameters of an estimation as obtained by the laboratory they use on a normal 'control' population and in disease states.

In this, the fourth edition, we have invited our colleagues in Cardiff, London and Newcastle to contribute chapters in their own fields of expertise. These have been edited in some detail in an attempt to maintain the constancy of style which we believe has been an important feature of the earlier editions.

Cardiff and London, 1989

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Contents

Anterior pituitary

Anatomy and embryology

The anterior and posterior parts of the pituitary gland have separate origins and function independently of one another. An upward evagination of the stomadaeum of ectodermal origin, Rathké's pouch, comes in contact with the infundibulum, a downgrowth from the floor of the diencephalon. Rathké's pouch then loses its attachment to the pharyngeal roof to form the anterior pituitary. From its upper part, cells proliferate to form the pars tuberalis, which encircles the pituitary stalk. In lower animals there is a glandular layer in contact with the posterior pituitary called the pars intermedia, but this is not present in the human, except in the fetus. The cells of the posterior pituitary develop from the infundibular process, becoming modified to form pituicytes. Many nerve fibres grow from the hypothalamic nuclei into the posterior pituitary via the pituitary stalk.

The human pituitary gland weighs between 0.5 and 0.9 g and is an ovoid reddish-grey body about 12 mm across, 9 mm anteroposteriorly and 6 mm in depth; it is somewhat larger in the female, especially in parous women, and smaller in old age. Almost three-quarters of the weight of the gland is contributed by the anterior lobe. The pituitary lies in the sella turcica, a depression in the sphenoid, which is covered by a layer of dura mater, the diaphragma sellae, through which the pituitary stalk passes. The position of the diaphragma sellae on the lateral skull X-ray is usually indicated by the line joining the tuberculum sellae and the most anterior convexity of the upper part of the dorsum sellae (Figs 1.1, 1.2).

Relations of the pituitary (Figs 1.1, 1.2)

Above, the pituitary is related to the hypothalamus and the third ventricle, behind which are the mamillary bodies. Laterally, and above, lie the cavernous sinuses and optic tracts, and above and in front, the optic chiasm, which may be in

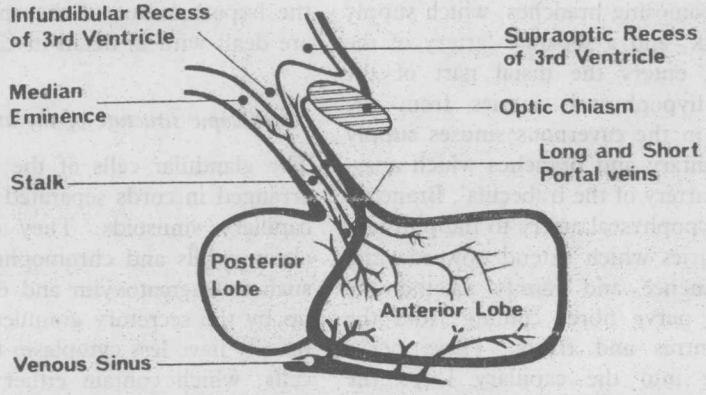


Fig. 1.1 The human pituitary gland and its stalk arising from the median eminence region of the hypothalamus, showing the short and long portal capillaries connecting the median eminence and stalk with the anterior pituitary. (After Daniel and Pritchard 1975)

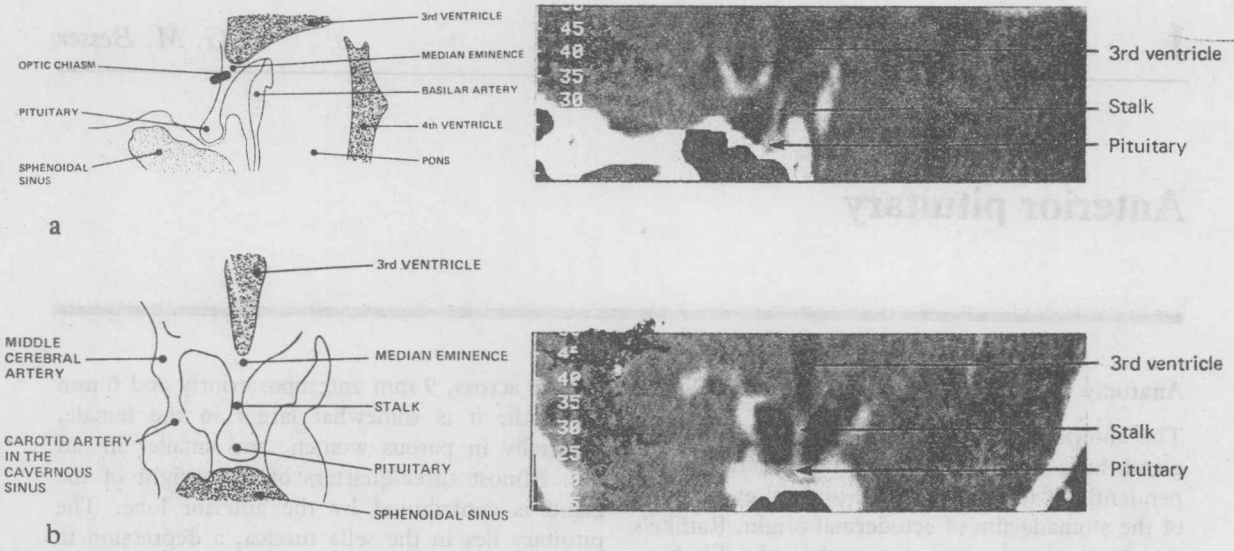


Fig. 1.2 (a) sagittal and (b) coronal reconstructions of CT scan of anterior hypothalamus and small pituitary gland in a normal subject showing the anatomical relationships. I.V. contrast has been given to show up surrounding arteries and the vascular pituitary stalk and gland. This should be compared with Figure 1.1.

