13.2.1 Disorders of the anterior pituitary gland 2

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Management—the availability of sensitive hormonal assays, re- placement hormones, and hypothalamic peptides, together with refined neuroimaging methods and neurosurgical techniques, has increased our ability to identify precisely and successfully treat most patients with diseases of the anterior pituitary gland. Growth hormone GH deficiency—in children this causes growth failure, and in adults features including decreased energy and quality of life, and increase in fat mass/decrease in muscle mass. The insulin tolerance test is con- sidered the ‘gold standard’ for diagnosis. Goals of GH treatment in adults are to achieve an appropriate clinical response while avoiding side effects, and an IGF-1 level in the middle of the reference range. GH excess—this causes acromegaly, which develops insidiously with multiple clinical features, most notably including local tumour effects, and increase in size of hands, feet, jaw, and skull. Biochemical diagnosis is made by confirming absence of suppression of GH in the oral glucose tolerance test, and by increased serum IGF-1 levels. Management options include: (1) surgery—with trans- sphenoidal surgery the treatment of choice for most patients; (2) drugs— including dopamine receptor agonists, somatostatin receptor lig- ands (e.g. octreotide, lanreotide) and GH receptor antagonists (e.g. pegvisomant); and (3) radiotherapy—generally offered for tumours that have recurred or persisted after surgery in patients with resist- ance to or intolerance of medical treatment. FSH and LH Gonadotropin deficiency—this presents in women with oligo/amenor- rhoea, loss of libido, dyspareunia, hot flushes, and infertility; and in men with loss of libido; impaired sexual function; mood impairment; loss of facial, scrotal, and trunk hair; decreased muscle bulk and en- ergy. Diagnosis in women is based on clinical features in association with FSH and LH levels that are ‘inappropriately normal’ or low in 13.2 Pituitary disorders

13.2.1 Disorders of the anterior pituitary gland 2259 premenopausal women and low in postmenopausal women; in men there is low morning serum testosterone with low or ‘inappropriately normal’ gonadotropins. Treatment comprises appropriate replace- ment therapy. Prolactin Prolactinomas are the most common pituitary adenomas and typ- ically present with galactorrhoea and hypogonadism, manifesting in men as impotence, infertility, and decreased libido, and in women as oligo/amenorrhoea and infertility. Secondary causes of hyperprolactinaemia must be excluded in any patient with an ele- vated serum prolactin and serum prolactin levels usually parallel tu- mour size in those with prolactinomas. Dopaminergic agonists (e.g. cabergoline, bromocriptine, pergolide, quinagolide) are the primary therapy. ACTH Chronic ACTH deficiency is associated with fatigue, pallor, anorexia, weight loss, hypotension, hyponatraemia, hypoglycaemia, and eo- sinophilia. The insulin tolerance test is considered the ‘gold standard’ for diagnosis. Glucocorticoid deficiency can be life-threatening and hence replacement with hydrocortisone (or other steroid) in a dose and timing to mimic the normal pattern of cortisol secretion should begin as soon as the diagnosis is confirmed. Cushing’s disease is caused by chronic exposure to endogenous glucocorticoids (Cushing’s syndrome) produced by the adrenal cortex in response to excess ACTH production by a pituitary corticotroph adenoma. TSH Central hypothyroidism is diagnosed when the concentration of thy- roxine is decreased and the level of TSH levels is usually normal or low. Clinical presentation is as for primary hypothyroidism. Treatment is with thyroxine. Other conditions Hypopituitarism—can be caused by a range of conditions including pituitary and nonpituitary tumours, hypophysitis, pituitary apoplexy, Sheehan’s syndrome (postpartum), brain injury (traumatic, surgical, irradiation, postinfective), and granulomatous diseases. Clinical manifestations depend mainly on the underlying disease, as well as the type and the degree of the hormonal deficits. Diagnosis and treatment of each pituitary hormone deficit is as just described. Pituitary adenomas—the most common cause of pituitary

disease; may be functioning (resulting in syndromes of hormonal excess) or nonfunctioning (presenting with mass effects). Treatment in- volves surgery, radiotherapy, or medical therapy as described earlier. Pituitary carcinomas are very rare. Pituitary apoplexy—occurs primarily in patients with pre-existing pituitary adenomas; results from acute haemorrhage or infarction of the pituitary gland and is characterized by sudden onset of head- ache, vomiting, visual disturbance, ophthalmoplegia, and altered consciousness. Initial management requires close monitoring of fluid and electrolyte balance and immediate replacement of deficient hormones, especially corticosteroids. Some authorities recommend urgent surgical decompression in some cases. Craniopharyngiomas—these epithelial tumours can present with pressure effects and/or compromised hypothalamo-pituitary function. First-line treatment usually comprises surgery with or without adjuvant external beam irradiation. Hypophysitis—may be primary (granulomatous, xanthomatous or lymphocytic) or caused by a known agent or systemic disease. Differential diagnosis is from pituitary adenoma. Optimal treatment for the inflammatory process has not been established and replace- ment of defective endocrine function is required. Introduction The pituitary gland or hypophysis cerebri was first described by Galen of Pergamon in the 2nd century ad, and is considered to be the ‘master gland’ integrating hormonal signals that control nu- merous endocrine and metabolic functions. Since the demonstra- tion of the hypothalamic control of pituitary function by Harris in Oxford in the 1950s, our understanding of the physiology and pathophysiology of the pituitary gland has broadened. The devel- opment of radioimmunoassays in the 1960s, the extraction of hypo- thalamic factors principally by Schally and Guillemin in the 1970s, the advances in immunocytochemistry, electron microscopy, and in situ hybridization methods, as well as the expansion of molecular biology have increased this understanding. Finally, the advances in modern imaging techniques and in pituitary surgery combined with the development of medical treatments for pituitary tumours have greatly expanded the therapeutic possibilities, providing successful and safe outcomes in most patients. Anatomy and embryology The pituitary gland consists of the anterior lobe (adenohypophysis), the posterior lobe (neurohypophysis), and an intermediate zone. The adenohypophysis derives from the stomodeal ectoderm which in- vaginates by the third week of gestation forming Rathke’s pouch. In the sixth week of gestation it comes in contact with the infun- dibulum. A remnant of the pharyngeal hypophysis may be found in adults, forming the pharyngeal pituitary located in the midline of the nasopharynx. The posterior lobe originates from the neural primordium as an outpouching from the floor of the third ventricle at the fourth week of gestation. The intermediate lobe arises from the posterior portion of Rathke’s pouch. This area normally contains microcytic remnants of Rathke’s pouch, which rarely become clin- ically significant. The portal system starts developing at the seventh week and is completed at around the 20th week of gestation. The body of the sphenoid bone and the sella turcica arise from the fusion of hypophyseal cartilage plates on either side of the developing pi- tuitary. The sella is well formed by the seventh week and matures by endochondral ossification. The pituitary measures around 13 mm transversely, 9 mm anteroposteriorly, and 6 mm vertically. It weighs approximately 100 mg. It increases during pregnancy to almost twice its normal size, and decreases in older people. The gland is centrally located at the base of the brain in the sella turcica within the sphenoid bone. It is attached to the hypothalamus by the pituitary stalk and a fine vascular network. The gland lacks leptomeninges. The sella turcica is lined by periosteal dura mater; the dura properly covers

 the lateral aspects of the cavernous sinuses and constitutes the sellar diaphragm. The cavernous sinuses are on either side of the sella, lat- eral and superior to

the sphenoid sinuses, and contain important neurovascular structures including the cavernous segments of the internal carotid arteries and the cranial nerves III, IV, V, and VI. The optic chiasm is located superiorly and is separated from the pituitary by the suprasellar cistern and the sellar diaphragm (Figs. 13.2.1.1 and 13.2.1.2). The anterior lobe comprises nearly 80% of the gland and includes the pars distalis, pars intermedia, and pars tuberalis. Staining char- acteristics divide the pars distalis into a central ‘mucoid wedge’ and two ‘lateral wings’. On light microscopy the cells of the anterior lobe show variation in size, shape, and histochemical staining features. They are organized in nests and cords, and are separated by a com- plex capillary network. The pars intermedia is poorly developed in humans and lies between the pars distalis and the posterior pituitary. Large numbers of cells in the central zone are basophilic and pro- duce adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyrotropic hor- mone (TSH). Most of the cells in the lateral wings are acidophilic and produce growth hormone (GH) and, less frequently, prolactin (PRL) (Table 13.2.1.1). The pars tuberalis is an extension of the anterior lobe along the pituitary stalk. It is formed by normal acini of pituitary cells dis- tributed around surface portal vessels. The anterior lobe also in- cludes follicular cells, derived from secretory cells and constituting follicles within the gland, and folliculostellate cells (less than 5% of the adenohypophyseal cells), which have a physiological role that is not clear. The anterior pituitary receives most of its blood supply from the hypothalamo-hypophyseal portal system (primary plexus, long portal venous system, and secondary plexus), which origin- ates from the capillary plexus of the median eminence and su- perior stalk derived from the terminal ramifications of the superior and inferior hypophyseal arteries. This system carries blood and hypophysiotropic hormones down to the stalk. The remainder of (a) Lamina terminalis Optic chiasm Sphenoid sinus Pituitary stalk with upper capillary loop of portal vessels Anterior pituitary Posterior pituitary Marrow in sphenoid bone Third ventricle Pineal gland Mamillary body Median eminence of hypothalamus Fourth ventricle Pons Medulla (b) Fig. 13.2.1.1 Sagittal MRI scan of normal pituitary gland and an anatomical line drawing. TRH Hypothalamus Somatostatin Pituitary − + T4 T3 TSH T3T4 Thyroid − − + Fig. 13.2.1.2 Diagram of the hypothalamo-pituitary–thyroid axis showing negative feedback loops. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

Table 13.2.1.1 Hormone-producing cells in anterior pituitary gland

Type of cell	Approximate percentage of adenohypophyseal cells	Distribution
Somatotrophs or GH cells	50%	Greatest density in lateral wings
Lactotrophs or PRL cells	20%	Mainly in posterior portions of lateral wings
Corticotrophs or ACTH cells	15–20%	Mainly middle and posterior portions of mucoid edge
Gonadotrophs or FSH and LH cells (produce FSH and LH in isolation or by the same cell)	10%	Evenly distributed throughout anterior lobe
Thyrotropes or TSH cells	5%	Mainly in anterior part of mucoid edge

