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Hypopituitarism is the deficiency of one or more pituitary hormones. It is relatively rare, with a prevalence of 45 per million and an annual incidence of about 4 per 100,000. It is, however, seen commonly in endocrine practice and, importantly, is associated with increased morbidity and mortality. Clinical manifestations are influenced by the etiology, severity, and rate of onset of pituitary hormone deficiency.

MORTALITY IN HYPOPITUITARISM

Hypopituitarism is associated with excess mortality compared with the normal population. There have been six major epidemiological studies of mortality rates in patients with hypopituitarism published between 1990 and 2001. These studies had certain features in common. Patients with acromegaly and Cushing’s disease were excluded due to their known excess mortality. The median age of the patients was between 46 and 52 years, and 51 to 62% of patients were males. The duration of follow-up was between 10 and 13 years. Major differences between the studies were the relative frequencies of pituitary adenomas, the use of radiotherapy, and the degree of documented hypopituitarism.

In all studies an excess mortality was recorded with standardized mortality rates (SMR) of 1.2 - 2.2. Most of the increase in mortality was attributed to a higher incidence of cardiovascular and cerebrovascular disease, risk ratios for malignancies and respiratory disease varied. Common independent factors carrying a worse prognosis included craniopharyngioma as the primary pathology (SMR 5-9) and female gender.

The exact contribution of hormonal deficiencies and/or sub-optimal hormone replacement to the excess mortality is unresolved. Many believe, that growth hormone deficiency plays an important role: it is the hormone deficiency with the highest prevalence in pituitary hypofunction, and the negative effects on the cardiovascular risk profile in patients with untreated growth hormone deficiency have been well documented (alterations in lipid fractions, blood vessel wall composition, nitric oxide availability and inflammatory mediators). As there is a very high prevalence of growth hormone deficiency in hypopituitary patients, documenting its contribution as an independent mortality risk factor is inherently difficult. Long-term controlled studies of growth hormone replacement therapy could potentially provide such information, but so far these studies have not been performed. Equally, other hormone deficiencies or their replacement had no consistent effect on mortality (i.e. untreated male gonadotropin deficiency was associated with reduced mortality in one study, but with excess mortality in another).

CAUSES

The causes of hypopituitarism are varied (Table 21-1). In adulthood, however, the most common cause is a pituitary adenoma or treatment with pituitary surgery or radiotherapy.

Pituitary and Hypothalamic Mass Lesions
Pituitary adenomas account for the vast majority of pituitary mass lesions, although secondary tumors do occur, with metastases to the pituitary gland reported from carcinomas of the breast, lung, colon, and prostate. Pituitary microadenomas are surprisingly common, being found in between 1.5% and 27% of patients at autopsy; these tumors are very rarely, if at all, associated with hypopituitarism and tend to run a benign course. Macroadenomas are less common, but are more frequently associated with pituitary hormone deficiencies; some 30% of patients with pituitary macroadenomas have one or more anterior pituitary hormone deficiencies. Evidence suggests the causative mechanism of hypopituitarism in these patients is compression of the portal vessels in the pituitary stalk, either secondary to the expanding tumor mass directly or to raised intrasellar pressure which explains the potential reversibility of pituitary dysfunction after surgery in some patients.

Craniohypophyseal lesions are the third most common intracranial tumor and account for the majority of parapituitary tumors. They are thought to arise from Rathke's pouch and may be cystic or solid, commonly showing calcification. Fifty percent occur in children less than 15 years old. Patients commonly present with GH deficiency and diabetes insipidus, with or without a visual field defect.

Derangement of central endocrine regulation also occurs with other parapituitary space-occupying lesions such as chondromas, chordomas, suprasellar meningiomas, astrocytomas of the optic nerve, and primary tumors of the third ventricle.
Pituitary Surgery

Hypopituitarism is a common consequence of pituitary surgery. The incidence and degree of hypopituitarism depend on a number of factors, including the size of the original tumor, the degree of infiltration, and the experience of the surgeon. The patient should be warned of a possible deterioration of pituitary function postoperatively, and assessment of pituitary function should be performed promptly after surgery. However, a decline in pituitary function postoperatively is not universal. Surgery for pituitary adenomas may be associated with a significant recovery of pituitary function. About half of the patients recover at least one pituitary insufficiency following transsphenoidal surgery. Postoperative improvement is more likely if there is no tumor on postoperative imaging and no neurological or pathological evidence that the tumor is of an invasive nature. The most likely pituitary hormone to recover is TSH, followed in order by ACTH, Gonadotropins and GH. There is evidence that in those patients in whom recovery of pituitary function occurs, the process begins immediately after surgery.

Radiotherapy

Deficiency of one or more anterior pituitary hormones may follow treatment with external radiation when the hypothalamic-pituitary axis lies within the fields of radiation. Hypopituitarism has been described in patients who received radiation therapy for nasopharyngeal carcinomas, tumors of the pituitary gland or nearby structures, and primary brain tumors, as well as in children who underwent prophylactic cranial irradiation for acute lymphoblastic leukemia or total body irradiation (TBI) for a variety of tumors and other diseases.

The radiobiologic impact of an irradiation schedule is dependent on the total dose, number of fractions, and duration. The same total dose given in fewer fractions over a shorter time period is likely to cause a greater incidence of pituitary hormone deficiency than if the schedule is spread over a longer time interval with a greater number of fractions. Equally, higher radiation doses tend to cause more severe hypopituitarism. Thus, after lower radiation doses, isolated GH deficiency ensues, while higher doses may produce panhypopituitarism (Fig. 21-1). Radiation dose also determines the speed of onset of hormonal deficiency. The greater the dose, the earlier GH deficiency will occur after treatment, so that between 2 and 5 years after irradiation 100% of children receiving more than 30 Gy (over 3 weeks) to the hypothalamic-pituitary axis showed subnormal GH responses to an insulin tolerance test (ITT) while 35% of those receiving less than 30 Gy (over 3 weeks) still showed a normal GH response (Fig. 21-2). Interpretation of the impact of radiation-induced damage to the hypothalamic-pituitary axis on growth hormone status is, however, complicated in the early years after irradiation, when discordant results may be seen to different growth hormone provocative agents.

Paradoxically, while high doses of cranial irradiation may render a child gonadotropin-deficient, lesser doses of irradiation may be associated with early puberty. The mechanism for early puberty after irradiation is likely to be related to disinhibition of cortical influences on the hypothalamus. With increased survival, follow-up evaluation of patients irradiated for tumors of the brain and surrounding structures will need to focus less on the possibility of tumor recurrence and more on the delayed effects of therapy, including the endocrine effects.

Genetic Causes

Our knowledge of genetic causes responsible for hypopituitarism has grown rapidly over recent years, and has elucidated the pathophysiology of previously described “idiopathic” pituitary hormone deficiencies. Gene mutations can (a) interfere with the development of different pituitary cell lineages (e.g. pituitary transcription factor defects), (b) cause alterations in hypothalamic releasing factors or their pituitary receptors (e.g. Kallmann syndrome), or (c) impair the production of pituitary hormones (e.g. isolated growth hormone deficiency).