contact with any part of the diaphragma sellae. The proximity of the gland to the optic pathways leads to visual disturbances if the gland enlarges beyond the sella turcica. The oculomotor nerves lie lateral to the edge of the pituitary fossa in the lateral walls of the two cavernous sinuses.

Blood supply of the pituitary gland

A superior hypophyseal artery arises from each internal carotid in the middle cranial fossa and divides into anastomosing branches, which supply the pituitary stalk, and a separate 'artery of the trabecula' which enters the distal part of the gland. Inferior hypophyseal arteries from the internal carotids in the cavernous sinuses supply the posterior pituitary and branches which anastomose with the 'artery of the trabecula'. Branches of the superior hypophyseal artery to the pituitary stalk form capillaries which extend upwards into the median eminence and ramify around the terminals of the nerve fibres coming from the hypothalamic centres and tracts. These nerve terminals release into the capillary loops the various hypothalamic pituitary regulating hormones by which synthesis and release of the hormones of the anterior pituitary are controlled by the hypothalamus. These hormones are carried to the anterior pituitary sinusoids by portal blood vessels passing down in and on the anterior surface of the stalk. The pituitary veins drain into the surrounding venous sinuses.

Neuroendocrine control of the anterior pituitary

The functional anatomy of the hypothalamus and pituitary stalk, and the neuroendocrine control by the hypothalamus of the anterior pituitary gland are dealt with in detail in Chapter 3.

Microscopic structure of the anterior pituitary

The glandular cells of the anterior pituitary are arranged in cords separated by a rich network of capillary sinusoids. They can be divided into chromophils and chromophobes by simple stains such as haematoxylin and eosin which are taken up by the secretory granules. The chromophobes usually have less cytoplasm than the chromophilic cells, which contain either acidophilic or basophilic granules. Some of the chromophobe cells represent differentiating chromophils, and others

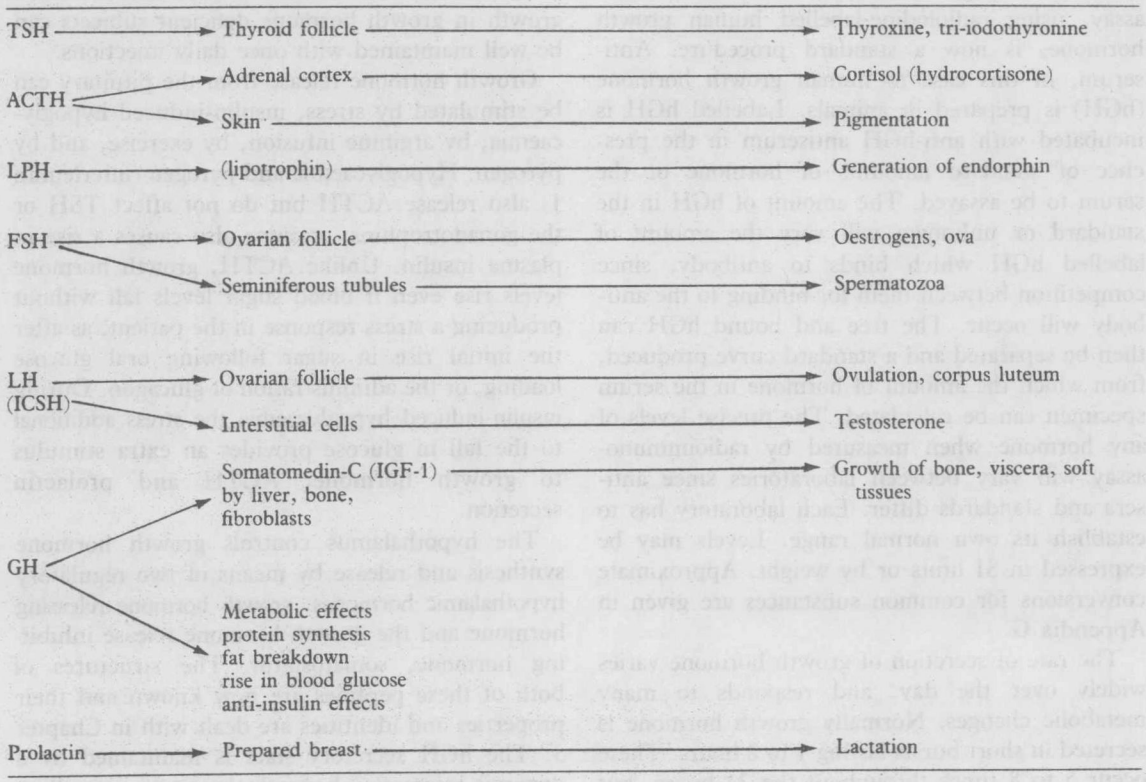
sparsely granulated basophils. By the use of immunohistochemical techniques and electron microscopy, separate types of cell can be identified for each of the anterior pituitary hormones. Immunocytochemistry involves the use of a specific antibody to a particular hormone which will bind to it in cells in a histological section, in this case of the pituitary. The hormone-antibody complex can then be labelled in the cell cytoplasm by staining with a second antibody to the gamma-globulin of the first antibody, e.g. anti-rabbit gamma-globulin if the first antibody was raised in a rabbit. The second antibody acts as a labelling stain because it is tagged either with an enzyme such as peroxidase which can be made to react with chemicals to produce a colour reaction, or with fluorescein and made to fluoresce with ultra-violet light. The hormone is contained within granules in the cytoplasm.