ACTH, adrenocorticotropic hormone; GH, growth hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyrotropic hormone.

 the blood supply is through the pituitary capsular vessels originating from the superior hypophyseal arteries. The venous drainage from the anterior pituitary is through the cavernous sinuses into the pe- trosal sinuses and the internal jugular veins. The anterior lobe has no direct innervation, apart from a few sym- pathetic nerve fibres spreading to the anterior lobe along blood ves- sels. The hypothalamic regulation is exerted via the neurohormonal link with the hypothalamic regulatory peptides reaching the pitu- itary via the portal vessels. General physiology The secretion of the anterior pituitary hormones is under elegant regulation exerted by hypothalamic peptides and, with the exception of prolactin, by the

negative feedback (at both the hypothalamic and pituitary level) of hormones from the target glands (Fig. 13.2.1.3). The hypothalamic peptides are secreted in the median eminence and are transferred to the anterior pituitary gland via the hypothalamic– pituitary portal system. They integrate environmental and neural in- formation and bind to specific high affinity cell membrane receptors of the particular pituitary cell type. Failure of the target gland results in decreased negative feedback and increased hypothalamic and pi- tuitary secretion. Primary overactivity of the target gland results in increased negative feedback and decreased hypothalamic and pitu- itary secretion. Additional 'short-loop' feedback, in which pituitary hormones affect the secretory activity of the hypothalamus, is also implicated in the network contributing to the meaningful function of the pituitary gland. Finally, the anterior pituitary synthesizes sev- eral peptides, growth factors, and cytokines that play an important part in autocrine and/or paracrine control of pituitary secretion and/or cell proliferation. Clinical features of pituitary disease The clinical features of pituitary disease, mostly associated with a space-occupying lesion, may result from local mass effects and/or pituitary hormone deficits or hypersecretion. The local mass effects depend on the size of the tumour and its anatomical position. Headache is usually the consequence of dural stretching. It can be variable (occipital, retro-orbital, bitemporal) and is often nonspecific. The neuro-ophthalmological effects in- clude visual field defects (usually bitemporal hemianopia or upper temporal quadrantanopia or any unilateral or bilateral visual field defect) from compression of the optic chiasm (Fig. 13.2.1.4) and squint, ptosis, or papillary dilatation from ocular nerve palsies caused by lateral tumour extension. Compression of the first or second branch of the trigeminal nerve may rarely result in facial pain. Very large pituitary tumours obstructing the fourth ventricle or the foramen of Monro cause hydrocephalus and expansion of the lateral ventricles. Inferior invasion and erosion of the sellar floor may result in recurrent sinusitis, cerebrovascular fluid rhinorrhoea, and recur- rent meningitis. Extension into the temporal lobe may rarely be as-sociated with temporal lobe epilepsy and to the cerebral peduncles with motor and/or sensory disturbances. Superior expansion to the hypothalamus may be associated with hypothalamic dysfunction Central input Posterior pituitary Target glands Peripheral hormones ADH Oxytocin LH/FSH Anterior pituitary Hypothalamus Negative feedback PRL TSH ACTH GH Releasing hormones and inhibiting factors Fig. 13.2.1.3 Regulation of the hypothalamic–pituitary–peripheral function. The anterior pituitary produces GH, LH/FSH, ACTH, TSH, and PRL. The secretion of these hormones is regulated by hypothalamic- releasing and hypothalamic-inhibiting factors and by negative feedback inhibition of their peripheral hormones. Reprinted from Schneider HJ, et al. (2007). Hypopituitarism. Lancet, 369, 1461–70, © (2007), with permission from Elsevier. Temporal visual field Nasal visual field Temporal retinal fibres Nasal retinal fibres compressed by tumour Optic nerve Optic chiasm X X Fig. 13.2.1.4 Neuro-ophthalmological pathways and the classical bitemporal hemianopia that results from compression of the central optic chiasm by a pituitary tumour. However, any degree of unilateral or bilateral visual deficit can occur depending on the anatomical site of the lesion.

 including disorders of appetite, thirst, temperature regulation, and consciousness. The pituitary hormone deficits attributed to a pituitary tumour tend to occur in a specific order, with GH and gonadotropins af- fected first, followed later by ACTH and TSH. Diabetes insipidus is almost never a presenting feature of pituitary adenomas. The clinical manifestations of hypopituitarism are presented separately for each anterior pituitary hormone. In case of a functioning pituitary adenoma, the clinical manifest- ations depend on the type or types of anterior pituitary hormone(s) hypersecreted and are also presented separately for each anterior

pi- tuitary hormone. Pituitary assessment strategy The investigation of suspected anterior pituitary disease includes testing for hormonal hyperfunction or hypofunction, radiological assessment, and neuro-ophthalmological evaluation. Testing of pituitary function The optimum methods for testing anterior pituitary function and the interpretation of the results are the subject of continuing de- bate. The diagnostic evaluation of pituitary hypofunction has many complementary limbs. First, it is necessary to demonstrate target organ hormonal insufficiency. Paired testing of both hormones in the pituitary–target organ feedback loop (e.g. serum testosterone and gonadotropins), sometimes in combination with provocative testing, will prove that target organ failure is consequent upon lack of stimulation by the relevant pituitary tropic hormone. Additional tests may be necessary to clarify whether the pituitary itself is at fault or whether the pituitary failure is secondary to understimulation by the hypothalamus. Basal pituitary function tests Measurements of basal levels of pituitary hormones with target gland hormone secretion are usually sufficient for cases of pituitary dysfunction involving TSH (thyroxine), FSH/LH (testosterone or oestradiol), and PRL. When interpreting basal measurements of pituitary hormones, several factors need to be taken into account: • With the exception of PRL, the interpretation of the anterior pitu- itary hormonal levels should be done in relation to the level of the target hormone. • The pulsatile secretion of the anterior pituitary hormones may make a single, random blood sample not representative of the total secretion (e.g. GH). • Specific factors including time of day, stress, fed, or fasting, asleep or awake, and stage of pubertal development may influence the results. Currently, the modern chemiluminescent assays and mass spec- trometry methods are used for measurement of hormone concentra- tions; these methods have the advantages of increased automation and improved sensitivity and specificity. GH The marked pulsatile secretion of GH results in values in a normal subject ranging from undetectable to more than 80 mU/litre. Furthermore, the GH secretion is influenced by several factors including nutritional status and stress. As a result of these variables, random levels are of limited value in clinical practice and dynamic endocrine tests are usually needed. FSH/LH Serum FSH and LH are secreted in a pulsatile manner. However, it is rare for tests other than basal measurements of gonadotropin hormones and sex-steroid levels to be required for the evaluation of the pituitary–gonadal axis. The gonadotropins need to be in- terpreted taking into account the simultaneous levels of the target gland hormone, as well as the clinical picture of the patient. Thus, in men, a low serum testosterone in conjunction with low or ‘inappro- priately normal’ gonadotropins suggests hypogonadotropic hypo- gonadism. In women, the interpretation is more complex because of the significant changes in the levels of the gonadotropins during the various phases of the menstrual cycle. A normal menstrual cycle with normal luteal phase serum progesterone (days 18–25 of the cycle) makes gonadotropin deficiency very unlikely. In cases of amenorrhoea, the measurements of gonadotropins, PRL, oestra- diol, and human chorionic gonadotropin (possible pregnancy) are needed. ACTH The ACTH molecule undergoes rapid proteolytic degradation and, therefore, blood samples must be collected in a cold syringe, placed in an ethylenediaminetetraacetic acid (EDTA) tube at 4°C, and immediately frozen. ACTH secretion is pulsatile with a circa- dian rhythm and it increases during stress. As a result, the inter- pretation of the measurements should take into account the time of sample collection, whether the sample was taken from an indwelling cannula in place for at least 30 min, and whether the patient was stressed. Simultaneous measurement of plasma cortisol is important to check the appropriateness of the ACTH levels. PRL PRL is secreted in a pulsatile fashion and also shows an increase in the early morning hours. Stress may cause mild elevations of the hormone and, therefore, the stress of venepuncture should be taken into account when assessing the results. TSH The new ultrasensitive assays for TSH have made dynamic testing unnecessary and random

sampling therefore provides meaningful information. Dynamic endocrine tests In general, the more dynamic the physiological system in health, the more likely will be the need for a dynamic test to investigate its possible malfunction in disease. The provocative tests include those that stimulate hormone release indirectly (e.g. insulin tolerance test) and those that stimulate hormone release directly by injecting pharmacological doses of synthetically manufactured peptides (e.g. short Synacthen test). Currently, the combined anterior pituitary function test with the administration of LH-releasing hormone (LHRH) and thyrotropin-releasing hormone (TRH) is not used in clinical practice, as basal hormone measurements provide the ne- cessary diagnostic information. Thus, only disorders of ACTH and