Combined Pituitary Hormone Deficits Due To Transcription Factor Defects

A cascade of pituitary transcription factors regulate the differentiation of cells of Rathke’s pouch into somatotrophs, lactotrophs, thyrotrophs, gonadotrophs and corticotrophs. Mutations in early-appearing transcription factors tend to cause more extensive hormone deficiencies (e.g. multiple pituitary hormone deficiencies in mutations of HESX1, PROP1, Pit-1 and LHX3/4), whereas others can cause isolated deficiencies (e.g. ACTH deficiency due to TBX19 mutations, growth hormone deficiency in Rieger syndrome due to PITX2 mutations).

PIT-1. Pit-1 (pituitary-specific transcription factor-1), also termed growth hormone factor-1 (GHF-1) or POU1F1, is a pituitary-specific transcription factor responsible for pituitary development and hormone expression in mammals. Pit-1 contains two protein domains, termed POU-specific and POU-homeo, which are both necessary for high-affinity DNA binding of the GH and prolactin genes. Pit-1 is also important for hormonal regulation of the prolactin and thyrotropin-beta subunit genes by thyrotropin-releasing hormone (TRH) and cyclic adenosine monophosphate (cAMP). Mutations of the Pit-1 gene have been found in dwarf mice strains (Snell mouse) displaying hypoplasia of GH, prolactin, and TSH-secreting cells of the anterior pituitary, demonstrating the importance of Pit-1 for the development of certain anterior pituitary cells. Humans with Pit-1 deficiency resemble Snell mice in that they lack GH and prolactin, have variable degrees of TSH deficiency, and often exhibit pituitary hypoplasia. At a clinical level Pit-1 abnormalities account for only a small minority of the total number of cases of hypopituitarism worldwide. Pit-1 gene
mutations have also been discovered in patients with idiopathic GH deficiency associated with preserved basal prolactin and TSH secretion. This illustrates the variability of phenotypic presentation among these patients.

PROP1. A further, more recent discovery is a novel pituitary paired-like homeodomain factor which seems to be an important prerequisite of the expression of Pit-1. This has been named PROP1 (Prophet of Pit-1). Several multicenter studies of patients with otherwise unexplained multiple pituitary hormone deficiencies found underlying PROP1 mutations in 40 to 50% of such patients. Individuals with a mutation of the PROP1 gene, which causes reduced DNA-binding and transcriptional activation activity, develop progressive hypopituitarism with GH, TSH and gonadotropin deficiency typically present by the end of the second decade. They may also have pituitary hyperplasia followed by degeneration, and late appearance of partial ACTH deficiency.

HESX1. HESX1 ("homeobox gene expression in embryonic stem cells"), also called Rpx ("Rathke’s pouch homeobox"), is a member of the paired-like class of homeobox genes and is first expressed during mouse embryogenesis in a small patch of cells in the anterior midline visceral ectoderm, which are destined to give rise to the ventral prosencephalon. Mice lacking HESX1 have variable anterior CNS defects and pituitary dysplasia. A comparable and equally variable phenotype in humans is septo-optic dysplasia (SOD), which is associated with hypopituitarism, the latter typically associated with milder phenotypes. LHX3 and LHX4 belong to the LHX3/LHX4. LHX3 and LHX4 belong to the Lhx ("LIM homeodomain transcription factor") family of transcription factors. LHX3 is expressed in the pituitary, can bind to Pit-1 and enhance Pit-1 activity. It also contributes to the development of the alpha-subunit of the glycoprotein hormones. Netchine et al. identified homozygous LHX3 defects leading to panhypopituitarism (with the exception of ACTH deficiency) and rigidity of the cervical spine. LHX4 has recently been implicated in familial hypopituitarism. An LHX4 germline splice-site mutation has been found in one family with multiple pituitary deficits, short stature, and abnormalities of the pituitary gland, cerebellum and skull base.

PII2. PII2 is another pituitary homeodomain transcription factor, defects of which are seen in Rieger syndrome due to mutations in the RIEG gene. Some of those patients have been found to have growth hormone deficiency, and possibly impaired prolactin secretion.

Isolated Growth Hormone Deficiency

Two types of genetic defects have been identified which cause isolated GH deficiency. These are mutations of the GH gene and of the growth hormone-releasing hormone (GHRH) receptor gene. The human GH (hGH) gene is located on chromosome 17 in a cluster of five genes: hGH-N encodes the gene for pituitary GH, hGH-V encodes the gene for placental GH and there are three genes for human chorionic somatomotropin (hCS). Children with gene mutations or deletions of hGH-N present with severe short stature and, in males, microgenitalia. They have the characteristic phenotypic features of GH deficiency. Four types of mendelian disorders of the growth hormone gene have been described: IGHD IA and IB are both inherited in an autosomal recessive manner resulting in absent or low GH levels. Patients with absent GH (IGHD IA) often develop anti-GH antibodies when treated with GH. IGHD II has an autosomal dominant mode of inheritance with variable clinical severity. IGHD III is an X-linked disorder often associated with hypogammaglobulinemia.

Mutations of the gene encoding the GHRH receptor can result in a severely truncated receptor lacking the seven membrane spanning domains. Such mutations have been identified in a number of kindreds with severe growth hormone deficiency ("dwarfism of Sindhi"). The GHRH receptor itself belongs to the family of G protein-coupled receptors. Heterozygous inactivating mutations in the Gs alpha gene, which are present in pseudohypoparathyroidism type Ia, can cause GHRH resistance (in addition to the well documented hormone resistance to PTH, TSH, gonadotropins and glucagon), thereby causing GH deficiency.

Isolated Gonadotropin Deficiency

To date, several gene mutations have been identified as causes of idiopathic hypogonadotropic hypogonadism (IHH) in humans, although the genetic basis of the condition is still unknown in the majority of patients. Inheritance is usually autosomal recessive, except for X-linked GHRH receptor gene. Mutations of the gene encoding the GHRH receptor gene can result in GnRH resistance at pituitary level thereby causing gonadotropin deficiency. The DAX1-orphan nuclear receptor is expressed at multiple levels throughout the reproductive axis, and mutations in the DAX-1/AHC
gene underlie the combined phenotype of adrenocortical failure and gonadotropin deficiency. Other genes implicated in IHH are PC1 (prohormone convertase, associated with defects in prohormone processing), OB and DB (leptin and leptin receptor, associated with obesity), whereas inactivating mutations of LH-beta and FSH-beta genes can cause isolated deficiencies of LH and FSH, respectively.

**Isolated ACTH and TSH Deficiencies**

Isolated deficiencies of TSH or ACTH are very rare; however, in a number of cases a genetic abnormality has been described or proposed. Mutations of the coding region of the TSH-beta subunit gene and TSH receptor gene have been found in a number of families as a cause of hereditary isolated TSH deficiency.