The acidophil cells secrete growth hormone and prolactin. The majority of the acidophils are grouped in the two postero-lateral wings of the gland. In males and non-pregnant females few prolactin secreting cells can be found, but there is marked hyperplasia of these cells under the influence of oestrogens during pregnancy so that the gland almost doubles its weight. The basophils all contain periodic acid Schiff (PAS)-positive (red) granules, the sources of the glycoprotein hormones TSH, FSH, LH, and the polypeptide hormones ACTH and LPH (lipotrophin). Basophils normally lie mostly in the middle of the lobe and anterior and anterolateral parts. The chromophobe cells are fewer in number when complex staining techniques are used. Many contain light purple PAS-positive granules which are a source of ACTH and LPH.

GROWTH HORMONE

Growth hormone makes up between 5 and 10% of the dry weight of the human pituitary gland; it is a protein with a molecular weight of 21 000

Table 1.1 Principal actions of anterior pituitary hormones



Daltons consisting of 191 amino-acid residues. Owing to similarities in structure and the fact that prolactin is present in the human pituitary gland in much smaller quantities than growth hormone, their separate identity was doubted for many years, but is now certain.

Human chorionic somatomammotrophin (placental lactogen, hCS or hPL) is the term applied to a protein produced by the placenta that has similarities in structure and action to growth hormone and prolactin. It appears in placental tissue by the 9th week of pregnancy and its concentration in the blood can be high enough to interfere with some radioimmunoassays for growth hormone. Its function has not yet been established. Measurement of the blood levels of placental lactogen in middle and late pregnancy provides a test of placental function; low levels suggest placental insufficiency.

Secretion of growth hormone

Sensitive and specific methods are available for the measurement of growth hormone in blood. Immunoassay, using radioiodine-labelled human growth hormone, is now a standard procedure. Antiserum, in this case to human growth hormone (hGH) is prepared in animals. Labelled hGH is incubated with anti-hGH antiserum in the presence of standard amounts of hormone or the serum to be assayed. The amount of hGH in the standard or unknown will vary the amount of labelled hGH which binds to antibody, since competition between them for binding to the antibody will occur. The free and bound hGH can then be separated and a standard curve produced, from which the amount of hormone in the serum specimen can be calculated. The precise levels of any hormone when measured by radioimmunoassay will vary between laboratories since antisera and standards differ. Each laboratory has to establish its own normal range. Levels may be expressed in SI units or by weight. Approximate conversions for common substances are given in Appendix G.

The rate of secretion of growth hormone varies widely over the day, and responds to many metabolic changes. Normally growth hormone is secreted in short bursts lasting 1 to 2 hours. These occur 5 to 8 times throughout the 24 hours, but always in the first few hours of sleep. They are infrequent during the day under quiet basal conditions. Secretion is also stimulated by stress, a fall in blood sugar, prolonged fasting, some amino acids, especially arginine, and exercise. Glucose causes prompt inhibition of growth hormone secretion by the pituitary. Protein administration has a similar but less marked effect. Corticosteroids reduce growth hormone output from the pituitary and also oppose its action at the tissues, but only when supra-physiological doses are given, providing a possible explanation for the reduction in growth in children receiving these compounds. The total daily secretion of children and adolescents is greater than adults, and more secretory bursts are found. Serum growth hormone levels in non-fasting adults are variable, being undetectable, that is less than 1 mU/l (0.5 ng/ml) for long periods between the secretory bursts, but then levels may reach 20 to 40 mU/l (10–20 ng/ml) or more. Endogenous growth hormone leaves the circulation rapidly, the half-life being about 20–25 minutes, but the metabolic effects last much longer; thus increased growth in growth hormone deficient subjects can be well maintained with once daily injections.

Growth hormone release from the pituitary can be stimulated by stress, insulin-induced hypoglycaemia, by arginine infusion, by exercise, and by pyrogen. Hypoglycaemia and pyrogen (interleukin 1) also release ACTH but do not affect TSH or the gonadotrophins; arginine also causes a rise in plasma insulin. Unlike ACTH, growth hormone levels rise even if blood sugar levels fall without producing a stress response in the patient, as after the initial rise in sugar following oral glucose loading, or the administration of glucagon. During insulin-induced hypoglycaemia the stress additional to the fall in glucose provides an extra stimulus to growth hormone, ACTH and prolactin secretion.