13.2.1 Disorders of the anterior pituitary gland 2263 GH secretion need dynamic endocrine testing with stimulation or suppression tests, according the presenting picture. The most commonly used tests in clinical practice are described next. Insulin tolerance test This test is considered the gold standard for assessing the integrity of the ACTH–cortisol axis, as well as the GH reserve. The hypogly- caemia induced by the intravenous injection of insulin is a powerful stimulus, which in the intact pituitary and hypothalamus induces ACTH and GH release, as well as a rise, therefore, in the serum cor- tisol levels. It has been proposed that the peak cortisol levels of pa- tients undergoing major surgery are comparable to those achieved during the insulin-induced hypoglycaemia. The test should be undertaken only under close supervision at skilled centres. The pa- tient should be fasted from midnight and the test started at 9.00 a.m. At 0 min, 0.1 to 0.15 IU/kg (or 0.3 IU/kg for those with acromegaly, Cushing’s syndrome, or other conditions with insulin resistance) of soluble human insulin is injected intravenously and blood is drawn at times 0, 30, 45, 60, 90, and 120 min. During the procedure, pulse rate, blood pressure, and manifestations of hypoglycaemia should be recorded. Blood glucose must fall to less than 2.2 mmol/litre (to provide an adequate stimulus) in order to interpret the cortisol and GH levels. A normal cortisol response is a rise to 500–550 nmol/ litre or above (depending on the hormone assay). Severe GH defi- ciency in adults is diagnosed if the peak GH is less than 3 µg/litre. Contraindications include ischaemic heart disease, epilepsy, or unexplained blackouts, severe long-standing hypoadrenalism, un- treated hypothyroidism, and glycogen storage disease. Many phys- icians are uncomfortable with the use of this test in older people. Short Synacthen test This test has been advocated as an alternative to the insulin tolerance test for assessing the ACTH reserve. The rationale for its use is that chronic underexposure of the adrenal glands to ACTH (following prolonged corticosteroid therapy or due to hypothalamic–pituitary disease) will result in a blunted cortisol response to exogenously administered ACTH. It involves the injection of a pharmacological dose (250 µg) of ACTH with measurement of the cortisol response 30 min later. The correlation between cortisol levels 30 min after the injection of Synacthen and the peak cortisol achieved during the in- sulin tolerance test is excellent; stimulated cortisol concentrations of 500–550 nmol/litre or less (depending on assay) suggest ACTH de- ficiency. This test does not differentiate primary from secondary ad- renal insufficiency. It requires no specialist staff and the only reported side effect is allergy in patients with atopy. It cannot be used in cases of acute hypopituitarism as it takes at least 2 weeks for the adrenal zona fasciculata to involute following withdrawal of ACTH stimu- lation. In recent years, much interest has arisen in the use of a lower dose of ACTH (1 µg), as the injected bolus of 250 µg is considered supraphysiological; this has not gained widespread acceptance. Glucagon stimulation test The glucagon stimulation test is used as an alternative to the insulin tolerance test for assessment of the ACTH/cortisol and GH reserve. The subcutaneous injection of glucagon causes a transient rise in plasma glucose and, during the subsequent fall in glucose, ACTH and GH

are released. The test involves the administration of 1 mg (or 1.5 mg if body weight >90 kg) glucagon subcutaneously with blood sampling for cortisol, GH, and glucose at times 0, 90, 120, 150, 180, and 210 min. The contraindications for this test include phaeo- chromocytoma or insulinoma, glycogen storage disease, and severe hypocortisolaemia. The interpretation of results relies on criteria established for the insulin tolerance test. The injection may cause nausea, abdominal pain, and vomiting. Glucagon is a less powerful stimulus to ACTH release and false-negative results may be seen in up to 20% of patients. In some false-negative results, no rise in the blood glucose is achieved after the glucagon injection. Growth hormone-releasing hormone (GHRH) plus arginine test The GHRH plus arginine test is used as an alternative to the insulin tolerance or glucagon test for assessment of the GH reserve. The protocol involves intravenous infusion of GHRH 1 μg/kg (maximum dose 100 μg) followed by arginine infusion 0.5 g/kg (maximum 35 g) over 30 minutes. With blood sampling for GH at times 0, 30, 45, 60, 75, 90, 105, and 120 min. The cut-offs for GH response are BMI- related and false normal GH response may be seen if GH deficiency is attributed to hypothalamic damage (e.g. following irradiation). Oral glucose tolerance test The evaluation of GH hypersecretion requires a suppression test. Increased blood glucose levels inhibit GH secretion and the admin- istration of oral glucose is used in suspected acromegaly. The test is performed at 9.00 a.m. with the patient fasted from midnight. Blood samples are drawn for measurement of glucose and GH at times 0, 30, 60, 90, and 120 min. Immediately after the first blood sample, 75 g of glucose are dissolved in water and given to the patient. In normal individuals serum GH should reach undetectable levels. Failure of suppression or a paradoxical rise in GH suggest acro- megaly. False-positive results may be seen in uncontrolled diabetes mellitus, obesity, liver disease, renal insufficiency, malnutrition, or anorexia. During late adolescence, when GH secretion is maximal, GH may also fail to be suppressed. Radiological assessment Currently, the imaging modality of choice for patients with suspected pituitary pathology is MRI. CT is an acceptable alternative if MRI is contraindicated. The advantages of MRI are direct multiplanar scanning, lack of ionizing radiation, and good anatomical tissue dis- crimination without the need for pharmaceutical contrast agents. The evaluation of the pituitary and the hypothalamus is optimal in sagittal and coronal planes. The only disadvantage of MRI (apart from the cost) is its relative insensitivity to pathological calcifica- tion and lack of signal from corticated bone. CT or even plain film radiography may be required to demonstrate pathological calcifi- cation. The structures of the sellar region are best visualized using T1-weighted sequences, which produce images with dark cerebro- spinal fluid, grey brain and pituitary, and white fat. Corticated bone returns low signal and appears dark, but bone marrow fat returns high signal and appears white. The nuclei of the hypothalamus cannot be distinguished, but if phospholipid vesicles are present in the neuro- hypophysis they are apparent as high signal areas. The need for routine intravenous administration of paramagnetic agents is controversial (however, it increases the pick-up rate of pituitary microadenomas). These agents do not cross the blood–brain barrier and, therefore, the pituitary gland and stalk enhance and appear whiter on T1-weighted

 images. The hypothalamus and the optic chiasm do not enhance if the blood–brain barrier is intact. Blood vessels, meninges, and mucosa of the paranasal sinuses will enhance. Dynamic MRI has been used to study the timing of intravenously administered gadolinium uptake by the hypophysis (see Figs. 13.2.1.1, 13.2.1.2). Apart from its complementary role to MRI in detecting patho- logical calcification, CT scanning is the imaging modality of choice for patients who are unable to undergo MRI (extreme claustrophobia, presence of cardiac pacemakers, or other implants such as intracra- nial aneurysm clips or traumatic metallic

fragments). Multislice spiral CT scanners produce images of sufficient quality to demon- strate sellar anatomy on unenhanced images. Intravenous injection of iodinated contrast media is used to improve tissue contrast and it is taken up by the hypophysis in the same way as gadolinium. Thus, macroadenomas or craniopharyngiomas enhance and are better de- lineated, but demonstration of microadenomas within a morpho- logically normal pituitary depends on differential uptake rates.
Neuro-ophthalmological evaluation The neuro-ophthalmological evaluation in suspected pituitary pathology includes assessment of the visual acuity (with the use of Snellen charts), assessment of the visual fields (by confrontation using a red pin and formally by the Goldmann perimetry test or by visual evoked responses), and fundoscopy (to check for optic at- rophy, retinal vein engorgement, or papilloedema). Vision is usually lost gradually, except in cases of pituitary apoplexy when it may be sudden. Successful decompression of the optic nerves and chiasm achieved surgically or by medical therapy results in marked im- provement of visual function; this becomes apparent within hours or days of surgery continuing thereafter for 6 months or more. The chance of complete reversal of any visual field defects is higher if the duration of compression of the optic chiasm is short (<1 year). Pituitary surgery Currently, the main aims of pituitary surgery are to cure any endo- crine excess and to reverse the pressure effects (particularly the visual compromise and the pituitary dysfunction) without causing mor- bidity or mortality. For all pituitary tumours, except prolactinomas, surgery is the treatment of choice. It is also indicated when other therapies have not been successful or in case of tumour recurrence. The trans-sphenoidal approach (via the translabial or transethmoidal route) with the microscopic or endoscopic technique) is most com- monly used and, compared with the transfrontal route, it is less time consuming, less traumatic, and associated with less morbidity. The trans-sphenoidal approach is less successful for large tumours with significant invasion to neighbouring structures. In pituitary aden- omas the tumour is usually soft and white and can be easily removed by curettes and suction. Other tumours may also be recognized during surgery, including meningiomas or craniopharyngiomas.
Complications include cerebrospinal fluid leakage, impaired anterior pituitary function, diabetes insipidus (most commonly temporary), the syndrome of inappropriate secretion of antidiuretic hormone (usually transient), visual deterioration, meningitis, headache (at- tributed to haematoma in the air sinuses, meningitis, hyponatraemia, or abscess), vascular damage, epilepsy, frontal lobe damage, hypo- thalamic damage, and intracranial oedema/haemorrhage. The success and complication rates are mainly associated with the size and extensions of the tumour and any previous therapy, as well as the experience and expertise of the neurosurgeon.
Pituitary radiotherapy After the improvement of surgical techniques and the availability of medical therapy for prolactinomas, pituitary irradiation is no longer prescribed routinely for the management of pituitary tumours. It is mainly reserved for patients who are not fit to undergo surgery, for those who have had an unsuccessful operation, or for those showing tumour recurrence. Conventional irradiation uses a linear accelerator and is admin- istered in a fractionated manner to a total dose of 4500 cGy in daily doses not exceeding 180 cGy over a 5- to 6-week period. Hormonal hypersecretion shows a rapid fall within the first 2 years with the de- cline continuing for up to 20 years. Radiotherapy is also considered an effective modality for decreasing the recurrence rates of pituitary tumours. With modern technology and careful planning, the use of multiple fixed fields from linear accelerators, and careful fractionation, the risk of radiation-induced late complications is small. These include hypopituitarism and visual impairment; oncogenesis and cognitive impairment occur infrequently. With increasing time after irradi- ation, anterior pituitary function assessment will show compromised reserve in gonadotropins and GH, followed later by ACTH and TSH. It has been reported that by 10 years after radiotherapy, 47% of pa- tients were

hypogonadal, 30% were hypoadrenal, and 16% were hypo- thyroid. Therefore, any patient who has received pituitary irradiation needs lifelong follow-up aiming for the early diagnosis of hormonal deficits. Notably, the total dose and the dose per daily fraction influ- ence the risk of hypopituitarism. Optic nerve/chiasmal damage can be avoided by keeping the daily fractionated dose to less than 200 cGy. From the available data, the incidence of late carcinogenesis cannot be estimated with certainty, but it is unlikely to be more than 1 to 2%. Recently introduced techniques include intensity modulated ra- diation therapy, proton beam radiation therapy, stereotactic radio- therapy, and stereotactic radiosurgery (producing a highly localized deposition of radiation on the target, at the perimeter of which there is a fast 'fall off' of the isodoses, thereby sparing the surrounding normal tissue from high doses of irradiation). Following stereo- tactic radiosurgery, there is a faster early reduction of the excessive secretory hormone product; hypopituitarism can also occur. The selection of the optimal radiation treatment modality should be based on the size and extent of the adenoma, the postoperative endocrine situation for secretory tumours, and the pituitary hor- mone reserve. For small, discrete tumours located in the fossa, radiosurgery seems to be a good option. This technique is also useful for patients with recurrence who have already received conventional radiotherapy. Anterior pituitary hormones GH Human GH is a single chain protein of 191 amino acids containing two disulphide bonds. It is produced by the somatotroph cells and it