Recently, a pituitary transcription factor causing isolated ACTH deficiency has been identified. TBX19 (the human T-box pituitary transcription factor, analogous to Tpit in the mouse), has an essential role in differentiation of POMC cells in the pituitary. At least two TBX19 gene mutations causing isolated ACTH deficiency have been described.

**Other Causes**

**Posttraumatic.** Pituitary dysfunction after severe head injuries tends to become apparent within 1 year after the trauma for the majority of patients, although in a significant proportion it can remain undetected. A systematic evaluation of patients recovering from severe traumatic brain injuries revealed completely intact pituitary function in only 31 percent. Another review identified certain characteristics in patients who develop posttraumatic hypopituitarism: the majority had been unconscious for at least several days, about half had associated skull fractures, whereas diabetes insipidus was present in only a third. The predominant autopsy findings in traumatic hypopituitarism are hypothalamic hemorrhage, anterior pituitary infarction and posterior pituitary hemorrhage (each accounting for about 25% of the cases), whereas pituitary stalk lesion are only seen in a small minority. The reported predominance of hypogonadism in the majority of patients has not been uniformly confirmed.

**Lymphocytic hypophysitis.** Lymphocytic hypophysitis, an immune-mediated diffuse infiltration of the anterior pituitary with lymphocytes and plasma cells, occurs predominantly in women and is often first evident in pregnancy or after delivery. The classic presentation is peripartum hypopituitarism, often with a pituitary mass and visual failure. ACTH deficiency is an almost universal feature which, when undiagnosed, has proved fatal. At an early stage the pituitary gland is enlarged and cannot be distinguished from a pituitary tumor by computed tomography or magnetic resonance imaging, while in the later stages the gland may atrophy, leaving an empty sella. Lymphocytic hypophysitis is more common in patients with other autoimmune endocrine diseases. Cytosolic autoantigens against the pituitary can be demonstrated in some cases, but are also present in normal patients, and thus the definitive diagnosis of this condition remains difficult without pituitary biopsy.

Spontaneous resolution of both the mass and the hypopituitarism have been reported and, in some cases, neurosurgical intervention has led to irreversible pituitary failure. Therefore, conservative management is appropriate in the majority of patients.

**Pituitary apoplexy.** Pituitary apoplexy is the abrupt destruction of pituitary tissue resulting from infarction or hemorrhage into the pituitary, usually into an underlying pituitary tumor. Severe headache accompanies a variable degree of visual loss or cranial nerve palsy. The consequent pituitary hormone deficiencies may develop rapidly. In Sheehan’s syndrome pituitary infarction occurs secondary to severe postpartum hemorrhage and ensuing circulatory failure. Once common, this complication is now mainly confined to areas where obstetric services are less well developed.

**Granulomatous diseases.** Granulomatous diseases, including sarcoidosis, tuberculosis, and Langerhans’ cell histiocytosis, can affect the hypothalamic-pituitary axis and cause hypopituitarism, including diabetes insipidus. Diabetes insipidus complicates sarcoidosis rarely (1%). It is more common, however, in Langerhans’ cell histiocytosis, with 15% of childhood cases developing diabetes insipidus, but it may also occur in patients presenting in adulthood.

**Iron overload states.** Iron overload states, that is, hemochromatosis and beta-thalassemia treated with frequent blood transfusions, are associated with pituitary hyposecretion secondary to siderosis and a reduction of pituitary cell number. The gonadotrophs are particularly vulnerable to this mode of damage; however, as affected patients live longer owing to improved medical care, other pituitary hormone deficits, including deficits of GH and ACTH, are seen more frequently.

**Hyperparathyroidism.** Primary hyperparathyroidism due to a solitary adenoma can be associated with significantly impaired basal and stimulated GH secretion. The pathogenetic mechanism is still speculative but normality is restored after surgical removal of the adenoma.

**CLINICAL FEATURES**

The clinical features of hypopituitarism are affected principally by the degree, type, and speed of onset of the pituitary hormone deficiency. Local pressure effects or hormonal hypersecretion can, however, complicate the clinical picture.

In many forms of hypopituitarism, for example secondary to a pituitary adenoma and following irradiation, a characteristic evolution of pituitary failure is apparent. Secretion of GH fails first, followed by luteinizing hormone (LH), follicle-stimulating hormone (FSH), and finally by failure of ACTH and TSH secretion. Prolactin deficiency is rare except as a component of Sheehan’s syndrome. Hyperprolactinemia is much more common, either
secondary to interference with the secretion or delivery of dopamine to the pituitary, releasing the normal lactotrophs from tonic inhibition, or because of hypersecretion from a prolactinoma. Diabetes insipidus is not generally a feature of pituitary disease, and the presence of diabetes insipidus usually denotes a hypothalamic or stalk disorder, except when occurring following hypothalamic or pituitary surgery. The symptoms and signs of individual hormone deficiencies are listed in Table 21-2.

Growth Hormone Deficiency

GH secretion is a continuous variable and a spectrum therefore exists from severe GH deficiency to mild GH insufficiency. Typically, the GH-deficient child has increased subcutaneous fat, especially around the trunk. The face is immature with a prominent forehead and depressed midfacial development; this is related to the lack of GH effect on endochondral growth at the base of the skull, occiput, and the sphenoid bone. Dentition is delayed. In males the phallus may be small, and the average age of pubertal onset is delayed in both boys and girls (Fig. 21-3).

GH continues to have significant functions in adult life. Severe GH deficiency in adults is associated with impaired quality of life and adverse changes in body composition, bone mineral density (BMD), lipid profile, insulin sensitivity, endothelial integrity, cardiac function, and life expectancy.36 Adults with GH deficiency have a higher proportion of body fat than matched controls and a high waist-to-hip ratio, reflecting the predominantly central distribution of fat. On average, BMD in adults, particularly young adults, with GH deficiency is about 1 to 2 SD below the age-matched normal mean.33 Correspondingly, a questionnaire-based study has estimated that the fracture rate in GH-deficient patients is increased twofold compared with that of an age-matched group.33 Studies in adults with varying degrees of hypopituitarism indicate that GH deficiency per se, rather than associated gonadotropin deficiency or overtreatment with glucocorticoid or thyroxine replacement, is responsible for the osteopenia. GH-deficient adults report more perceived health problems and a lower quality of life than controls. The conclusions from studies of the lipid profiles in GH-deficient adult patients are not in complete agreement. Nonetheless, a significant number of authors have reported a modest increase in total plasma cholesterol and a rise in the ratio of low-density (LDL) to high-density lipoprotein (HDL). In contrast to the pediatric experience, adults with hypopituitarism show elevated fasting and postprandial plasma insulin levels in comparison with controls, and data from euglycemic-hyperinsulinemic clamp studies confirm that these patients are insulin-resistant.34 These adverse changes in the overall vascular risk profile underline the suggestion that GH deficiency is responsible for the increased cardiovascular mortality in hypopituitarism.