The hypothalamus controls growth hormone synthesis and release by means of two regulatory hypothalamic hormones, growth hormone releasing hormone and the growth hormone release inhibiting hormone, somatostatin. The structures of both of these peptides are now known and their properties and identities are dealt with in Chapter 3. The hGH secretory state is maintained by a dynamic interaction between these two controlling

factors, somatostatin being secreted during the periods between hGH bursts, then being switched off while hGH releasing hormone is switched on to produce the secretory bursts. The metabolic factors affecting growth hormone release probably act largely at a hypothalamic level by altering this interaction.

Metabolic effects of growth hormone

The mechanism by which growth hormone produces its metabolic effects, particularly growth, is not fully understood. However it is clear that growth hormone does not act directly on cartilage and other tissues to stimulate growth but rather acts on most organs, particularly liver, bone and cartilage, to cause the production of an intermediate, the polypeptide growth factor called somatomedin-C. A number of growth factors are now described, but somatomedin-C appears to be directly related to growth of bone and muscle, and probably other tissues. It appears to mimic many of the actions of insulin, so it is also called 'insulin-like growth factor-1' or IGF-1. While it does circulate in the blood and may be measured there by radioimmunoassay, concentrations in blood do not bear a close relation to hGH levels, or to growth in the young, since the principal activity appears to be due to somatomedin-C produced directly in bone and other tissues where it diffuses between cells to act locally. This local effect is called a 'paracrine' action as opposed to a classic 'endocrine' action, in which a hormone is secreted by one tissue, and then circulates in blood to act at a distant site. The somatomedin-C in blood may just represent 'spill-over' from the tissues.

Somatomedin-C is a polypeptide with a molecular weight of 7 600 Daltons and contains approximately 70 amino-acid residues. Increased growth hormone secretion causes a somatomedin-C rise in blood which begins some 8 hours later lasting 12 to 24 hours.

The effect of growth hormone on protein synthesis may, in part, be mediated by an increased transport of certain amino acids into the cell, though the hormone can also stimulate protein synthesis in cell-free preparations. Growth hormone can still exert its effects when messenger-RNA synthesis is blocked by actinomycin and when new protein synthesis is inhibited by puromycin, so it is unlikely that the primary site of action of the hormone is via production of m-RNA. It may in some way affect the efficiency of the ribosomes, the site of protein synthesis.

CLINICAL EFFECTS OF GROWTH HORMONE EXCESS

Acromegaly and gigantism

The increased secretion of growth hormone that may result from a pituitary adenoma leads to excessive body growth affecting both the skeleton and the soft tissues. Very rarely this occurs prior to fusion of the epiphyses and results in pituitary gigantism. In adults, skeletal overgrowth is more obvious in the hands, feet, cranial sinuses, jaw, and supraorbital ridges, and soft-tissue overgrowth is manifested in coarse features, thick skin and heel pads, and enlarged viscera. Gigantism and acromegaly may occur together in adolescence. The main clinical features in acromegaly are shown in Table 1.2.

The tumour classically is of the acidophilic type but is often chromophobe. Both types immunostain for growth hormone and the cell cytoplasm is heavily granulated particularly in the acidophilic type.

Local effects of the tumour:

1. Headache
2. Enlargement of the sella turcica or erosion of its margins
3. Visual field defects, papilloedema, optic atrophy, ocular palsies
4. Diabetes insipidus
5. Hypopituitarism.

Associated endocrine features

Non-toxic goitres are not uncommon but hyperthyroidism only occasionally occurs, probably on the basis of a multinodular goitre. The absolute value for the basal metabolic rate is increased in acromegaly, but this is normal when corrected for surface area. Hypothyroidism rarely results from destruction of pituitary thyrotrophic cells by the tumour, more commonly being a result of stalk obstruction by tumour or the effects of surgery or radiation to the pituitary.

Table 1.2 Features of acromegaly

Clinical	%
General effects due to metabolic disturbances	
Skin and subcutaneous tissue overgrowth	100
Skeletal overgrowth	100
Skull vault, sinuses, supraorbital ridges lower jaw producing prognathism and increased interdental spaces, vertebrae producing thoracic kyphosis and new bone formation anteriorly in lumbar region.	
Excessive sweating	95
Goitre — diffuse or nodular	20
Clinical diabetes mellitus	15
Hypertension	14
Greasy skin, acne, gynaecomastia, galactorrhoea, cardiomyopathy	sporadic
Local effects due to presence of pituitary mass	sporadic
Headaches	
Visual field defects — usually bitemporal hemianopia	
Diplopia and squint — oculomotor nerve palsy	
hypopituitarism — hypogonadism with infertility, impotence, or decreased menstruation; ACTH or TSH deficiency	
Diabetes insipidus	

Biochemical	%
Resting serum growth hormone detectable throughout the day	100
Non-suppression of growth hormone to below 1 mU/l (0.5 ng/ml) during oral glucose tolerance test	100
Urine calcium above 6 mmol/(300 mg)/24 hr	50
Chemical diabetes mellitus — impaired glucose tolerance	25

Deficiency of gonadotrophin secretion, especially LH, is a common occurrence in acromegaly and gigantism. It is usually due to obstruction of the pituitary stalk by the tumour so that the gonadotrophin producing cells are not activated by the hypothalamic gonadotrophin releasing hormone, the normal stimulus to secretion. Only rarely are the gonadotrophs actually destroyed. Prolactin secretion is increased in about half the patients either due to the presence of a mixed growth hormone and prolactin secreting tumour or to pituitary stalk compression producing disinhibition of the pituitary prolactin cells as discussed later. The hyperprolactinaemia and LH deficiency cause hypogonadism that results in delayed closure of the epiphyses in gigantism, and in loss of libido and impotence in men, and infertility and decreased frequency of menstruation with reduced loss in women. Prolactin-induced inappropriate lactation (galactorrhoea) may be a feature of acromegaly.

