Fundamentals of Clinical Endocrinology

Reginald Hall
John Anderson
George A Smart
Michael Besser

Third Edition

Fundamentals of Clinical Endocrinology

REGINALD HALL, BSc, MD (Dunelm), FRCP
Professor of Medicine, Welsh National School of Medicine, Cardiff

JOHN ANDERSON, MB, BS (Dunelm), FRCP
Academic Sub-Dean and Senior Lecturer in Medicine, University of Newcastle upon Tyne, and Physician to the Royal Victoria Infirmary, Newcastle upon Tyne

GEORGE A. SMART, BSc, MD (Dunelm), FRCP
Former Director, British Postgraduate Medical Federation, Professor Emeritus of Medicine, University of London, Honorary Consultant Physician, National Hospital for Nervous Diseases, London

MICHAEL BESSER, BSc, MD (London), FRCP
Professor of Endocrinology and Honorary Consultant Physician, St. Bartholomew's Hospital and Medical College, University of London

THIRD EDITION

PITMAN MEDICAL

First Published 1969
Second edition 1974
Third edition 1980
Reprinted 1981

Catalogue Number 21.1405.81

PITMAN BOOKS LIMITED
39 Parker Street, London WC2B 5PB

PITMAN PUBLISHING INC.
1020 Plain Street, Marshfield, Massachusetts

Associated Companies
Pitman Publishing Pty Ltd, Melbourne
Pitman Publishing New Zealand Ltd, Wellington
Copp Clark Pitman, Toronto

British Library Cataloguing in Publication Data
Fundamentals of clinical endocrinology.
—3rd ed.
1. Endocrine glands—Diseases
I. Hall, Reginald
616.4 RC648

ISBN 0–272–79559–3

Text set in 10/11 pt Linotron 202 Melior, printed and bound in Great Britain at The Pitman Press, Bath

FUNDAMENTALS OF CLINICAL ENDOCRINOLOGY

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.

Dr John Gray contributed the chapter on Disorders of Sex Differentiation; the Departments of Medical Illustration and Photography of Newcastle University and St. Bartholomew's Hospital reproduced many of the illustrations. We also wish to thank Pitman Medical and in particular Mr Stephen Neal and Mr D. Dickens for their patience and cooperation in the production of this book.

Newcastle upon Tyne
and London, 1979

R. Hall
J. Anderson
G. A. Smart
M. Besser

CONTENTS

CHAPTER ONE

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 stomodaeum of ectodermal origin, Rathke's pouch, comes in contact with the infundibulum, a downgrowth from the floor of the diencephalon. Rathke'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 partly 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 possibly in the fetus. The cells of the posterior pituitary develop from the infundibular process, becoming modified to form pituicytes. Many nerve fibres grow into the posterior pituitary via the pituitary stalk from the hypothalamic nuclei.

The human pituitary gland weighs between 0.5 and 0.9 g and is an ovoid reddish-grey body about 15 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 posterior clinoid processes (Figure 1.1). The size of the

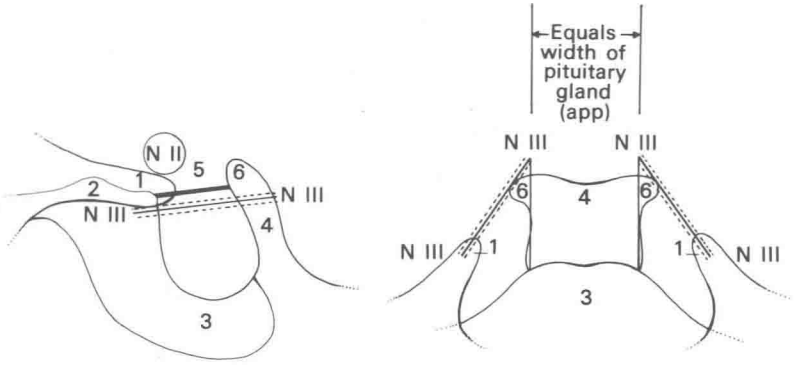


Figure 1.1 The pituitary fossa and its relationships: 1, anterior clinoid process; 2, tuberculum sellae; 3, sphenoid sinus; 4, dorsum sellae; 5, diaphragma sellae; 6, posterior clinoid process; NII, optic chiasm; NIII, oculomotor nerve. (From Fraser, R. and Joplin, G. F. (1954), *British Journal of Radiology* **32**, 527)