Gonadotropin Deficiency

Gonadotropin deficiency may result from deficient secretion of pituitary gonadotropins, faulty secretion of GnRH, and hyperprolactinemia, which impairs the pulsatile release of GnRH and thus causes secondary hypogonadism. Gonadotropin secretion can also be reduced in some functional disorders, most commonly in women, for example, with excessive weight loss or exercise. The clinical features of secondary or hypogonadotrophic hypogonadism are similar to those of primary gonadal failure.

In males the clinical features of gonadotropin deficiency differ according to whether the deficiency was acquired before or after pubertal age. If acquired before pubertal age, clinical examination reveals a small penis, small testes, and eunuchoid proportions (span exceeds height by greater than 5 cm) (Fig. 21-4). Hypogonadism acquired postpubertally is associated with a reduction in testicular size, loss of facial and body hair, and thinning of the skin, leading to the characteristic finely wrinkled facial skin of the "aging youth". Other effects include a decrease in skeletal muscle mass, BMD, sexual function, libido, and general well-being. Azospermia is an almost inevitable consequence of hypogonadotropic hypogonadism, but there are exceptions. In the "fertile eunuch" variant, partial LH deficiency may result in low circulating testosterone levels and gynecomastia but preserved testicular size and fertility; presumably, intratesticular testosterone levels remain high enough to maintain spermatogenesis.

In a teenage girl, hypogonadotropic hypogonadism is associated with primary amenorrhea and absent breast development. In the adult woman, amenorrhea or oligomenorrhea, infertility, breast atrophy, vaginal dryness, and dyspareunia occur; pubic and axillary hair remain unless ACTH deficiency is also present.

ACTH Deficiency

ACTH deficiency is the most life-threatening component of hypopituitarism. In addition to the other causes of pituitary failure discussed earlier, functional ACTH deficiency may occur following discontinuation of exogenous glucocorticoids or ACTH, even when these agents have only been administered for a few weeks. Isolated acquired ACTH deficiency has also been well documented, although its occurrence is rare.35 The features of glucocorticoid deficiency due to ACTH deficiency are similar to those of Addison's disease. Weakness, tiredness, nausea, vomiting, and orthostatic hypotension are common. Weight loss and anorexia may mimic anorexia nervosa or a malignancy. Examination may reveal pallor of the skin, in contrast to the hyperpigmentation of Addison's disease, and in females particularly, there is loss of secondary sexual hair. In severe ACTH deficiency, particularly in childhood, hypoglycemia can occur: cortisol deficiency results in increased insulin sensitivity and a decrease in hepatic glycogen reserves. Hyponatremia, although less commonly seen than in Addison's disease due to preservation of aldosterone secretion, may be the
presenting feature of ACTH deficiency, particularly in the elderly. Acute cortisol insufficiency should be considered in the differential diagnosis of a patient with a history of anorexia and weight loss, increasing fatigue and weakness, and nausea and vomiting. The clinical features may include hypovolemic shock, fever, and an acute abdomen. A history of an acute headache, pituitary surgery, or irradiation may provide important pointers to the diagnosis.

Thyroid-Stimulating Hormone Deficiency

TSH deficiency occurs late in most pituitary disorders. Symptoms include fatigue, weakness, inability to lose weight, constipation, and cold intolerance, in keeping with the symptoms of primary hypothyroidism. Symptoms are, however, generally milder than in primary hypothyroidism, because some residual TSH secretion is often preserved.

Antidiuretic Hormone Deficiency

Polydipsia and polyuria with nocturia are the classic features of diabetes insipidus resulting from ADH deficiency. If the patient is unable to keep up with the fluid loss, hyponatremia and hypovolemia ensue. The features of diabetes insipidus may be masked in the presence of ACTH deficiency, due to the consequent hydropenia and reduced glomerular filtration rate. Only when cortisol replacement therapy is commenced the polyuria and polydipsia of diabetes insipidus may be revealed.

Prolactin Deficiency

Whilst prolactin deficiency per se is not known to have distinct clinical features, it almost always signifies more severe degrees of hypopituitarism, and growth hormone deficiency is inevitable.35

DIAGNOSIS AND ENDOCRINE ASSESSMENT

Clinical examination can provide important clues to the cause and duration of hypopituitarism, and the physician must not neglect an assessment of height, weight, and pubertal status. Examination of the visual fields is essential, and should be supported by either Goldmann or computer-assisted perimetry. The latter is more sensitive in detecting visual field defects that other techniques are unable to demonstrate.

Imaging of the Pituitary Fossa

Imaging of the pituitary fossa is indicated when there is clinical evidence of a visual field defect or biochemical evidence of hypopituitarism. Computed tomography (CT) and magnetic resonance imaging (MRI) have superceded the plain radiograph. MRI is the scanning technique of choice, as it offers higher resolution than CT scanning, and is able to demonstrate microadenomas as small as 3 mm in diameter. If a pituitary adenoma is demonstrated, careful note should be taken of any extension of the tumor outside the pituitary fossa. In diabetes insipidus the normal high-intensity posterior pituitary signal may be absent and other causes of hypopituitarism may show classic CT or MRI findings, for example, craniopharyngioma.

An empty sella is not an uncommon finding. It refers to an enlarged or normal sized pituitary fossa filled with cerebrospinal fluid. An empty sella may be caused by a congenital sellar diaphragmatic defect (primary), or may develop after lymphocytic hypophysitis, infarction of a pituitary tumor, Sheehan's syndrome, pituitary surgery or radiation (secondary). The pituitary gland is usually flattened against the floor of the sella and the pituitary stalk may be laterally deviated. The majority of patients with primary empty sella have normal pituitary function, but 15% have mild hyperprolactinemia, and it has been described in association with headache, endocrine dysfunction (particularly GH deficiency in children), and visual disturbances. The majority of patients with secondary empty sella have endocrine disturbances37, the severity is related to the underlying pathogenesis of the condition.

Endocrine Testing

The endocrine assessment of a patient with suspected hypopituitarism usually involves measurement of both baseline and stimulated hormone levels. Basal hormone levels yield much useful information, and therefore serum concentrations of prolactin, TSH, T₄, cortisol, LH, FSH, testosterone in men, and estradiol in women, should be measured. As a general rule, suspected anterior pituitary hormone deficiency should be confirmed and corrected before possible ADH deficiency is investigated, as ACTH deficiency can mask the presence of ADH deficiency. Another important principle is that of retesting. This is important in two broad clinical contexts. The first is in young adults who received GH replacement in childhood. Over the last 10 years there have been a number of studies in which the status of children who received GH replacement during childhood was reassessed after completion of growth and puberty. At reassessment, GH status was considered normal in 20% to 87%35 of patients, most of whom had originally been classified as having isolated idiopathic GH deficiency. Those young adults with organic GH deficiency in childhood as a consequence of either a mass lesion, pituitary surgery, or irradiation to the hypothalamic-pituitary axis rarely reverted to normal GH secretory status. Hence the etiology of the childhood diagnosis of GH deficiency should affect the strategy of retesting. Patients with isolated GH deficiency should undergo two tests of GH secretory status, whereas those with additional anterior pituitary hormone deficits require only one test at reassessment. The second cohort in whom retesting is indicated are those patients in whom progression of the hypopituitarism may be expected. This includes patients who were subject to irradiation of the hypothalamic-pituitary axis, following surgery, and in
patients with an evolving pituitary or hypothalamic lesion. Following irradiation, endocrine testing should be performed on a yearly basis for at least 10 years, and again at 15 years. This is of particular importance because although the classic sequence of pituitary hormone deficits (GH, gonadotropins, ACTH, and TSH) occurs in the majority of patients, other patterns may occur, most notably ACTH deficiency before gonadotropin deficiency.40

Growth Hormone Deficiency

GH replacement therapy has been offered to GH-deficient children for more than 30 years, but it only became a licensed indication for GH-deficient adults in the United States, in a number of European countries, and in New Zealand in 1996. Thus, in contrast to the long-standing pediatric literature and interest in the biochemical diagnosis of GH deficiency, the concerns of the endocrinologist treating adults have been addressed only recently.