 has several similarities to prolactin and the placental lactogen mol- ecule. Nearly 75% of the hormone circulates as a 22-kDa protein, 5 to 10% as a smaller 20-kDa isoform, and the remainder consists of glycosylated and sulphated isoforms. GH is secreted in an episodic manner (pulses occurring every 3–4 h) that is modified by age and sex. The most profound discharge occurs during deep sleep (phases III and IV). Its secretion is under complex neuroregulatory control. The hypothalamic participation is exerted through GH-releasing hormone (GHRH) and somatostatin, which reach the pituitary gland via the hypothalamo-pituitary portal vessels. GHRH stimulates both synthesis and secretion of GH, whereas somatostatin inhibits the re- lease but not the synthesis of the hormone. Ghrelin, the endogenous ligand of the GH secretagogue receptor localized mainly in the stomach, may also be implicated in the control of GH secretion. The somatotroph cell is also regulated by negative feedback at the pitu- itary level by the circulating insulin-like growth factor 1 (IGF-1) and by 'short-loop' feedback on the hypothalamus by GH. The secretion of GH is greater in women and it shows a decrease with age in both sexes. Amino acids (e.g. arginine, leucine), sleep, exercise, stress, a fall in blood glucose, poorly controlled diabetes mellitus type 1, hep- atic cirrhosis, anorexia nervosa, central α-adrenergic agonists, and acetylcholine agonists enhance GH secretion. Oestrogens increase the pulse amplitude of GH. β-Antagonists augment the stimulatory effect of other stimuli. Agents lowering acetylcholine tone suppress GH release. Hyperglycaemia in normal subjects acutely suppresses GH secretion. Obesity is associated with decreased GH release and emotional deprivation may inhibit GH secretion in children. GH levels are decreased in pregnancy due to the negative feedback by the GH variant secreted by the placenta. GH exerts its actions through a specific 638-amino acid receptor belonging to the class I haematopoietin or cytokine/GH/PRL re-ceptor superfamily. It shows a wide distribution including muscle, adipose and immune tissues, liver, mammary gland, bones, kidneys, brain, and embryonic stem cells. It is a single membrane-spanning type I glycoprotein with an extracellular ligand-binding domain, a single 24-amino acid hydrophobic transmembrane region, and an intracellular domain. The signal transduction requires dimerization of the receptor, which is facilitated by the GH binding. The down- stream signalling

pathways resulting in GH actions include, but are probably not limited to, the signal transducer and activator of tran- scription, mitogen-activated-kinase (MAP), and phosphoinositide 3-kinase (PI3) pathways. Abnormalities in the GH receptor occur in Laron's dwarfism, which is characterized by failure of growth, high levels of GH, and low IGF-1. Up to 60% of the circulating serum GH is bound to the GH- binding protein, which corresponds to part of the extracellular do- main of the GH receptor. The binding reduces the clearance rate of the hormone and thus prolongs its half-life. The effects of GH are mediated either directly or mainly indir- ectly via the production of IGF-1 by the liver, bones, and other types of tissues. IGF-1 is a polypeptide of 70 amino acids and acts in an endocrine, paracrine, or autocrine fashion. It circulates bound to a group of binding proteins; IGF binding protein-3 is the main carrier of IGF-1 and plays an important role in regulating its bio- activity. IGF-1 induces cell proliferation and inhibits apoptosis. Its levels are determined by sex and genetic factors, are highest during late adolescence, and decline throughout adulthood. The produc- tion of IGF-1 is suppressed in malnourished patients, as well as in those with liver disease, hypothyroidism, or poorly controlled dia- betes. Although IGF-1 levels usually reflect the integrated secretory activity of GH, subtly elevated GH levels may not uniformly induce high IGF-1. The main actions of GH are the promotion of skeletal growth, mainly of long bones, and the regulation of several metabolic ac- tions. In the muscles GH promotes the incorporation of amino acids and protein synthesis, and in the adipose tissue it promotes free fatty acid release. Disorders of GH secretion GH deficiency The manifestations of GH deficiency are shown in Table 13.2.1.2. Given its pulsatile secretion, the measurements of random GH levels do not distinguish between normal and compromised GH secretion; multiple sampling for GH would be ideal but in clinical practice this is not a practical procedure. Therefore, the diagnosis of GH deficiency requires stimulation testing, unless all other pituitary hormones are deficient and the IGF-1 is low (in these patients the likelihood of GH deficiency is 99%). The biochemical criteria for the diagnosis of adult GH deficiency are complicated by the lack of normative data that are age-adjusted and sex-adjusted, by the assay variability, and by the stimulus used. Among the available tests the insulin tolerance test is considered the gold standard. Severe GH de- ficiency in adults is diagnosed if the peak GH is less than 3 µg/litre. In children the secretory capacity of GH is higher and a cut-off of 10 µg/litre is used. The GHRH plus arginine test has been shown to re- liably detect severe GH deficiency in a lean adult population when a cut-off of 9 µg/litre is used. The response to this test declines greatly with increasing body mass index and the above cut-off in obese pa- tients is associated with a high proportion of false-positive results. Furthermore, as GHRH directly stimulates the pituitary, it can give a falsely normal GH response in patients with GH deficiency of hypo- thalamic origin. Other alternative tests, but less commonly used in clinical practice, include the GHRH plus GH-releasing peptide- 6 test, the glucagon test, the arginine test, the l-dopa test, and the clonidine test. Normal serum levels of IGF-1 do not exclude a diag- nosis of GH deficiency. The main targets of GH therapy in children with GH deficiency are to normalize height during childhood and to reach normal adult height. The benefits of treatment with GH among adult patients have been reported in several domains: body composition (decrease in total body fat content, increase in muscle mass), exercise capacity, bone health (increase in bone mineral density with greater effects Table 13.2.1.2 Manifestations of GH deficiency Children Adults Growth failure Relative increase in fat mass Relative decrease in muscle mass Increased serum low-density lipoprotein cholesterol Decreased bone mineral density Increased risk of cardiovascular disease Increased inflammatory cardiovascular risk markers Decreased energy and quality of life

 at vertebral sites), cardiovascular risk factors (decrease in blood pressure, reduction of C-reactive protein, increase in high-density lipoprotein, and decrease in low-density lipoprotein and total chol- esterol), and quality of life. In adults, the dosing plans have evolved from weight-based dosing to individualized dose-titration strategies with the goals being an appropriate clinical response, an avoidance of side effects, and an IGF-1 level in the middle of the age-adjusted reference range. In general, women require higher doses of GH to achieve the same IGF-1 response (much higher GH doses were also needed to achieve the same IGF-1 levels in women receiving oral oestrogen replacement, but this does not apply when oestro- gens are offered as patches). Furthermore, as GH secretion normally decreases with age, older patients require lower doses of GH. The duration of GH replacement therapy in adults is unclear; if bene- fits are apparent, there is no particular reason to stop treatment. On the other hand, if there are no benefits following around 1 year of treatment, discontinuing GH therapy may be appropriate. Most adverse effects are dose related and are attributed to fluid reten- tion (paraesthesias, joint stiffness, peripheral oedema, arthralgia, and myalgia). In children, there is a risk of slipped capital femoral epiphysis. With the current dosing regimens, there may be a slight excess risk of diabetes mellitus. Other complications of GH therapy include retinopathy, benign intracranial hypertension, and gynae- comastia. GH replacement may cause a decrease of serum free thy- roxine levels (perhaps due to increased deiodination of thyroxine) and of serum cortisol levels (revealing central hypoadrenalism that had been masked, probably due to enhanced conversion of cortisone to cortisol during the GH-deficient state). GH treatment is contra- indicated in the presence of an active malignancy. Acromegaly Acromegaly is the syndrome resulting from GH hypersecretion. Its incidence is estimated to be approximately three cases per 1 million persons per year, and its prevalence is about 60 per million. More than 90% of patients with acromegaly have a be- nign monoclonal GH-secreting pituitary adenoma surrounded by nonhyperplastic pituitary tissue. Cosecretion of PRL has been described in about 25% of GH-secreting adenomas. More than 70% of somatotroph tumours are macroadenomas at diagnosis. Younger patients usually present with more rapidly growing tu- mours. Rarely, acromegaly is associated with familial occurrence [including multiple endocrine neoplasia type 1 or 4, familial isolated pituitary adenoma (related in several cases with muta- tions in the aryl hydrocarbon receptor-interacting protein (AIP) gene), and Carney’s syndrome]. X-linked acrogigantism (X-LAG) is a new syndrome of pituitary early-onset gigantism, caused by microduplications on chromosome Xq26.3, encompassing the gene GPR101. Acromegaly may also be seen in the McCune- Albright syndrome. Excess production of GH-releasing hormone (as in central hypothalamic tumours, usually gangliocytomas, and peripheral neuroendocrine tumours, e.g. of the lung) can result in somatotroph hyperplasia and acromegaly. Clinical features The clinical features of acromegaly are shown in Box 13.2.1.1. Disease features develop insidiously, and the diagnosis may often take 10 years from presentation. GH-secreting adenomas arising before the closure of epiphyseal bone are associated with ac- celerated growth and gigantism. Box 13.2.1.1 Clinical features of acromegaly Local tumour effects • Pituitary enlargement • Visual field defects • Cranial nerve palsy • Headache Somatic systems • Acral enlargement including thickness of soft tissue of hands and feet Musculoskeletal system • Gigantism • Prognathism • Jaw malocclusion • Arthralgias and arthritis • Carpal tunnel syndrome • Acroparesthaesia • Proximal myopathy • Hypertrophy of frontal bones Skin and gastrointestinal system • Hyperhidrosis • Oily texture • Skin tags • Colon polyps Cardiovascular system • Left ventricular hypertrophy • Asymmetric septal hypertrophy • Cardiomyopathy • Hypertension • Congestive heart failure Pulmonary system • Sleep disturbances • Sleep apnoea (central and obstructive) • Narcolepsy Visceromegaly • Tongue