Adrenal function is usually normal except in the late stages of the disease, where progression of the tumour or therapy may damage the corticotrophin-producing pituitary cells. Hirsutism is not infrequent in women and may be associated with the accompanying hyperprolactinaemia which may result in excessive adrenal androgen production by unknown mechanisms.

Diabetes insipidus is more likely to result from effects of hypothalamic damage due to upward extension of the tumour or to the effects of surgical or radiation treatment, than to destruction of the posterior pituitary. It may be masked by the presence of hypopituitarism when cortisol secretion is impaired, because polyuria is impossible when circulating corticosteroid levels are low.

Overt diabetes mellitus occurs in about 15% of acromegalics, and impaired carbohydrate tolerance is present on testing in an equal additional number. Growth hormone has anti-insulin effects and directly or indirectly appears to reduce the uptake and utilisation of glucose by muscle, causing increased insulin demands. This results in increased levels of immunoreactive insulin being found in the blood of acromegalics prior to and during the early stages of diabetes. Pancreatic beta cell reserve may be adequate except in subjects with a hereditary predisposition to diabetes, and it is the latter group which develops carbohydrate intolerance. This is usually reversible if the growth hormone levels can be reduced to normal.

Multiple endocrine adenomas, functioning and non-functioning, may occur in acromegaly, affecting the parathyroid, thyroid, adrenal, and pancreas.

Other clinical features

Muscle and joint symptoms are frequent in acromegaly. Weakness is common, and synovial thickening, bony and cartilaginous overgrowth all predispose to arthritis. A wide joint space due to overgrowth of articular cartilage is a feature of the condition. Osteoporosis, if present, is usually due

to long standing hypogonadism, possibly associated with muscle weakness and inactivity. Acroparaesthesiae are common from compression of the median nerve in the carpal tunnel by overgrowth of bone and soft tissue. The heart is often enlarged, and ischaemic heart disease and hypertension may contribute to congestive heart failure. An enlarged heart may be present, even in young patients, without evidence of hypertension or ischaemic heart disease, due to a primary acromegalic cardiomyopathy and heart failure, and arrythmias may result. Renal size, blood flow, and glomerular filtration rate are all increased, and the liver, spleen and intestines enlarge. These all function normally and are probably in proportion to the total body mass and surface area, merely reflecting the generalised visceromegaly. Some patients with acromegaly have pigmentation of the skin or acanthosis nigricans, more likely due to the associated hyperinsulinism which can act on the skin in this way, than to the elevated growth hormone itself.

Diagnosis of acromegaly and gigantism

In most patients, the diagnosis is obvious and the only problem is to determine the activity of the disease and to look for complications. The onset and rate of progress of the disease can often be determined by obtaining serial photographs from the patient. Increasing sizes of gloves, rings, and shoes, may also be a useful guide. Finger size, hand and foot volumes can help in assessing the response to treatment. X-rays of the skull usually show enlargement of the sella turcica or erosion of its margins as well as the prominence of the jaw and supraorbital ridges. A computerised tomographic (CT) scan of the pituitary and suprasellar region is required to demonstrate the pituitary tumour and the extent of any suprasellar extension. An assessment of soft tissue overgrowth, for example of the heel pad, can also be made by radiology, and the increased skin thickness can be measured with skin calipers or the thickness of the fingers with jeweller's rings. Urinary calcium excretion is high, exceeding 6 mmol (300 mg)/24h on a normal diet in about 50% of patients. Elevation of the serum phosphate level is seen in a few patients but is not of much diagnostic help. Glucose tolerance is impaired in one quarter of patients.

The final confirmation of the diagnosis of acromegaly rests with the demonstration of an elevated plasma growth hormone level throughout the 24 hr day. Serum growth hormone levels should be undetectable normally in 2 out of 4 blood samples obtained through an indwelling needle in ambulant patients at rest when sampling is spread through the day, but remains detectable, usually ranging from 10 mU/l (5 ng/ml) to many hundreds of mU/l, in acromegalics. However, mild, but clinically important acromegaly may occur in early cases with levels persistently between 2 and 5 mU/l (1–2.5 ng/ml) through the day. During an oral glucose tolerance test serum growth hormone should become undetectable (less the 1 mU/l or 0.5 ng/ml) at some stage (see Appendix), but fails to suppress, and often rises, in acromegaly. Thyrotrophin releasing hormone and gonadotrophin releasing hormone, which do not alter growth hormone secretion in normal subjects, usually elevate levels in active acromegaly, and this may be of diagnostic value. It is important to exclude coexisting deficiency of gonadotrophins, TSH, and of corticotrophin during an insulin tolerance test, as suggested later in Appendix A. In patients with elevated growth hormone levels larger doses of insulin than normal (for example 0.3 units/kg) may have to be used in this test to reduce the blood sugar sufficiently — to less than 2.2 mmol/l (40 mg/100 ml), since these patients show insulin resistance.