GH secretion is a spectrum between normality and abnormality and therefore with rare exceptions, the diagnosis of GH deficiency must be made on arbitrary grounds. The more severe the GH deficiency, the less arbitrary the diagnosis, whereas the "lesser degrees of GH deficiency" merge into normality. Today, in many countries, children with all forms of GH insufficiency from mild to severe are considered for GH replacement, whereas in other countries only those with severe GH deficiency receive GH replacement. In adulthood, however, it is only severe GH deficiency that has been proved to be associated with any benefit from GH replacement and thus in adulthood the purpose of investigation is to diagnose severe GH deficiency.

GH secretory status in elderly patients with two or three additional provocative tests should take into account the underlying pathology: e.g., radiation induced growth hormone deficiency might only be evident using an ITT, whilst arginine stimulated peak growth hormone levels appear to be a less sensitive indicator of growth hormone deficiency under those circumstances.41 The pathophysiologic state of obesity is difficult to distinguish from organic GH deficiency in an adult. There is substantial evidence that morbid obesity is accompanied by suppression of GH release and that substantial weight loss may restore spontaneous and stimulated GH secretion. Even in clinically nonobese healthy adults, relative adiposity, in the abdominal region in particular, is a major negative determinant of GH secretion.40 A study of age- and sex-matched subjects, however, suggested a much more profound reduction in total GH secretion in a group of individuals with organic GH deficiency compared with obese subjects.43 Nonetheless, in the obese individual with pituitary disease and no other pituitary deficit, a reduced GH response to any of the standard provocative tests may reflect organic GH deficiency or obesity itself and distinction between the two is not easy at the present time.

GH secretion in healthy elderly adults is reduced compared with that in young adults. GH secretion declines by approximately 14% per decade from young adult life. Normal aging is associated with changes in body composition similar to those seen in patients with GH deficiency. In the clinical setting this raises the question: can the GH status of elderly patients with organic pituitary disease be distinguished from that of the normal elderly? Toogood et al.44 have established that GH secretion is significantly reduced in the elderly with pituitary disease compared with normal controls of similar age. This work suggested that the arginine stimulation test is a reasonable choice to assess GH status in elderly patients with two or three additional pituitary hormone deficits, particularly in an age group in which an ITT carries an increased theoretical risk of morbidity or mortality.

Serum insulin-like growth factor-1 (IGF-1) levels are stable throughout the day, mainly due to complexing of IGF-1 with IGF-binding proteins. Thus assessing GH status with a single estimation of the circulating IGF-1 level, which is known to be GH-
dependent, was an attractive proposition and led to the hope that dynamic GH provocation tests would prove unnecessary. However, IGF-1 levels are affected by a number of other variables, including nutritional status, hepatic function, hypothyroidism, age, and pubertal status. Even in otherwise matched individuals, there is considerable overlap between values in GH-deficient and GH-sufficient individuals, particularly in those patients who developed GH deficiency in adulthood or who were rendered GH-deficient by irradiation. Thus, an IGF-1 estimation is extremely useful for retesting young adults with a diagnosis of childhood-onset GH deficiency, moderately helpful (positive predictive value ~30% to 50%) in middle-aged adults (25 to 55 years old), and rarely helpful in the elderly (>60 years).

Within the limitations of the tests we suggest that it is reasonable to perform only one provocative test of GH release in adult patients with two or three additional pituitary hormone deficiencies, as these patients are almost inevitably severely GH-deficient. In the patient with a possible diagnosis of adult-onset isolated GH deficiency or GH deficiency plus one additional pituitary hormone deficit, two provocative tests of GH release would be appropriate. The same strategy can be applied to reassessing the GH secretory status of young adults who received GH replacement for childhood GH deficiency. However, IGF-1 estimation itself should be considered adequate in those in whom multiple pituitary hormone deficits exist, and could serve as one of the two tests of GH status in the much larger cohort of patients with a putative diagnosis of isolated GH deficiency in whom retesting is required.

**Gonadotropin Deficiency**

Adult gonadotropin deficiency is relatively easy to diagnose: in women of postmenopausal age gonadotropin levels are clearly low or undetectable, while in premenopausal women amenorrhea (or less commonly oligomenorrhea), in addition to low estradiol levels and low or normal gonadotropin levels, provides sufficient evidence of the diagnosis. In adult men a similar picture of low testosterone levels and low or inappropriately normal gonadotropin levels is seen.

A more difficult diagnostic situation lies in the distinction between isolated gonadotropin deficiency and constitutional delay of puberty in males. Clinically, delayed puberty is defined by failure to develop signs of puberty by the age of 14 years (2 standard deviations above the mean of chronological age for the onset of puberty). Over 90% of boys 14 years old or older with delayed puberty have no endocrine abnormality, and will go through puberty spontaneously at a later date. No biochemical tests reliably improve this epidemiologic prediction. The key clinical response is to deal with the pubertal needs of the child and return to the diagnosis later. If during androgen therapy testicular volumes increase, the diagnosis of constitutional delay in growth and puberty rather than gonadotropin deficiency is supported further.

**ACTH Deficiency**

In normal people, the highest plasma cortisol levels are found between 6 AM and 8 AM, and the lowest before midnight. Plasma cortisol and ACTH concentrations are elevated during physical and emotional stress, including acute illness, trauma, surgery, infection, and starvation.

If a 9 AM cortisol level is below 100 nmol/L, particularly in an unwell patient, cortisol deficiency is highly likely whereas a baseline level above 500 nmol/L indicates normality; many authors suggest that dynamic assessment of the hypothalamic-pituitary-adrenal (HPA) axis is not necessary under these circumstances. Unless the patient is known to have pituitary disease, a paired plasma ACTH level will help distinguish between primary and secondary glucocorticoid deficiency: in primary cortisol deficiency (Addison’s disease), the ACTH level will be high; whereas, in secondary glucocorticoid deficiency, the ACTH level will be low or inappropriately normal.