• Thyroid gland • Salivary glands • Liver • Spleen • Kidney • Prostate Endocrine and metabolic systems Reproduction • Menstrual abnormalities • Galactorrhoea • Decreased libido, impotence, low levels of sex hormone-binding globulin Multiple endocrine neoplasia type 1 • Hyperparathyroidism • Pancreatic islet cell tumours Carbohydrate • Impaired glucose tolerance • Insulin resistance and hyperinsulinaemia • Diabetes mellitus Lipid • Hypertriglyceridaemia

13.2.1 Disorders of the anterior pituitary gland 2267 Whether acromegaly is associated with an increased relative risk of cancer is controversial and has been extensively reviewed. Some studies have suggested increased risk of colon cancer in patients with acromegaly necessitating screening colonoscopy at diagnosis with follow-up according to standard guidelines. Acromegaly is associated with increased mortality and factors contributing to this include the higher prevalence of hypertension, hyperglycaemia, or overt diabetes, cardiomyopathy, and sleep ap- noea in this population. In some studies, increased IGF-1 levels are associated with higher mortality. However, GH levels seem to be more consistently independent predictors of mortality than are IGF-1 levels. Diagnosis The biochemical diagnosis is made by confirming ab- sence of suppression of GH in the oral glucose tolerance test and by increased serum IGF-1 levels. With the use of most commercial assays, nadir GH levels of less than 1 µg/litre during the oral glucose tolerance test rule out the diagnosis. With very sensitive GH assays this cut-off is less than 0.4 µg/litre. Treatment The goals of treatment in patients with acromegaly include the improvement/reversal of the manifestations and comorbidities related with the GH hypersecretion, the reduction of the mortality risk and restoration of the abnormal biochemistry. Further aims include the decrease or stabilization of the tumour size, improvement or preservation of the pituitary function, and prevention of recurrence. It should be noted that, with the currently available therapeutic options, normal GH secretion dynamics are only rarely achieved and it is, therefore, more appropriate to de- fine disease control. A biochemical target goal of an age normalized serum IGF-I value suggests control of the acromegaly. Furthermore, a random GH less than 1 mg/litre is another therapeutic goal and correlates with control of the disease. It has also been proposed that a normal IGF value and undetectable GH value are sufficient for indicating remission after surgery. Given the variability between Gh and IGF-I assays, it is important to use the same assay in the same patient throughout his management. Management options include surgery, drugs, and radiotherapy. Trans-sphenoidal surgery remains the treatment of choice for most patients. The success rate depends on the size and extensions of the tumour, the presurgical GH levels, as well as the experience and expertise of the neurosurgeon. Biochemical control has been reported for up to 80% of microadenomas and for up to 40% of macroadenomas. Tumours that have invaded the cavernous sinus cannot be completely removed surgically and the hypersecretion of GH almost invariably persists postoperatively in such patients. Although up to 10% of tumours recur, many recurrences prob- ably represent persistent growth of residual nonresectable tumour tissue. Medical treatment includes dopamine receptor agonists, som- atostatin receptor ligands, and GH receptor antagonists. Dopamine receptor agonists are less costly than other agents, but are only oc- casionally effective in selected patients. The doses required are usually much higher than in prolactinomas and biochemical con- trol has been reported in around 15% of the patients. Side effects include gastrointestinal upset, nasal congestion, fatigue, postural hypotension, and headache. Cardiac valve abnormalities occur with high doses of cabergoline used for patients with Parkinson’s dis- ease but have not been observed in most studies of patients with prolactinomas treated with conventional doses. Somatostatin re- ceptor ligands, such as octreotide and lanreotide, bind to somato- statin receptors resulting in suppression of GH secretion. They also act

on the liver to block the synthesis of IGF-1. Octreotide and lanreotide are selective for somatostatin receptors type 2 and 5, which are expressed in more than 90% of the GH-secreting ad- enomas. Depot preparations—long-acting-release octreotide and a long-acting aqueous-gel preparation of lanreotide—allow for injec- tions every 14 to 28 days maintaining highly effective drug levels. IGF-I normalization has been reported in 17–35% of both drug- naive and postoperative patients. In 59% of patients, there is reduc- tion in tumour volume of more than 50% and tumour shrinkage usually correlates with hormonal control. Surgical debulking of macroadenomas not amenable to total resection enhances the effi- cacy of subsequent somatostatin analogue treatment. Somatostatin analogues are indicated following unsuccessful surgery and after ra- diation therapy, during the period when GH levels remain elevated. They can also be offered as primary treatment to patients with large extrasellar tumours who have no evidence of central compressive effects, those who are too frail to undergo surgery, and those who decline an operation. Transient diarrhoea, nausea, and abdominal discomfort may occur, but typically resolve within 8 to 10 weeks. Blood glucose levels may rise in some patients. Gallbladder sludge or asymptomatic gallstones develop within 18 months in up to 20% of patients and these conditions should be managed according to standard guidelines. Selective activation of other somatostatin re- ceptors by specific somatostatin receptor ligands results in additive suppression of GH; the ligand pasireotide (SOM230) suppresses levels of GH in patients with resistance to octreotide but is associated with hyperglycaemia in 57% of the patients. Lastly, pegvisomant, a pegylated GH receptor analogue showing enhanced activity for the GH receptor, also prevents the functional GH-receptor signalling. As a result of this, it blocks the GH-mediated IGF-1 generation in nearly 90% of patients, although in a surveillance study IGF-I was controlled in 63% of the patients (this may be attributed to com- pliance and inadequate dose titration). It is indicated for patients whose GH levels are inadequately controlled with other modalities or in those experiencing significant drug side effects. During treat- ment with pegvisomant, GH levels increase and IGF-I is the bio- marker for monitoring the efficacy of treatment. Elevated hepatic aminotransferase levels have been reported requiring monitoring of the liver function tests monthly for the first 6 months of treatment and 6-monthly thereafter with consideration of discontinuation of pegvisomant if the transaminases are greater than 3-fold elevated. Mineral • Hypercalciuria, increased levels of 25-hydroxyvitamin D3 • Urinary hydroxyproline Electrolyte • Low renin levels • Increased aldosterone levels Thyroid • Low thyroxine binding globulin levels • Goitre Source data from Melmed S (2006). Acromegaly. N Engl J Med, 355, 2558–73, with permission.

 Tumour growth may occur in 3–5% of patients, but it is not clear whether this is due to the tumour natural history or to reduced nega- tive feedback by the lower IGF-1 levels. Probable tumour size should be monitored at 6-month intervals to detect possible continued enlargement for the first year of treatment. If the tumour remains stable, yearly imaging is recommended. Combined treatment with somatostatin analogues and pegvisomant restores IGF-1 concentrations to normal in over 90% of patients and in about 20% decreases tumour size, whereas pegvisomant (PEG-V) monotherapy does not induce a clinically relevant decrease in the size of pituitary tumours. Transient elevations in serum transaminase ac- tivities are the main adverse effects of this combination treatment re- ported, in up to 27% of patients. Radiotherapy is generally offered for tumours that have recurred or persisted after surgery in patients with resistance to or intolerance of medical treatment. Twenty-two per cent of patients achieved a level less than 2.5 ng/ml (5 mU/litre) by 2 years, 60% by 10 years, and 77% by 20 years. The time taken to achieve this depends on the pre- irradiation concentration of GH. IGF-I

concentrations normalize in 63% of patients by 10 years. In patients offered stereotactic radio- therapy and followed up to 15 years, remission rates of 10–60% have been reported. Although the overall efficacy of stereotactic radio- therapy may be similar to conventional radiotherapy, time to remis- sion may be shorter with stereotactic radiotherapy. FSH/LH The gonadotropins, TSH, and human chorionic gonadotropin β belong to the family of glycoprotein anterior pituitary hormones. They share a common α subunit and each has a unique β subunit conferring biological and immunological specificity. The LH β and FSH β subunits both have 115 amino acids and two carbohydrate side chains. A terminal sialic acid may be present on the carbohy- drate side chain of the FSH β subunit, thus decreasing its metabolic clearance. The regulation of FSH and LH secretion is exerted by the inte- gration of the gonadotropin-releasing hormone (a hypothalamic decapeptide) signal and the (stimulatory and inhibitory) feedback effects of gonadal steroids and peptides. Gonadotropin-releasing hormone interacts with the membrane receptor and regulates the synthesis and release of gonadotropins. The major feature of the pituitary–gonadal axis is that its constituents exhibit a pulsatile pattern of hormonal release. The frequency and the amplitude of gonadotropin-releasing hormone pulses are important in differen- tially regulating LH and FSH secretion. Gonadotropin concentra- tions are very low in children and the nocturnal augmentation of gonadotropin release marks the onset of sexual development. In women, LH levels rise slightly during the follicular phase, peaking at the time of the midcycle surge and then decline during the luteal phase. The FSH levels start rising during the late luteal phase, increase during the early follicular phase of the next cycle, and decline just before the midcycle FSH surge. During the luteal phase, the FSH levels show a decline and increase again before the next menses. In the follicular phase, most of the LH pulses are fol- lowed by a release of oestrogens from the ovary, whereas in the mid and late luteal phase the LH pulses induce progesterone se- cretion. Both oestradiol and progesterone inhibit the release of LH acting at the hypothalamic and pituitary level. However, in the fol- licular phase there is enhanced release of oestradiol, which acts in a stimulatory way and induces the large discharge of LH responsible for ovulation. During this surge, LH levels remain increased for 36 to 48 h, during which time ovulation occurs, oestradiol levels de- cline, and luteinization of the follicle results in increasing produc- tion of progesterone. The ovary exerts a negative feedback on FSH secretion mainly through the secretion of inhibin, a glycoprotein hormone synthesized in the granulosa cells of the ovarian follicle and counterbalanced by activin. In the late follicular phase, inhibin levels increase and, in combination with oestradiol, inhibit the syn- thesis and release of FSH, an inhibition that it is overcome at the preovulatory gonadotropin discharge. The hypothalamic control of FSH and LH secretion is very sensitive to environmental conditions, such as stress or changes to nutrition or energy homeostasis. Stress activates the corticotropin-releasing hormone pathways, which may inhibit the gonadotropin-releasing hormone neurons through opiate pathways. Reduction in the daily food intake leads to a reduc- tion in the gonadotropin-releasing hormone secretion translated into a reduced and nonpulsatile secretion of FSH and LH into the circulation. The regulation of the gonadal axis is equally complex but more static in men. It is assumed that gonadotropin pulses in men follow the scarce pulses of gonadotropin-releasing hormone and, in fact, are highly variable and of small amplitude. Testosterone exerts a negative feedback on LH secretion, and Sertoli cells secrete activin and inhibin in order to regulate FSH secretion. The gonadotropins are responsible for the gonadal sex- steroid production by the Leydig cells of the testis and the ovarian follicles, secondary sexual development, maintenance of secondary sexual characteristics, and fertility. Disorders of FSH/LH secretion FSH/LH deficiency Gonadotropin deficiency presents with oligomenorrhoea/amen- orrhoea, loss of libido, dyspareunia, hot flushes, and infertility in women,