Prognosis

Patients with active acromegaly have about twice the expected mortality rate, death usually being due to cardiovascular complications or strokes. For this reason the condition should be treated whenever there is evidence of activity on metabolic and growth hormone studies. Acromegaly only rarely burns itself out spontaneously if the tumour infarcts, although the progression of the changes in physical appearance may become static after several years. In such patients the growth

hormone levels are still elevated and the metabolic consequences and the complications remain.

Treatment of gigantism and acromegaly

Ideally treatment should eradicate the tumour and arrest the progress of the disease, and cause improvement of the soft tissue and bony manifestations and metabolic abnormalities, without the production of hypopituitarism.

Surgery

Surgery ideally removes the tumour with prompt resolution and reversal of the disease. Unfortunately successful complete removal without recurrence is achieved only rarely. The best surgical technique is via the trans-sphenoidal route, access being from behind the upper lip or through the nose, in the midline, across the sphenoidal sinus entering the pituitary fossa from below and extracranially. Using the dissecting microscope the pituitary tumour may be removed without disturbing brain structures or the optic chiasm. Even extrasellar extensions may be removed by this route although when very large the operation has to be done from above using a craniotomy. Such surgery may be required urgently if there are visual field defects to relieve pressure on the optic chiasm, by one or other route. If the growth hormone-secreting tumour is small, less than 1 cm in diameter, then in good hands there is an 80% chance of complete tumour removal with normalisation of growth hormone levels without recurrence, leaving the normal pituitary intact and functioning normally. Unfortunately such small tumours are unusual. Tumours bigger than this are cured by surgery only rarely (less than 20%) since they often infiltrate bone and the surrounding meninges and dura mater and the tumour frequently regrows from these cells. Postoperatively circulating growth hormone levels should be measured, as preoperatively, in several samples obtained via an indwelling needle, and during an oral glucose tolerance test. If levels remain abnormal, that is, they never become undetectable, then external pituitary radiotherapy is required and medical treatment with bromocriptine, or somatostatin octapeptide (see below) should be considered as interim therapy until the radiotherapy is fully effective. Surgery with or without radiotherapy often results eventually in hypopituitarism and should be assessed and treated as suggested later in this chapter.

Conventional high-voltage radiation therapy giving courses totalling 4500 rad causes clinical improvement but only slowly, though progress of the disease may be halted early. Irradiation must be given slowly, in individual doses (fractions) of less than 200 rad per session to avoid damage to the normal tissues such as the optic chiasm and hypothalamus. Skilled and time-consuming radiation field planning is necessary. Preferably a linear accelerator should be used, but failing this a cobalt unit. A satisfactory fall in growth hormone levels occurs in the majority (over 90%) of patients but may take between 2 and 10 years or more to fall to a mean value of less than 2 mU/l (1 ng/ml). Improvement occurs much earlier since growth hormone levels decline progressively. High energy heavy-particle radiation produces faster results but the risk of complications is greater.

Medical therapy of acromegaly

Because the response to surgery is often incomplete or temporary and that to radiotherapy slow, there is a need for an interim medical treatment which may hold growth hormone levels down until ablative therapy is effective, or to be used alone in some frail patients.

Dopamine agonists

Dopamine itself and dopamine agonists result in elevation of circulating growth hormone in normal subjects, but paradoxically such drugs lower growth hormone levels in acromegaly and may, therefore, be used for the medical management of acromegaly. The dopaminergic compounds act to lower growth hormone at the pituitary level in acromegaly but act at the median eminence in normal subjects. Bromocriptine, a semisynthetic ergot derivative, is a long acting dopamine agonist which can be given by mouth and is highly effective in acromegaly although it was originally introduced to lower elevated serum prolactin levels.

Doses which are higher than those used in hyperprolactinaemia are required in acromegaly. Occasionally doses as low as 10–20 mg/day suffice but often 30–60 mg/day are needed. The drug must be taken during meals and, as with hyperprolactinaemia, it must be started at low doses and then slowly increased to avoid the initial side-effects of anorexia, vomiting and dizziness. Constipation may be a problem on high doses, as may vasospasm of the fingers in the cold. Very rarely psychosis may be induced by this drug, but it is reversible on stopping it.

About 75% of acromegalic patients respond rapidly to bromocriptine with reduction in circulating growth hormone, shrinkage of soft tissues especially of the face, hands and feet, cessation of headaches and sweating, improvement of glucose tolerance, hypertension and greasiness of the skin. Visual fields may improve if the tumour shrinks, as it does in about 50% of patients on bromocriptine. The pituitary fossa may become smaller, although this and other changes in the bones may take 3 or 4 years to occur. While marked improvement is often seen, patients are rarely cured by bromocriptine alone; growth hormone levels although much lower are rarely normal, i.e. undetectable for much of the day. Thus control of acromegaly is best achieved by the use of bromocriptine together with surgery or irradiation. Dopamine agonists other than bromocriptine are available (lisuride, pergolide) and are effective; other long acting agents are being developed.