sella turcica is very variable in adults and, also, depends on age. Acheson (1956) defines the length of the pituitary fossa as the distance from the tuberculum sellae to the dorsum sellae, and the depth as the distance from the line joining these points to the lowest part of the sella (Table 1.1). A

Table 1.1 Length and depth of the adult pituitary fossa on x-ray (measured in mm)

	Male			*Female*		
	No.	*Mean*	*s.d.*	*No.*	*Mean*	*s.d.*
Length	80	13.5	1.8	49	13.3	1.4
Depth	80	7.2	1.2	49	7.1	1.1

(Acheson, R. M. (1956). Measuring the pituitary fossa from radiographs. *British Journal of Radiology* **29**, 76)

tube-film distance of 3 feet is specified, a lateral radiograph being taken with strict head positioning. Tumours in the pituitary fossa may initially declare themselves by erosion of the bony margins. The earliest changes are often asymmetrical so that a lateral x-ray of the fossa may show more than one contour to the floor. This 'blistering' or 'double floor' appearance is often the first sign of the pituitary tumour and precedes frank ballooning of the sella.

Relations of the pituitary (Figure 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 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.

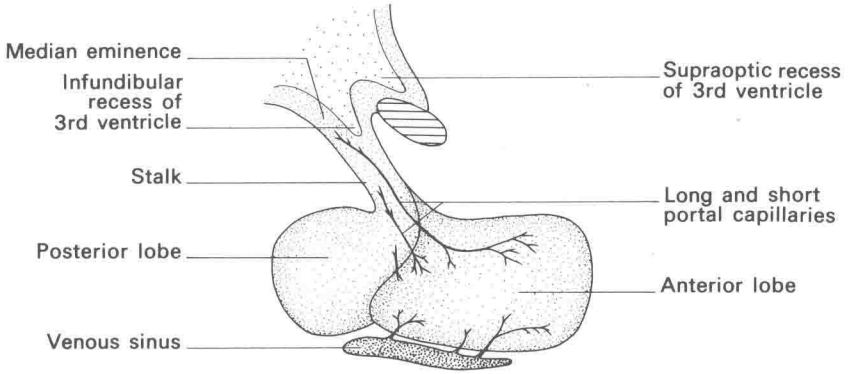


Figure 1.2 The human pituitary gland and its stalk arising from the median eminence region of the hypothalamus, showing the short and long portal capillaries connecting the median eminence and stalk with the anterior pituitary. (After Daniel and Pritchard, 1975)

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 hypothalamic centres and tracts from which they pick up the various regulatory hypothalamic hormones by which synthesis and release of the hormones of the anterior pituitary are controlled by the hypothalamus. These are carried to the anterior pituitary sinusoids by portal veins passing down 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 is dealt with in detail in Chapter 3.