and with loss of libido, impaired sexual function, mood im- pairment, loss of facial, scrotal, and trunk hair, and decreased muscle bulk and energy in men. Hypogonadism in both sexes is associated with decreased bone mineral density. In children, gonadotropin de- ficiency causes delayed or arrested puberty. The diagnosis in women is based on oligomenorrhoea/amenor- rhoea combined with low or ‘inappropriately normal’ FSH and LH levels. In postmenopausal women, the FSH and LH levels are in- appropriately low. In men, there is low serum testosterone (9.00 a.m. sample, as levels show considerable diurnal variation) with low or ‘inappropriately normal’ gonadotropins. The treatment consists of appropriate replacement therapy (un- opposed oestrogens for women who have undergone hysterectomy or combined oestrogen-progestogen preparations for those with in- tact uterus to prevent endometrial hyperplasia). Oestrogens are avail- able in many forms with different potency (oral, transdermal, topical gels and lotions, intravaginal creams and tablets, vaginal rings). The choice of the oestrogen (and progestin) preparation needs to rely on the risk of adverse effects, cost, patient convenience, and pref- erence. The follow-up of gonadal hormone replacement includes evaluating the effectiveness by symptom control and monitoring for oestrogen/progestogen side effects. The patients require annual re- view to evaluate use and assess risk and benefit profile. Hormonal replacement therapy should be used until the mean age of natural

 menopause; further management decisions should rely on current recommendations for the general female population. For induc- tion of fertility, gonadotropins, or pulsatile gonadotropin-releasing hormone (the latter only in hypothalamic dysfunction) are used. Serum androgen levels in women with hypopituitarism are low; the pros and cons of replacing androgens in such cases are under inves- tigation. In men, testosterone replacement using one of the avail- able preparations (gel, intramuscular injections) is suggested. The dose is adjusted to normal testosterone concentrations. Serum LH cannot be used to monitor the adequacy of therapy. Monitoring for prostate-specific antigen, prostate size, and haematocrit (erythro- poietin is stimulated by testosterone) are recommended regularly. For the induction of fertility, gonadotropin therapy, or pulsatile gonadotropin-releasing hormone (the latter only in hypothalamic dysfunction) are available options. Gonadotroph adenomas Gonadotropinomas are pituitary adenomas secreting intact LH and/ or FSH. They are rare, as most tumours expressing gonadotropins secrete a subunit without causing biological effects (nonfunctioning pituitary adenomas). Both types of tumours are most commonly diagnosed in middle-aged men and present with symptoms related to a pituitary mass. FSH-secreting tumours cause testicular enlarge- ment in men and ovarian hyperstimulation syndrome in premeno- pausal women. Treatment includes surgical excision combined or not with radiotherapy. PRL PRL is released by the lactotroph cells of the adenohypophysis. It is composed of 199 amino acids and has three disulphide intramo- lecular bonds. Its molecular structure is similar to GH and to pla- cental lactogen with which it shares a common phylogenetic origin. PRL physiology differs from that of other anterior pituitary hor- mones in that its secretion is mainly under tonic inhibition (affecting both synthesis and release) by dopamine released from the hypo- thalamus. Hypothalamic stressors, such as the insulin tolerance test, are able to release PRL and exogenous administration of TRH re- leases PRL in addition to TSH, operating through specific lactotroph receptors. Oestrogens induce hyperplasia of the lactotroph cells and enhance PRL secretion. The increase in pituitary volume in preg- nant women may be in part due to the large oestrogenic production by the fetoplacental unit. In the third trimester, PRL concentrations may rise as high as 8000 mU/litre. During pregnancy, the develop- ment of the synthetic and secretory potential of the breast appar-

atus is under the influence of several hormones (oestrogen, insulin, cortisol, placental mammotrophic hormones). Before delivery, lac- tation is inhibited by high levels of oestrogen and progesterone. The rapid fall of these hormones after delivery allows PRL to initiate lac- tation. After delivery, maternal levels of PRL fall if there is no breast- feeding, but remain increased in response to suckling. Conditions associated with hyperprolactinaemia are shown in Box 13.2.1.2. PRL receptors have a wide distribution in the body. They are mostly found in the mammary gland and their activation is respon- sible for the initiation and maintenance of physiological lactation. In mammary tissue primed with oestrogens and progesterone, PRL induces the synthesis of milk proteins. The actions of PRL at other sites have not been clarified; it has been suggested that PRL is also involved in the immune functions. Disorders of PRL secretion PRL deficiency A clinical syndrome associated with PRL deficiency is not recog- nized and the only known manifestation of PRL deficiency is the inability to lactate following delivery. Prolactinomas Prolactinomas are pituitary adenomas expressing and secreting PRL. They are the most common pituitary adenomas with an estimated prevalence in the adult population of 44 per 100 000 people. Their frequency varies with age and sex; between the ages of 20 and 50 years they are most commonly diagnosed in women. In the paediatric/ado- lescent age group, prolactinomas are rare but represent about half of all pituitary adenomas. Most of the prolactinomas are small, intrasellar tumours. Occasionally, they can be aggressive or locally invasive and cause compression of vital structures. Malignant prolactinomas that are resistant to treatment and disseminate inside and outside the central nervous system are very rare. Mixed GH-secreting and PRL- secreting tumours are well recognized and are usually associated with acromegaly and hyperprolactinaemia. Occasionally, prolactinomas may be a component of multiple endocrine neoplasia1 (MEN1); they are the most common pituitary adenomas in this syndrome). Box 13.2.1.2 Causes of hyperprolactinaemia Physiological • Stress • Pregnancy • Lactation • Nipple stimulation/suckling • Sexual intercourse • Sleep Drugs (commonly used in clinical practice) • Antipsychotics–neuroleptics (e.g. phenothiazines, butyrophenones) • Antidepressants (e.g. tricyclic and tetracyclic antidepressants, mono- amine oxidase inhibitors, selective serotonin reuptake inhibitors) • Opiates • Cocaine • Antihypertensive medications (e.g. verapamil, methyldopa, reserpine) • Gastrointestinal medications (e.g. metoclopramide, domperidone) • Protease inhibitors? • Oestrogens Pathological • Primary hypothyroidism • Hypothalamic–pituitary disease — Hypothalamic tumours — Granulomatous disease (sarcoidosis, tuberculosis, Langerhans cell histiocytosis) — Cranial irradiation — Pituitary stalk section (e.g. following surgery) — Prolactinoma — Mixed GH/PRL-secreting adenoma — Tumours causing stalk compression • Renal or hepatic failure • Polycystic ovarian syndrome • Chest wall stimulation (e.g. repeated breast self-examination, following herpes zoster infection) • Ectopic secretion (e.g. bronchogenic carcinoma, hypernephroma)

 Presentation The clinical features of a prolactinoma predominantly result from hyperprolactinaemia. These include galactorrhoea and primary (in children) or secondary hypogonadism (in men, impo- tence, infertility, and decreased libido; in women, oligomenorrhoea/ amenorrhoea and infertility). Hyperprolactinaemia interrupts the pulsatile secretion of gonadotropin-releasing hormone, in- hibits the release of LH and FSH, and directly impairs gonadal steroidogenesis. In the case of large tumours, symptoms related to pressure effects may also be present. Most prolactinomas in women are microadenomas. Men usually present with larger tumours and neurological manifestations probably due to the delayed recognition of symptoms associated with the high PRL levels. Postmenopausal women with hyperprolactinaemia are often recognized only when a large adenoma produces mass effects.