Somatostatin therapy

Somatostatin lowers growth hormone in acromegaly but its action is too brief to be therapeutically useful. Recently an analogue containing only eight instead of 14 amino-acid residues, but which is very long-acting, has been used. Until recently a research preparation, it appears highly effective in holding down growth hormone levels, often to normal, and reversing all the clinical and metabolic features of acromegaly, but it must be injected 3 times a day subcutaneously in doses of 50–200 μg. The analogue, octreotide, may well become the medical treatment of choice in acromegaly. It may cause transient or dose-related steatorrhoea due to suppression of a number of gut hormones (see Ch. 3).

Ancillary measures

When growth hormone levels return towards normal, or the clinical condition is static, consideration of plastic surgery to the face, especially the nose and eyelids, and partial resection of the mandibles to restore the occlusion of the teeth and improve facial appearace, is important, and often restores the patient's morale if clinical resolution is not complete. Special dentures may improve chewing.

GROWTH HORMONE DEFICIENCY

In the absence of growth hormone, linear growth is impaired and bone maturation is delayed, though usually to a lesser extent. Growth hormone deficiency in the fetus does not lead to reduction in body length or weight at birth. The explanation for this finding is not clear; possibly maternal or placental growth stimulating factors may be effective, and it has been suggested that under normal conditions growth in utero is little affected by pituitary hormones. Careful observations on children lacking growth hormone indicate that the growth impairment develops within a few months of birth, though most cases are not diagnosed until after the age of 2 or 3 years.

Deficiency of growth hormone may be congenital or acquired. While it presents occasionally with neonatal or infantile hypoglycaemia, congenital isolated growth hormone deficiency is recognised more frequently between the ages of 4 and 9 years. The children show a characteristic immaturity of appearance though the body proportions are in step with the chronological age. Height is more affected than skeletal maturity though both are impaired, and height is usually below the third percentile after the fourth year of life. Even in the absence of growth hormone growth in height continues at a slow rate, usually at less than 1 cm a year, and the duration of growth is also prolonged because of the delay in bone maturity. Patients are usually somewhat overweight for height. The cause of isolated growth hormone

deficiency is usually a hypothalamic defect impairing normal secretion of hypothalamic growth hormone releasing hormone. Pathological studies of the pituitary are rare but in some cases have shown a relative deficiency of eosinophils secondary to the lack of the trophic hypothalamic hormone. It usually occurs sporadically, affecting predominantly males, but familial cases have been reported. Perinatal brain trauma may be responsible for pituitary damage in some cases.

Congenital growth hormone deficiency may occur in isolation, but often there is also a deficiency of gonadotrophins causing failure of sexual development which may be partial or complete. Gonadotrophin deficiency is difficult to diagnose until the time of puberty as the normal levels in infancy are so low. Less frequently, thyroid stimulating hormone and ACTH may be lacking. Hypoglycaemic attacks may be due to secondary adrenal insufficiency, but growth hormone deficiency is important as an additional factor and this may require urgent replacement in babies if hypoglycaemic. In adult life the patient with short stature due to childhood growth hormone deficiency retains childish immature features and normal body proportions but is usually chubby. The bones are slender, the skin fine and, eventually characteristically wrinkled. Muscular weakness and fatiguability are a result of poor muscular development.

Acquired growth-hormone deficiency results from a wide variety of disease processes causing partial or complete hypopituitarism (see Table 1.4, p. 29), e.g. craniopharyngioma, Hand-Schüller-Christian disease, hamartomas, pituitary adenoma, sarcoidosis, tuberculosis, meningitis and trauma. It is becoming more frequently seen in children who have had brain tumours such as gliomas and medulloblastomas successfully treated by brain radiotherapy which induces deficiency of hypothalamic growth-hormone-releasing hormone. Local manifestations are usually obvious, such as calcification in or above the sella turcica in craniopharyngioma or tuberculous meningitis. The pituitary fossa is usually abnormal on X-ray with pituitary tumours and intrasellar craniopharyngiomas. Growth-hormone deficiency is only rarely an isolated finding in acquired hypopituitarism, and impaired secretion of other anterior pituitary hormones is usual.

Diagnosis

The clinical feature of short stature due to growth-hormone deficiency may suggest the diagnosis, in particular the fine skin, delicate features, and normal body proportions with relative obesity. Height is usually less than the third centile, and bone and teeth development are immature. Individual children normally grow along their own centile line (Fig. 1.3). If a patient is gradually developing growth hormone deficiency while still in the growing period of life the characteristic feature with repeated, say 3-monthly, measurements is that linear growth deviates from that patient's own growth pattern, falling away from his or her centile line towards lower values. Growth picks up again when replacement therapy is given (Fig. 1.3).