Microscopic structure of the anterior pituitary

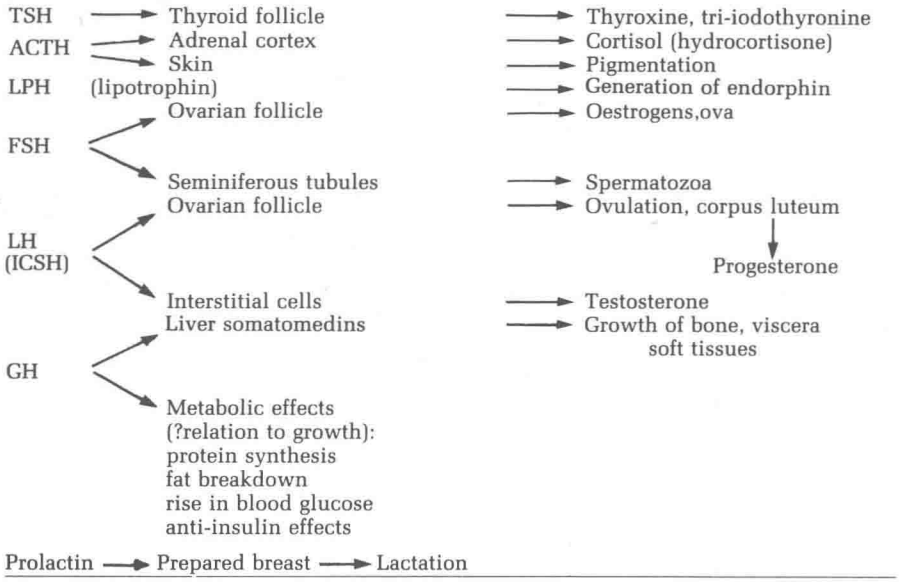
The glandular cells of the anterior pituitary are arranged in cords separated by a rich network of capillary sinusoids. They can be divided into chromophils and chromophobes by simple stains such as haematoxylin and eosin which are taken up by the secretory granules. The chromophobes usually have less 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 more elaborate histochemical staining methods, electron microscopy, and immunofluorescence techniques, separate types of cells can be identified for each of the anterior pituitary hormones.

The acidophils secrete growth hormone and prolactin. The majority of the acidophils are grouped in two posterolateral 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 source 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.

Table 1.2 Principal actions of anterior pituitary hormones



GROWTH HORMONE

Growth hormone makes up between 5 and 10 per cent of the dry weight of the human pituitary gland; it is a protein with a molecular weight of 21 000 consisting of 191 amino-acid residues. Clear evidence is now available that prolactin exists separately from growth hormone in man. Owing to similarities in structure and biological actions and the fact that prolactin is present in the human pituitary gland in much smaller quantities than growth hormone, their separate identities were doubted for many years.

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 (see page 14). It appears in placental tissue by the ninth week of pregnancy and its concentration in the blood can be high enough to interfere with some radioimmunoassays of growth hormone. Its function has not yet been established. Measurement of the blood levels of placental lactogen in middle and late pregnancy provides a reliable test of placental function; low levels suggest placental insufficiency.

Secretion and transport of growth hormone

Sensitive and specific methods are now available for the measurement of growth hormone in blood. Immunoassay, using radioiodine-labelled human growth hormone, is now a standard procedure in most centres. Antiserum to human growth hormone (hGH) is prepared in animals.

Labelled hGH is incubated with anti-hGH 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 bound 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 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 and these bursts occur mainly during the first half of the night during the period of deep sleep. They are infrequent at other times. Secretion is 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 providing a possible explanation for the reduction in growth in children receiving these compounds. The total daily secretion of children and adolescents is much greater than adults, and many more secretory bursts are found. Serum growth hormone levels in non-fasting adults are variable, usually being less than 4 mU/l (2 ng/ml)* except during the secretory bursts. Endogenous growth hormone leaves the circulation rapidly, the half-life being about 20–25 minutes, but the metabolic effects must last much longer, for increased growth in growth hormone deficient subjects can be maintained with only one or two injections each week.

Growth hormone release from the pituitary can be stimulated by insulin-induced hypoglycaemia, by arginine infusions, by exercise, and by pyrogen. Hypoglycaemia and pyrogen also release ACTH but do not affect TSH or the gonadotrophins; arginine causes a rise in plasma insulin, possibly as a result of growth hormone release. 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 secretion and also causes ACTH and prolactin levels to rise. The effects of growth hormone on the metabolism of carbohydrate and fat are discussed in Chapter 14.

The hypothalamus controls growth hormone synthesis and release by means of two regulatory hypothalamic hormones, growth hormone releasing hormone and growth hormone release inhibiting hormone, or somatostatin. The peptide structure of somatostatin is known. Its actions are dealt with in Chapter 3. The metabolic factors affecting growth hormone release probably act largely at a hypothalamic level.