Investigations When evaluating a patient with persistently ele- vated serum PRL, secondary causes of hyperprolactinaemia should first be ruled out by a careful clinical history, physical examination, pregnancy test, routine biochemical analysis (to assess kidney and liver function), and TSH measurement. If the patient is on a medi- cation known to increase serum PRL, it is important to determine if the drug is indeed the cause by withdrawing it (if this can be done safely). When the drug cannot be stopped, the evaluation should include MRI of the sella to exclude a mass lesion. In the case of prolactinomas, serum prolactin levels usually parallel tumour size. PRL values between the upper limits of normal and 100 mg/litre (2000 mU/litre) may be due to psychoactive drugs, oestrogen, func- tional (idiopathic) causes, or microprolactinoma. Macroadenomas are typically associated with levels of more than 250 mg/litre (5000 mU/litre). It should be stressed, though, that such values are not absolute; prolactinomas may present with variable elevations in PRL and there may be dissociation between tumour mass and hor- monal secretion. Furthermore, the interpretation of a moderate elevation of PRL in a patient with a pituitary macroadenoma needs to be done cautiously, as the hyperprolactinaemia may be attrib- uted to compression of the pituitary stalk by a tumour other than a prolactinoma. Recent data suggest that serum PRL of more than 2000 mU/litre is almost never encountered in nonfunctioning pi- tuitary macroadenomas. Values above this limit in the presence of a macroadenoma are probably associated with a prolactinoma (after acromegaly or Cushing’s disease have been excluded). Alternatively, the empirical confirmation of the diagnosis can be obtained by treat- ment for several months with dopamine agonists with serial assess- ment of serum PRL levels and adenoma size. Normalization of PRL combined with a substantial reduction of the initial adenoma size confirms the diagnosis of a prolactinoma. Normalization of PRL with no change or only a small reduction in tumour volume may suggest a pituitary adenoma other than a prolactinoma. No change in serum PRL and no reduction in tumour volume indicate a drug- resistant prolactinoma (5% to 10% of cases). Two potential pitfalls in the diagnosis of a prolactinoma should always be taken into account: (1) the presence of macroprolactin and (2) the ‘hook effect’. Macroprolactin is a complex of PRL and, gen- erally, an immunoglobulin G antibody. Serum PRL concentrations are increased due to the reduced rate of clearance of this complex. Macroprolactin has reduced bioactivity and is present in signifi- cant amounts in up to 20% of hyperprolactinaemic sera, resulting in pseudohyperprolactinaemia and the potential for misdiagnosis (thus, macroprolactinaemia is suggested in the presence of high PRL levels with no menstrual irregularities). For confirmation of macroprolactinaemia, polyethylene glycol precipitation is the most practical method. The ‘hook effect’ may be observed in cases of very high serum PRL concentrations, such as those observed in giant prolactinomas. The high levels of circulating PRL causes antibody saturation in the immunoradiometric assay, leading to artefactually low results. To overcome this effect, an immunoradiometric PRL assay should be performed at a serum dilution of 1:100 or, alter- natively, should include a washout between the binding to the first antigen and the second step in order to eliminate excess unbound PRL. Currently, dynamic tests of PRL secretion are not used in clin- ical practice. Treatment The primary goal of therapy in patients with microprolactinomas is to restore gonadal and sexual function by normalizing PRL levels. In patients with macroadenomas, reduc- tion of tumour size is also important. Dopaminergic agonists such as cabergoline, bromocriptine, pergolide, and quinagolide are the primary therapy. Bromocriptine, pergolide, and cabergoline are all ergot derivatives. The only non-ergot derivative that is used in clinical practice is quinagolide. These drugs normalize PRL levels and significantly reduce the volume of the tumour in most pa- tients. Dopamine inhibition of PRL secretion is mediated by the D2- dopamine receptors expressed by normal and tumorous lactotrophs. For microprolactinomas, bromocriptine is successful in 80% to 90% of patients in

normalizing serum PRL levels, restoring gonadal func- tion, and shrinking tumour mass. For macroprolactinomas, normal- ization of serum PRL levels and tumour shrinkage occur in about 70% of patients. Tumour shrinkage can often be observed within a week or two after commencing treatment, but in some cases may not be observed for several months. Continued tumour shrinkage may occur for many months or even years. Visual field defects im- prove in most patients. The therapeutic doses are in the range of 2.5 to 15 mg/day and most patients respond while on 7.5 mg/day or less. Cabergoline is effective in most patients, including those who did not previously respond to bromocriptine. Normalization of serum PRL has been reported in 86% of cases (92% with idio- pathic hyperprolactinaemia or microprolactinoma, and 77% with macroprolactinoma). Following 12 to 24 months of treatment with cabergoline, a greater than 20% decrease of baseline tumour size has been reported in more than 80% of cases, with complete disappear- ance of tumour mass in 26% to 36% of them. The initial dose of cabergoline is 0.5 mg once weekly and doses up to 1 mg twice weekly are usually effective. Large comparative studies of cabergoline and bromocriptine have suggested the superiority of cabergoline in terms of patient tolerability and convenience, reduction in serum PRL, res- toration of gonadal function, and decrease in tumour size. Although there is less experience with pergolide and quinagolide in the pri- mary treatment of patients with prolactinomas, these drugs appear to have similar efficacy and adverse event profiles when compared with bromocriptine. The adverse effects of dopamine agonists may be grouped into gastrointestinal (most commonly nausea, vomiting, constipation, dry mouth, dyspepsia), cardiovascular (most com- monly postural hypotension, digital vasospasm causing blanching of the extremities in response to cold), and neurological (headache and drowsiness). Other less common adverse effects are psychiatric manifestations (including psychosis and hypomania), cerebrospinal

 fluid rhinorrhoea (due to tumour shrinkage and an eroded pituitary sellar floor), leg cramps, flushing, and nasal congestion. Symptoms tend to occur after the initial dose and with dosage increases, but can be minimized by introducing the drug at a low dosage at bedtime, by taking it with food, and by very gradual dose escalation. Rarely, in patients with Parkinson’s disease treated with very high doses of bromocriptine, pulmonary infiltrates, fibrosis, pleural effusions, pleural thickening, and retroperitoneal fibrosis have been reported; however, these effects are dose-dependent and are unlikely to occur at the low doses used for the treatment of prolactinomas. Recently, the occurrence of valvular insufficiency in patients who have been treated with high doses of cabergoline or pergolide for Parkinson’s disease has been described. Nonetheless, the relevant literature on patients with prolactinoma (managed with lower doses that those used in Parkinson’s patients) is generally reassuring. When a patient does not respond adequately to a dopamine agonist, the prolactinoma is considered resistant. For these patients possible treatment approaches include a trial of an alternative dopamine agonist, escalation of the dopamine agonist beyond conventional doses, surgical tumour resection, or radiotherapy. Trans-sphenoidal surgery does not reliably lead to a long-term cure, and recurrence of hyperprolactinaemia is frequent. The surgical outcomes are highly dependent on the experience of the neurosurgeon, the size of the tumour, and the serum PRL levels. The success rate of surgery in microadenomas is about 75% and for macroprolactinomas approxi- mately 34%. The indications for surgery mainly include resistance or intolerance to medical therapy and unstable pituitary apoplexy. The very high rate of efficacy of dopamine agonists combined with the high complication rates of radiotherapy render treatment with this modality rarely necessary; it is reserved for patients who do not re- spond to dopamine

agonists, those who are not cured by surgery, or for malignant prolactinomas. When beginning dopaminergic treatment, women must be warned that restoration of fertility may be immediate (even before their first normal menstruation). In women with a macroprolactinoma wishing to become pregnant, it is necessary to plan conception to occur after the normalization of the serum PRL and the significant reduction of the adenoma size. The considerable experience with patients taking bromocriptine during pregnancy suggests that the incidence of abortions, ectopic pregnancies, or congenital malfor- mations is no higher than that in the general population. The experience with cabergoline is less, but there is no evidence to suggest that such treatment may be unsafe. The relevant information on pergolide and quinagolide is much more limited and, therefore, they should not be used in pregnancy or when pregnancy is desired. Given that for women with microprolactinomas the risk of clinic- ally relevant tumour expansion is less than 2% during pregnancy, dopamine agonists can be safely stopped as soon as pregnancy has been confirmed. The patients need to be advised to report severe headaches or visual deterioration. In women with macroadenomas, symptomatic tumour expansion occurs in 20 to 30% of them; man- agement options include stopping the dopamine agonist when preg- nancy is confirmed with close surveillance thereafter, or continuing the dopamine agonist throughout the pregnancy. If visual field de- fects or progressive headaches develop, an MRI without gadolinium (not a CT) should be performed, and if the tumour has significantly increased in size, a dopamine agonist should be restarted. If the en- larged tumour does not respond to medical treatment, alternatives include delivery if the pregnancy is far enough advanced or trans- sphenoidal surgery. There are no data to suggest that breastfeeding leads to prolactinoma enlargement. Treatment withdrawal When the serum PRL has been normal for at least 2 years and the size of the tumour decreased by more than 50%, the dose of the dopamine agonist can be gradually decreased, as at this stage low doses are likely to maintain stable PRL levels and tumour size. After pregnancy, normoprolactinaemia may occur. Women with hyperprolactinaemia who pass through the meno- pause require reassessment of the need for continuing treatment. If a patient has normal PRL levels after treatment with dopamine agonists for at least 5 years and the tumour volume is markedly de- creased, a trial of tapering and discontinuation of these drugs may be initiated. In such cases, careful monitoring for detection of recur- rence of hyperprolactinaemia and tumour enlargement in advised. ACTH ACTH is a single chain 39-amino acid peptide released by the corticotroph cells. The initial synthesis is of a larger 231-amino acid peptide (pro-opiomelanocortin, POMC) that following proteo- lytic cleavage produces several peptides and hormones, including ACTH, melanocyte-stimulating hormone, and β-endorphin. ACTH is secreted in a pulsatile manner. The secretion is under positive hypothalamic control by the corticotropin-releasing hormone, which exerts tropic and releasing actions on the corticotroph cells. Arginine vasopressin also stimulates ACTH release acting synergis- tically with corticotropin-releasing hormone. ACTH exerts a nega- tive feedback effect at the hypothalamic level. ACTH and cortisol secretion follow a diurnal rhythm, with highest amounts in the early morning and lowest concentrations around midnight. The secretory bursts start at around 3.00 a.m. and are maximal in the last few hours before waking up. This pattern is mainly regulated by the light–dark and the sleep–wake cycles and may be altered by a major time shift. Any stressful event may induce a large discharge of ACTH into the circulation followed by a similar increase in the release of cortisol. Serum cortisol exerts feedback regulatory action on the pituitary but also at the hypothalamic level reducing ACTH release. This nega- tive feedback may be imitated by synthetic glucocorticoids such as dexamethasone. The first 24 amino acids of the ACTH are identical across species and are associated with its biological activity. ACTH acts through G protein-coupled receptors predominantly found in the fascicular and reticular zones in the adrenal cortex where it

stimulates the se- cretion of glucocorticoids and androgens. It also contributes to the release of mineralocorticoids. ACTH is also responsible for the maintenance of the adrenal growth and size. Disorders of ACTH secretion ACTH deficiency Chronic ACTH deficiency is associated with fatigue, pallor, an- orexia, weight loss, hypotension, hyponatraemia, hypoglycaemia, and eosinophilia. Children may present with delayed puberty and failure to thrive. In its most severe form, when left untreated, it may be fatal due to vascular collapse especially during superim- posed illness. In contrast to primary adrenal insufficiency, in which the ACTH levels are increased, there is no hyperpigmentation or hyperkalaemia.