X-rays of the pituitary fossa are required to exclude or define a local lesion, and bone X-rays (usually the non-dominant hand and wrist) are

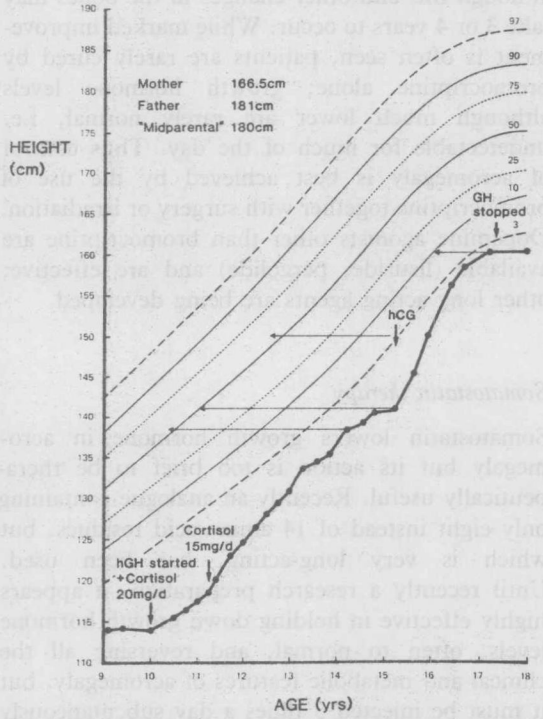


Fig. 1.3 Growth response to growth hormone therapy (12 units per week) in a hypopituitary child with a craniopharyngioma. The hydrocortisone (cortisol) replacement is shown. Puberty was induced with chorionic gonadotrophin (hCG) at age 15 yrs 6 mths. Parental heights are shown.

required to assess bone age. If there are visual field defects these must be formally assessed by perimetry usually using a Goldman apparatus. A CT scan of the pituitary and hypothalamic region is required to identify a mass in or above the gland. Direct measurement of serum growth hormone and cortisol output by radioimmunoassay in response to insulin-induced hypoglycaemia is necessary to assess the possibility of growth hormone and ACTH deficiency (see Appendix). After a dose of soluble insulin of 0.15 unit/kg body weight given intravenously, serum growth-hormone levels normally exceed 40 mU/l (20 ng/ml) within the next two hours if hypoglycaemia is adequate (the lowest blood glucose level falling below 2.2 mmol/l (40 mg/100 ml) accompanied by a tachycardia and little sweating). The patient should not be left unattended during an insulin tolerance test, which should be terminated with glucose and hydrocortisone if serious manifestations of hypoglycaemia develop. The patient should be given a meal at the end of the test and kept under observation in hospital for several hours. If the hypoglycaemia has not been sufficient and there has been no response the test should be repeated using a larger dose of insulin, e.g. 0.2 units/kg. Before concluding that there is deficiency of growth-hormone output many believe that it is wise to demonstrate that there is no rise also in response to another stimulation test such as intravenous arginine infusion, or during the third or fourth hour after administration of 1 mg subcutaneous glucagon, and these tests are preferred if the patient has a history of fits or fainting attacks, is under 7 years of age, or if the basal cortisol is low (see Appendix). Growth hormone is normally secreted as the blood sugar falls again, having risen after glucagon administration. In the peripubertal phase growth-hormone secretion may be equivocal even in normal children. Thus if the bone age is 10 years or more, in either sex, the stimulatory test should be performed after administration of oestrogen to sensitize the gland to secret growth hormone, e.g. give stilboestrol 0.5 mg twice daily for 48 hours before testing. Some clinicians screen their patients for growth-hormone deficiency by taking blood after physical exercise, or at intervals for two hours after a drink of Bovril, but these tests are unreliable.

Laron et al (1966) observed that the insulin response to the infusion of arginine was reduced in certain patients with dwarfism who had signs of growth-hormone deficiency but had high serum concentrations of immunoreactive hGH. In these patients the growth hormone fails to cause production of somatomedin-C probably due to defective receptors. On the other hand, in constitutional short stature, as in pygmies, somatomedin production is normal but there is a subnormal tissue response.

Clinical and laboratory evidence of deficiency of other pituitary hormones should be sought, and this topic is dealt with in the section on hypopituitarism (see page 29). The differential diagnosis of pituitary dwarfism from delayed onset of adolescent growth and development, constitutional dwarfism, gonadal dysgenesis, and other varieties of dwarfism will be considered in the chapter on Disorders of Growth (Ch. 4).

Treatment of short stature due to growth-hormone deficiency

The main object of treatment is to increase the height of the patient and to correct deficiencies of other hormones as necessary. Shortness of stature has many adverse psychological effects on the individual, being particularly poorly tolerated in the female. Parental anxiety is ever present and the clinical situation needs handling with particular tact and discretion. As supplies of biosynthetic human growth hormone increase so does the need for early and critical diagnosis.

Before treatment with growth hormone can be considered, deficiency of the hormone should be proved by growth hormone assay during adequate insulin-induced hypoglycaemia or a glucagon or arginine test. X-rays of the hand and wrist should be performed to confirm that the epiphyses are not fused. This is usually so except when gonadal function is normal or when the patient has been treated with sex hormones to increase sexual development or to induce menstruation. It is usual to observe the patient for at least 6 months to demonstrate inadequate linear growth, since particularly after operation in the region of the hypothalamus, normal growth may be seen in the absence of measurable growth hormone. This phenomenon is unexplained. Such children