* N.B. The precise levels of any hormone either in SI units or by weight may vary between centres since antisera and hormone standards differ. Conversion factors between SI units and weight equivalents also may vary. Each laboratory has to establish its own normal ranges.

Growth hormone in blood appears to be transported in bound form but there is no agreement on the nature of the carrier protein; both albumin and an alpha two macroglobulin may be involved.

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 to stimulate growth but rather acts on the liver, and possibly other organs, to cause the production of intermediate polypeptide growth factors called the somatomedins or the 'sulphation factors'. Several somatomedins seem to exist ranging in molecular weight between 5000 and 9000. They appear to have related but differing actions and may represent intermediates with growth promoting effects on different tissues such as cartilage, fibroblasts and muscle.

Its effect 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 on m-RNA. It may in some way affect the efficiency of the ribosomes, the site of protein synthesis.

CLINICAL EFFECTS OF GROWTH HORMONE

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 adolescents. The main clinical features in acromegaly are shown in Table 1.3.

The tumour classically is of the acidophilic type but is often chromophobe.

Local effects of the tumour

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

Table 1.3 Features of acromegaly

Clinical *General effects due to metabolic disturbance*	%
Skin and subcutaneous tissue overgrowth	100
Skeletal overgrowth 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	100
Excessive sweating	60
Goitre—diffuse or nodular	20
Clinical diabetes mellitus	12
Hypertension	14
Greasy skin, acne, gynaecomastia, galactorrhoea, cardiomyopathy	sporadic
Local effects due to presence of pituitary mass	sporadic
Headache	
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 above 4 mU/l (2 ng/ml)	100
Non-suppression of growth hormone to below 4 mU/l (2 ng/ml) during oral glucose tolerance test	100
Urine calcium above 300 mg (6 mmol)/24 hours	50
Chemical diabetes mellitus—impaired glucose tolerance	25

Associated endocrine features

The basal metabolic rate is increased in acromegaly, but this is usually a manifestation of growth hormone activity rather than hyperthyroidism. Non-toxic goitres are not uncommon but hyperthyroidism only occasionally occurs, probably on the basis of a multinodular goitre. Hypothyroidism may be a late result of destruction of pituitary thyrotrophic cells by the tumour, or a result of surgery or radiation to the pituitary.

Damage to the gonadotrophin producing cells is a common occurrence in acromegaly and gigantism. The hypogonadism that results is responsible for the delayed closure of the epiphyses in gigantism, and for loss of libido and impotence in men, and infertility and decreased frequency of menstruation with reduced loss in women. Persistent lactation (galactorrhoea) may be a feature of acromegaly or may precede it by many years.

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. Hirsuties 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 12 per cent 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 effect might be mediated through one of the somatomedins. This results in increased levels of immunoreactive insulin 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.

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, and is then usually due to a primary cardiomyopathy. Renal size, blood flow, and glomerular filtration rate are all increased. Some patients with acromegaly have pigmentation of the skin.

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. 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. An air encephalogram or a computerised tomographic (CT) scan of the suprasellar region may be required to demonstrate the extent of the suprasellar extension of the tumour. 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. Urinary calcium excretion exceeds 350 mg

(6 mmol)/24 h on a diet containing less than 500 mg calcium/day in about 50 per cent of patients. This effect of growth hormone on urinary calcium excretion requires the presence of the parathyroids. Elevation of the serum phosphate level is seen in a few patients but is not of much diagnostic help. Tests of carbohydrate metabolism may give useful indirect evidence of growth hormone hypersecretion. The glucose tolerance test is abnormal in one-quarter of patients.