If cortisol deficiency is suspected in an unwell patient, baseline cortisol and ACTH samples should be taken, and replacement therapy should be commenced immediately. Provocative testing can be performed at a later date. The ITT is the gold standard for the assessment of the HPA axis and pituitary GH reserve. Neuroglycopenia occurs when the blood glucose is less than 2.2 mmol/L resulting in the release of ACTH, cortisol, and GH. A serum cortisol response of greater than 500-550 nmol/L is considered to indicate normality. The ITT is not without risk however, and loss of consciousness and seizures are recognized, albeit rare, complications. Thus it is contraindicated in those with known ischemic heart disease or a history of seizures; extreme age is a relative contraindication. When performed in an experienced endocrine unit the ITT is associated with a low risk of complications.

Other provocative tests useful for assessment of the HPA axis include the short Synacthen test and the intramuscular glucagon stimulation test. Each test has advantages and disadvantages, with some groups favoring the ITT and others the short Synacthen test. Of principle importance, however, is that the peak cortisol level achieved must be interpreted in light of the provocative test used. A typical cortisol cutoff level for the standard short Synacthen test is 550 nmol/L at 30 minutes. However, different cutoffs have been applied by various authors (460-600 nmol/L), depending on whether greater emphasis is placed on achieving a higher sensitivity or specificity, and the type of cortisol assay. When glucagon is used as the provocative agent, the peak cortisol response occurs later (the test should be continued for 180 minutes) and it is smaller in magnitude than that seen in response to an ITT, and in a number (up to 20%) of normal persons a response is not seen.

As a consequence, while some patients can be classified as having “barn door” ACTH deficiency requiring glucocorticoid replacement therapy (i.e., cortisol response of <450 nmol/L to an ITT), a proportion fall into a gray zone where the results of
Thyroid-Stimulating Hormone Deficiency

In secondary hypothyroidism one might expect to find reduced concentrations of free or total T₄ in association with a serum TSH concentration below the normal range, analogous to the biochemical findings in secondary hypogonadism. This picture is, however, only found in the minority of patients, the majority having normal or occasionally elevated TSH levels. The mechanism behind this apparent contradiction is poorly understood, and a number of different explanations have been explored. One such is that in some cases of hypothalamic hypothyroidism TSH may have reduced bioactivity, suggesting that TRH regulates not only the secretion of TSH but also its specific molecular and conformational features.

The TSH response to TRH (TRH test) has been proposed as a tool to help differentiate between hypothalamic and pituitary hypothyroidism. Classically, in hypothyroidism secondary to a hypothalamic lesion and hence TRH deficiency, the TSH response is delayed (the 60-minute response is greater than the 20-minute response), while in hypothryoidism of pituitary origin, damage to the thyrotrophs results in an absent or impaired TSH response. Studies have revealed no clear-cut differences in biologic endpoints however between patients with hypothryoidism of pituitary and hypothalamic origin. Furthermore, the information gained has no therapeutic implications.

Antidiuretic Hormone Deficiency

The diagnosis of ADH deficiency first requires confirmation of excess urine output. Polyuria is defined as the excretion of greater than 3 L of urine per 24 hours (40 mL/kg/24 hours). Any patient with normal serum sodium and plasma osmolality who has a fluid output of less than 2 L/24 hours is likely to be normal and does not warrant further investigation.

Once excess urine output is confirmed, the usual first-line investigation is an 8-hour fluid deprivation test. For this basis the test is the rise in plasma osmolality resulting from a lack of fluid intake for several hours, stimulating ADH secretion. The test should be performed under strict observation because severe fluid and electrolyte depletion can occur. Plasma osmolality, urine volume, and osmolality are measured hourly for 8 hours following which a synthetic analog of ADH (desmopressin) is given IM. The urine osmolality is then remeasured. In a normal subject, ADH is secreted throughout the test, water is normally absorbed, and there is a subsequent elevation of urine osmolality. In diabetes insipidus the urine fails to concentrate (normals achieve a urine osmolality at least twice the plasma osmolality) due to a lack of ADH, hence plasma osmolality rises. Urine concentrates adequately only after administration of desmopressin. Sometimes in cases where there has been long-standing polyuria, failure of urine concentration in response to desmopressin occurs not because of nephrogenic diabetes insipidus but because of a wash-out of interstitial solutes, including urea. This may lead to diagnostic difficulties. In cases where the results of a water deprivation test are inconclusive, the introduction of specific and sensitive radioimmunoassays for ADH has provided a further diagnostic avenue. A definitive diagnosis of ADH deficiency can be established by infusing hypertonic saline for 2 hours to increase plasma osmolality above 300 mosmol/kg, with regular 20- to 30-minute blood sampling to estimate plasma osmolality and ADH.

The ADH level following a period of fluid restriction reflects the 2 types of diabetes insipidus: in nephrogenic diabetes insipidus ADH values are above the normal reference range while in cranial diabetes insipidus values are at the lower end or below the normal reference range.

TREATMENT OF HYPOPITUITARISM

The treatment of hypopituitarism can be separated into those therapies directed at the underlying disease process and endocrine replacement therapy (Table 21-3). Endocrine replacement therapy should aim to mimic the normal hormonal milieu as far as possible, thus improving symptoms while avoiding overtreatment. It remains to be seen whether present regimens normalize the excess mortality in hypopituitary patients.

Growth Hormone Deficiency

Until 1989, the sole indication for GH therapy was in children with GH deficiency. With the availability of recombinant DNA-derived GH, the situation has gradually changed as the biologic consequences of GH deficiency in adult life have been appreciated.

GH replacement therapy in adulthood induces favorable changes in body composition, with studies demonstrating a 15.5% reduction in fat mass and a 6% increase in lean body mass following 12 months of therapy. Correspondingly, there is an improvement in indices of physical performance and maximal oxygen uptake. In response to GH therapy the initial change in BMD over the first 3 to 6 months is a decrease, believed to be due to increased bone remodeling activity. Markers of bone formation and resorption are increased early and remain elevated for at least 1 year. The subsequent response of bone differs between childhood-onset and adult-onset GH deficiency. By 6 months of treatment the BMD is significantly increased in childhood-onset GH deficiency and continues to rise over 18 months of GH replacement. In adult-onset GH deficiency BMD is not increased at 12 months, although there is a significant increase at
24 months in those with lower baseline BMD scores. There is evidence from placebo-controlled randomized studies that significant improvement occurs in vitality, well-being, and overall quality of life in GH-deficient adults in response to GH replacement. The exact mechanism for the improved sense of well-being remains controversial: possible explanations include increased exercise capacity, improved hydration status with normalization of extracellular volume, and a direct CNS effect.

The majority of GH replacement studies show favorable changes in the lipid profile. The most frequent finding has been a reduction in total cholesterol, LDL cholesterol, LDL:HDL cholesterol ratio and apolipoprotein-B concentrations, with no significant change in either HDL cholesterol or triglyceride concentrations. Some studies suggested that GH replacement therapy increases lipoprotein(a) levels, although poor assay standardization to date limit its use as a reliable predictor of cardiovascular risk.