The final confirmation of the diagnosis of acromegaly rests with the demonstration of an *elevated plasma growth hormone level* (normally less than 4 mU/l (2 ng/ml) fasting and at rest) which *fails to suppress* normally (to less than 4 mU/l (2 ng/ml)) during an oral glucose tolerance test (*see* Appendix). 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 (*see* page 41), TSH (Chapter 5), and of corticotrophin during an insulin tolerance test (*see* page 42 and Appendix). However, in patients with elevated growth hormone levels larger doses of insulin than normal (for example 0.3 units/kg) 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. For this reason the condition should be treated whenever there is evidence of activity on metabolic and growth hormone studies. Acromegaly rarely burns itself out although the progression of the changes in physical appearance may become static after several years. In such patients the growth hormone levels usually are still elevated and the metabolic consequences and the complications remain. Rarely the pituitary tumour may infarct and result in a spontaneous cure.

Treatment of gigantism and acromegaly

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

Ablative therapy

Partial hypophysectomy via a craniotomy, transfrontally, is indicated for extrasellar extensions involving the visual pathways. Total hypophysectomy often causes remission of the disease but is a very specialised technique usually necessitating permanent replacement therapy for hypopituitarism. In patients with large tumours total hypophysectomy is not always possible. Recently attempts have been made to remove the adenoma selectively leaving behind only normal pituitary gland, using a

trans-sphenoidal route from below the fossa. If the tumour is small, less than 1 cm in diameter, this may be possible, but frequently hypopituitarism may occur or persistence of the acromegaly due to inadequate removal. Often the tumour infiltrates the bone or meninges and these portions are irremovable. Any surgery which is followed by persisting evidence of active acromegaly should be followed by irradiation, and consideration of medical treatment with bromocriptine (see below) at least until the radiotherapy has resulted in eradication of the remaining active disease.

Conventional high voltage radiation therapy giving courses totalling 4500 rad does not always cause clinical improvement, though progress of the disease may be halted. 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 about half the patients but a partial biochemical and clinical response is seen in a higher proportion although the full effects may not be seen for four or more years. High energy heavy-particle radiation produces better results but the risk to vision is greater.

Needle application of radioactive seeds into the pituitary allows a greater dose of radiation to be given, and if judged correctly may improve the disease without producing hypopituitarism. Implants of ^{198}Au or ^{90}Y, or both, have been used, and satisfactory remissions produced. Yttrium-90 is at present the isotope of choice, seeds being inserted by a transnasal route so that most of the pituitary receives a dose of 50 000–150 000 rad, though a smaller dose may be considered in patients of childbearing age. Reimplantation may sometimes be necessary if a remission is not produced in a year or two. The complications of this form of treatment are visual impairment caused by radiation, oedema or haemorrhage into the pituitary gland, diabetes insipidus due to damage to the hypothalamus and median eminence, cerebrospinal rhinorrhoea, which may lead to meningitis, and third nerve palsies.

Medical therapy with 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 either at the pituitary level or at the median eminence. Bromocriptine (2 brom-alpha-ergokryptine) a semisynthetic ergot derivative is a long acting, dopamine agonist which can be given by mouth and which 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 usually 30–60 mg/day are needed. To avoid dyspepsia the drug must be

taken during meals and as with hyperprolactinaemia (page 18) 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.

About 75 per cent of acromegalic patients respond 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 and hypertension and greasiness of the skin. Visual fields may improve and the pituitary fossa may become smaller although this and other changes in the bones may take three or four years to occur. However, it seems that the tumour shrinks. Control of acromegaly is usually best achieved by the use of bromocriptine together with ablative therapy such as surgery or irradiation. The latter may take four or more years to be fully effective so bromocriptine is useful either for interim therapy or if other measures fail.

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 eye lids, and partial resection of the mandibles to restore the occlusion of the teeth and improve facial appearance, is extremely important and often restores the patient's morale if clinical resolution is not complete.

GROWTH HORMONE DEFICIENCY

Pituitary dwarfism

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 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 the age of 2 or 3 years.

Deficiency of growth hormone may be congenital or acquired.

Congenital hypopituitary dwarfism is usually recognised a year or two after birth. 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. The cause of the condition is uncertain but may be due to a hypothalamic lesion preventing normal secretion of hypothalamic growth hormone releasing