GH replacement at higher doses can cause an increase in insulin resistance with higher fasting glucose, fasting insulin and glycated hemoglobin levels within 6 months after treatment. Most of those abnormalities improve over subsequent years, probably reflecting changes in body composition. However, patients receiving growth hormone treatment will have to be monitored for alterations in glucose homeostasis; insulin resistance does not appear to be normalized on longterm GH therapy.

Several studies to date have also documented favorable effects of growth hormone treatment on impaired endothelial function, cardiac structure, and systemic vascular resistance but no change in fibrinogen levels.

Growth hormone replacement therapy in the transition period from teenage years to adulthood deserves special consideration. Bone mass accrual continues for a number of years beyond achievement of final height, and is greatly influenced by growth hormone status. Therefore continuation of growth hormone replacement therapy in severely growth hormone deficient young adults should be strongly recommended as an important preventative measure to avoid the complications of osteoporosis in later life.

The majority of modern regimens use a low starting dose, that is, 0.3mg/day as a single subcutaneous injection. This should then be increased every 4 to 6 weeks, based on clinical response and IGF-1 levels, until a steady replacement dose is reached. Since improvements in physiologic well-being and quality of life do not occur in all GH-deficient patients on replacement therapy, it is suggested that patients started on GH primarily for a quality-of-life indication should have an initial trial period of therapy; only those with definite improvement should continue treatment thereafter. Improvements in quality of life and body composition often only occur after several months of maintenance therapy and therefore a trial of 6 months of GH at the correct maintenance dose is necessary to determine if treatment is beneficial. At the end of this trial, patients should be reassessed using a disease-specific questionnaire and with measurements of body composition and lipids. In patients started on GH for osteoporosis or osteopenia, therapy is reassessed following BMD estimation at 2 years. Such selection criteria are not being applied universally. In some countries GH replacement is regarded simply as hormone substitution, for an established deficiency and therefore treatment is lifelong without the need for any qualifying criteria. The low-dose regimen is rarely associated with the side effects such as peripheral edema, arthralgia, and myalgia described when higher doses of GH replacement, particularly weight-based dosing regimens, were used. Monitoring of GH replacement should include regular measurement of weight, blood pressure, hemoglobin A1c, lipid profile, IGF-1, fat distribution (waist-hip ratio), and assessment of quality of life by disease-specific questionnaire and patient interview.

Gonadotropin Deficiency

In both sexes, sex steroid replacement therapy is important for the maintenance of normal body composition, skeletal health, and sexual function, and it is the most appropriate form of replacement therapy in patients not desirous of fertility.

Estrogen replacement. In women this can be provided by many standard hormone replacement therapy preparations. Progesterone must be given (cyclically or continuously) in all women with an intact uterus to prevent the possible effect of unopposed estrogen on the endometrium, that is, dysfunctional bleeding or endometrial cancer. The dose of estrogen should not be supraphysiological (as in the oral contraceptive pill) unless there is a clear indication, such as strong patient preference, or in a patient with partial gonadotropin deficiency still having occasional menstrual cycles, with a desire for contraception. Estrogen can be delivered as a tablet, patch, gel, or implant. While estrogen replacement therapy can minimize the risk of osteoporosis, its long-term effects on the cardiovascular system in young hypopituitary women remain unknown. Estrogen replacement therapy would typically be continued until the age of 50. Continuation after this time should be based on a discussion of the risks and benefits between the patient and physician, supported by BMD measurement.

Androgen replacement. Androgen replacement therapy for men is available in many modalities. The choice of preparation depends on local availability and the wishes of the patient. IM injection of testosterone 17 alpha-hydroxy esters every 2 to 3 weeks is a commonly used regime of testosterone replacement. In some men, however, this mode of administration is associated with disturbing fluctuations in sexual function, energy level, and mood, mirroring the changes in testosterone concentrations. Changing to smaller doses on a more frequent basis or another preparation can be helpful. Transdermal testosterone systems are an alternative, and are available as either patch systems (nonscrotal or scrotal), or the recently introduced testosterone gel.
Both are able to maintain physiologic testosterone profiles in the majority of patients, but skin irritation, the need for scrotal shaving or a drying time after gel application, are some of the potential drawbacks of either transdermal system.

Less commonly used ways of administering testosterone are testosterone implants and oral androgen replacement therapy. Subcutaneous implants consist of three to six 200-mg pellets, which can maintain normal testosterone levels for up to 6 months. The implantation of the pellets requires minor surgery and may be complicated in a minority of patients by local infection, extrusion, and scarring. Oral androgen replacement therapy is available using testosterone undecanoate, a 17alpha-hydroxyl ester of testosterone. However, this requires frequent dosing (two to four times daily) and often subnormal testosterone levels are achieved due to variable absorption.

Androgen replacement therapy should always be monitored to ensure physiologic mean testosterone levels. Suboptimal replacement doses result in low trough levels, whereas supraphysiologic doses can promote secondary polycythemia and progression of prostate cancer, therefore regular monitoring of hemoglobin and prostate specific antigen is recommended.

An area of debate at present is the therapeutic use of testosterone in women. In postmenopausal women, particularly those who have undergone bilateral oophorectomy, there is evidence that combined estrogen and testosterone replacement results in substantial benefits in those who complain of loss of libido and impaired sexual function despite adequate estrogen replacement. The rationale behind such therapy is, that following bilateral oophorectomy circulating testosterone levels fall by 50%. This reduction tends to be even greater in women with hypogonadotropic hypogonadism, who are likely to be ACTH as well as gonadotropin deficient; thus symptomatic patients may benefit from low-dose testosterone replacement therapy. Regimens using a 50-mg testosterone implant every 6 months have been employed. This practice is, however, not universal, and insufficient research has been performed in the hypogonadotropic hypogonadal woman. Testosterone replacement regimens are not approved for the latter indication by most regulatory authorities.

**Gonadotropin and GnRH therapy.** In the hypogonadotropic hypogonadal patient fertility can be achieved with gonadotropin therapy. In males excellent success rates can be achieved, provided primary testicular dysfunction does not coexist. Testosterone replacement should be discontinued before initiating therapy. The choice of therapy lies between gonadotropin replacement or GnRH. The former is the traditional therapeutic approach; initially LH "activity" is provided by human chorionic gonadotropin (hCG) administered SC or IM at a dose of between 1000 and 2000 IU two to three times weekly. Spermatogenesis is unlikely within the first 3 months of therapy. Treatment with hCG alone is continued for 6 months with regular sperm counts to monitor progress. If adequate spermatogenesis is not achieved, then FSH in the form of human menopausal gonadotropin (hMG), or a more purified preparation of FSH, is added. The dose of FSH is increased if adequate spermatogenesis is not achieved following 6 months of combination therapy. The alternative regimen in patients with idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome is pulsatile GnRH therapy. GnRH is administered SC via a catheter attached to a minipump. Its use implies a hypothalamic defect with essentially normal pituitary gonadotrophs. This regimen appears to have few advantages over gonadotropin therapy in males, but may cause less gynecomastia. Both regimens may take up to 2 years to achieve adequate spermatogenesis, and thus once effective, consideration should be given to storing several samples of frozen sperm for any future attempts at pregnancy.

In women with hypogonadotropic hypogonadism, pregnancy rates of 83% following therapy with either pulsatile GnRH or gonadotropins are reported. These are better than rates achieved in women undergoing ovulation induction for other pathologic conditions. Again, the choice of therapy lies between gonadotropin therapy or pulsatile GnRH, but in women there are obvious advantages to GnRH therapy if the patient has enough residual gonadotroph function.

Pulsatile GnRH therapy is more likely than hMG to result in development and ovulation of a single follicle, thereby reducing the risks of ovarian hyperstimulation and multiple gestation. However, in practice, GnRH therapy may not be practicable, and in more than 50% of women with organic pituitary disease, residual gonadotroph function is not sufficient to support this method.

**ACTH Deficiency**

Any patient identified as having ACTH deficiency should be repeatedly educated about its clinical implications. It is crucial for the patient to understand the need to increase the replacement dose two- to three-fold in case of an intercurrent illness or when undergoing surgery. Every patient with ACTH deficiency should wear an appropriate medic-alert bracelet or necklace. Many patients also benefit from being issued with an i.m. hydrocortisone pack and taught how to self-administer intramuscular hydrocortisone in the event of protracted vomiting.

As mentioned earlier, the decision to begin cortisol replacement therapy should be based not only on the results of dynamic testing but also on clinical assessment. The next decision is the choice of glucocorticoid. Hydrocortisone is the logical choice, as it directly replaces the missing hormone. Alternatives include cortisol acetate, which is metabolized to cortisol, and therefore can be monitored in the same way as hydrocortisone. Its onset of action is slower and its biologic activity is slightly longer, providing relative disadvantages and advantages over hydrocortisone, respectively. Other synthetic glucocorticoids, that is, prednisolone and dexamethasone, have significant
disadvantages; monitoring is difficult and in the case of dexamethasone the limited number of pharmaceutical preparations available make small dose adjustments impossible.

There is now growing evidence that the traditional hydrocortisone regimen of 20 mg in the morning and 10 mg in the evening is far from ideal. First, this regimen is not physiologic, as the plasma half-life of cortisol is less than 2 hours. Thus twice-daily dosing regimens are associated with very low cortisol levels in the late afternoon, and studies of a twice-daily regimen have demonstrated that quality-of-life scores are lower at this time. Thus dosing three times daily is recommended. Second, the total daily dose of 30 mg hydrocortisone is also supraphysiologic as production rates in the normal individual are significantly lower than previously believed. Thus a hydrocortisone regimen of 10 mg in the morning, 5 mg at noon, and 5 mg in the evening, is likely to be a better starting schedule. Monitoring of therapy usually involves the use of an 8-hour hydrocortisone day curve, aiming to achieve normal cortisol levels. Such monitoring allows the detection of minor degrees of over- or under-replacement which are unlikely to be clinically obvious. Minor over-replacement is associated with reduced BMD and it is likely that other factors, including blood pressure, insulin sensitivity, and body composition, may also be adversely affected.

Thyroid-Stimulating Hormone Deficiency

Secondary hypothyroidism is treated with thyroxine (T4) replacement therapy in the same way as primary hypothyroidism. The normal starting dose in a young patient without evidence of cardiac disease is 100 μg/day. In the elderly or in a patient with evidence of ischemic heart disease, therapy should be started at lower doses, that is, 25 to 50 μg/day.

A complicating factor in secondary hypothyroidism, however, is that measurement of serum TSH is obviously unhelpful in the monitoring of T4 replacement therapy. Thus the biochemical objective should be to restore the serum free T4 concentration to the normal range.

Treatment of TSH deficiency always needs to be considered in the context of other pituitary hormone deficiencies. In a patient with suspected hypopituitarism, thyroxine therapy should be delayed until ACTH deficiency has been excluded or treated, as there is a risk of worsening the features of cortisol deficiency. Over-replacement with T4 over long periods may be associated with reduced BMD, an increased risk of osteoporotic fracture, and an increase in the rate of development of atrial fibrillation; thus excessive doses of T4 should be avoided.

Antidiuretic Hormone Deficiency

Desmopressin is the drug of choice for the treatment of ADH deficiency. It is a synthetic analog of arginine vasopressin with two minor alterations in its molecular structure: a switch of arginine from the L- to the D- form in position 8, and deamination of cysteine in position 1. This results in a two- to fourfold increase in antidiuretic activity, prolongation of the biologic half-life to 6 to 8 hours, and absence of pressor activity, the latter eliminating side effects noted with arginine vasopressin, including hypertension, renal colic, coronary artery spasm, and abdominal colic. Desmopressin is available in a number of preparations, including oral, intranasal, and parenteral. Dosages vary as much as 10-fold between individuals, with no apparent relationship to age, sex, weight, or degree of polyuria. The drug should be started at low dose and increased gradually until urine output is controlled. Overdosage carries a risk of hyponatremia, and sodium levels should be checked after commencing or changing therapy.

STRATEGIES TO PREVENT HYPOPITUITARISM

Hypopituitarism increases morbidity and mortality in affected patients, requires therapy with complex drug regimens, and incurs significant cost to the healthcare provider. The introduction of GH replacement therapy has exacerbated the problem, with a yearly cost in U.S. dollars of $4500 to $6000 per patient. Thus attention has turned to strategies that might reduce the incidence of hypopituitarism.

One area worthy of consideration is the routine use of radiotherapy following surgery for nonsecreting pituitary adenomas. Data suggest that recurrence rates following transcranial pituitary surgery are as high as 25% to 75%, whereas recurrence after transsphenoidal surgery are reported to be between 12% and 22%. Data from Bradley et al. indicate that in the subgroup of patients with complete tumor removal as judged by the surgeon, without radiologic and surgical evidence of spread into the parapituitary structures or evidence of rapid tumor growth, there is a 90% recurrence-free survival at 5 years. It should be pointed out, however, that surgical results are highly operator-dependent in terms of tumor recurrence and that regular clinical and radiologic surveillance is mandatory. Nonetheless, by avoiding radiotherapy as a routine procedure, the incidence of long-term hypopituitarism will be significantly reduced.

Medical therapy offers an alternative to radiotherapy or surgery in patients with prolactinomas and now in patients with acromegaly. Dopamine agonist drug therapy can shrink prolactinomas in size and restore normoprolactinemia in many patients, 70% of macroadenomas shrinking by 25% or more, and restoration of normoprolactinemia and normal gonadal function occurs in at least 75% of patients. Whether these agents are also associated with a restoration of other aspects of pituitary function is less clear. Variable recovery from both ACTH and TSH deficiency has been described, but the data regarding GH status, particularly in adults, are scanty. Furthermore the advent of greater use of medical therapy for acromegaly with somatostatin analogs and a GH receptor antagonist, and the less frequent use of conventional radiotherapy should mean fewer
hypopituitary patients in the future; the same advantage may also hold up for stereotactic surgery versus conventional radiotherapy.

REFERENCES