 Given the diurnal rhythm of ACTH and cortisol secretion, random serum cortisol measurements are not always helpful in the diagnosis of ACTH deficiency. It has been proposed that sec- ondary adrenal insufficiency is present when morning cortisol con- centrations are less than 100 nmol/litre (in the absence of previous steroid treatment); values greater than 500–550 nmol/litre exclude this diagnosis. Levels between these values need a stimulation test. Hypoglycaemia (blood glucose <2.2 mmol/litre) induced by the in- sulin tolerance test is considered the gold standard for the assessment of the entire hypothalamic–pituitary–adrenal axis. A maximum cor- tisol response to a peak concentration greater than 500–550 nmol/ litre generally excludes adrenal insufficiency. ACTH deficiency causes adrenal atrophy and ACTH-receptor downregulation. Based on these, the standard 250 μg (1–24) ACTH (Synacthen) test may be useful for the diagnosis of secondary adrenal insufficiency, if done at least 4 weeks after the onset of ACTH deficiency. Stimulated cor- tisol concentrations at 30 min of 500–550 nmol/litre or less suggest ACTH deficiency. Other tests checking the ACTH reserve, which are less commonly used, include the glucagon and the metyrapone test. Glucocorticoid deficiency can be life-threatening and, therefore, substitution should begin as soon as the diagnosis is confirmed. The replacement involves the administration of hydrocortisone or other steroids (prednisolone or dexamethasone) in a dose and timing to mimic the normal pattern of cortisol secretion. The most commonly used regime involves 10 to 25 mg hydrocortisone/day; it is divided into two or three doses/day (e.g. 10 mg, 5 mg, and 5 mg). There is no reliable biochemical test to assess the adequacy of replacement and the least dose necessary to relieve clinical symptoms is recom- mended. All patients should be supplied with an emergency card or bracelet giving information about their diagnosis, and instructions on stress-related dose adjustments should be clearly offered. In case of vomiting or during the perioperative period, parenteral steroid administration is needed. GH replacement may unmask ACTH de- ficiency and glucocorticoid replacement may unmask underlying diabetes insipidus. Cushing’s disease Cushing’s disease refers to the chronic exposure to endogenous glucocorticoids (Cushing’s syndrome) produced by the adrenal cortex caused by excess ACTH production by a pituitary corticotroph adenoma (see ‘Pituitary adenomas’ and ‘Pituitary carcinomas’, next). Nelson’s syndrome Nelson’s syndrome is defined by the association of an expanding pituitary tumour and high levels of ACTH secretion after bilateral adrenalectomy for Cushing’s disease. Its prevalence ranges from 8% to 29% with a time interval between adrenalectomy and the diagnosis of the syndrome of 0.5 to 24 years (most com- monly thought to be within 2 years). Apart from high basal ACTH levels after adrenalectomy and the presence of a pituitary adenoma remnant after adrenalectomy, there is no general agreement on the predictive factors for the development of Nelson’s syndrome. Notably, pituitary irradiation prior to adrenalectomy has been found to be protective in some studies, but not all. The clinical manifest- ations include those from the mass effect (headaches, deterioration of vision, ophthalmoplegia) and hyperpigmentation as a result of the increased ACTH levels. Early diagnosis

is important and moni- toring with measurement of ACTH levels and pituitary imaging at 6 months and yearly after the adrenalectomy are recommended. Cases of pituitary tumour with distant metastases have also been described. Treatment should be aggressive and includes surgical ex- cision and pituitary irradiation. TSH TSH is a glycoprotein hormone consisting of two noncovalently bound subunits: the α subunit, which is common to all anterior pi- tuitary glycoprotein hormones and the β subunit, which is unique for TSH and confers its biological specificity. The α subunit has a molecular weight of 20 to 22 kDa, is composed of 92 amino acid res- idues, and contains two N-linked carbohydrate groups. The β sub- unit has a molecular weight of 18 kDa, is composed of 110 amino acid residues, and contains one N-linked complex carbohydrate. The glycosylation is important for the normal bioactivity of TSH. TSH is secreted in a pulsatile manner (with low amplitude peaks), as well as in a circadian fashion (with elevation in the late hours of the evening). The hypothalamic tripeptide TRH stimulates TSH release, whereas thyroid hormones exert a negative feedback at the hypo- thalamic and pituitary levels. Somatostatin and dopamine inhibit TSH secretion. TSH binds to specific thyroid cell plasma membrane receptors and regulates both synthesis and secretion of thyroid hormones. Disorders of TSH secretion TSH deficiency Central hypothyroidism is diagnosed when the concentrations of thyroxine are decreased and the TSH levels are usually normal or low. The clinical manifestations include tiredness, cold intolerance, constipation, hair loss, dry skin, hoarseness, cognitive slowing, leth- argy, weight gain, bradycardia, facial puffiness, delayed relaxation phase of the deep tendon reflexes, and hypotension. In children, de- velopmental delay and growth retardation are also present. TSH de- ficiency is treated with l-thyroxine with the aim of achieving normal serum free thyroxine levels (serum TSH cannot be used as a guide of adequate replacement). An increase in the dose of l-thyroxine may be necessary during pregnancy or new oestrogen or GH re- placement. As thyroid hormone replacement increases the rate of metabolism of glucocorticoids and may therefore lead to an adrenal crisis in cases of coexisting hypoadrenalism, thyroxine should be ad- ministered after hydrocortisone substitution has been initiated. Thyrotropinomas TSH-secreting pituitary adenomas account for less than 1% of all pi- tuitary adenomas with an overall prevalence of about 1 in one million of the population. They show no gender difference and the majority are diagnosed between the third and sixth decade of life. The signs of thyrotoxicosis may vary from severe to absent. More than 90% of the patients present with goitre. Compression features including head- aches and visual field defects due to tumour invasion or suprasellar extension may be also present. Coexistent oversecretion of other pi- tuitary hormones may also occur resulting in additional symptoms. The biochemical profile of TSH-secreting pituitary adenomas in- cludes elevated circulating thyroxine with normal or increased TSH levels (as opposed to undetectable levels of TSH in Graves' disease, which causes primary hyperthyroidism). Other markers of thyroid hormone action may be increased as well, such as sex hormone- binding globulin, cholesterol, angiotensin-converting enzyme, or

 C-terminal cross-linked telopeptide of type 1 collagen. Most tu- mours are macroadenomas. Diagnosis It is essential to differentiate a TSH-secreting pituitary adenoma from the syndrome of pituitary resistance to thyroid hormone, in which mutations in the gene coding for the thyroid hormone receptor β prevent the detection of peripheral thyroid hormones by the pituitary resulting in increased levels of TSH and hyperthyroidism. While it is mainly the pituitary gland being in- sensitive to thyroid hormones, other tissues do not show resistance to thyroid hormones in this form of the syndrome. Detection of a mutation in the gene coding for thyroid hormone receptor β con- firms the diagnosis.

Nevertheless, in about 10% of patients, no muta- tions can be found. The combination of the TRH stimulation test, α subunit levels, and the α subunit/TSH ratio are helpful in the differ- ential diagnosis. Thus, in cases of TSH-secreting pituitary adenoma, the α subunit level is increased, the molar ratio of α subunit to TSH is more than 1.0, and TRH administration is associated with a less than twofold increase of TSH. Treatment The first-line therapy for patients with TSH-secreting pituitary adenoma is trans-sphenoidal resection of the tumour, after which about one-third of all patients will be cured. If surgery is contraindicated or declined, the administration of somatostatin analogues should be considered. About 85% of the patients re- spond to somatostatin analogues with decrease of thyroxine levels. Occasionally, external pituitary irradiation is indicated. Criteria of cure go beyond the establishment of euthyroidism and include the normalization of α subunit levels, α subunit/TSH ratio, peripheral markers of thyroid hormone action, and dynamic tests, as well as pi- tuitary imaging. Long-term follow-up including clinical, biochem- ical, and radiological monitoring is mandatory. Hypopituitarism Hypopituitarism, first described by Simmonds in 1914, results from the decreased secretion of pituitary hormones. It is caused by an inability of the gland to produce hormones and/or an insufficient supply of hypothalamic-releasing hormones. It is associated with an increased mortality (with causes of premature mortality being cardiovascular and cerebrovascular disease) and its main causes are shown in Box 13.2.1.3. The clinical manifestations of hypopituitarism depend mainly on the underlying disease, as well as the type and degree of the hor- monal deficits. Tumoural masses in the sellar region with suprasellar extension may be associated with visual impairment, headaches, oculomotor nerve palsy, or damage to other cranial nerves within the cavernous sinus. Hypopituitarism may be subclinical, diagnosed only following hormonal investigations, or of acute and severe clin- ical onset requiring hospital admission. ACTH, TSH, and antidiur- etic hormone deficiency are potentially life-threatening, whereas FSH/LH and GH deficiencies are associated with chronic morbidity. The clinical manifestations and the diagnosis and treatment of each pituitary hormone deficit are described in previous paragraphs. It should be noted that as thyroid hormone replacement increases the rate of metabolism of the glucocorticoids and may lead to an adrenal crisis, glucocorticoid substitution should begin before thyroid hor- mone treatment is offered.
Pituitary adenomas Pituitary adenomas are the most common cause of pituitary dis- ease. They are benign lesions arising from adenohypophyseal cells and account for up to 25% of intracranial tumours. Based on their secretory activity, they are classified as functioning (resulting in the syndromes of hormonal excess previously described) and non- functioning (presenting with mass effects). Tumours measuring less than 10 mm in diameter are considered microadenomas and those larger than 10 mm macroadenomas. Immunohistochemically they are grouped according to their hormone content; generally, the clinical classification overlaps the histopathological one. On CT, macroadenomas are isodense or hypodense relative to brain tissue with variable patterns of enhancement after contrast administration. Calcification may be seen occasionally. On MRI, they have homoge- neous low intensity on T1-weighted images and, after contrast ad- ministration, homogeneous enhancement that is less intense than the enhancement in the adjacent pituitary. Cysts or areas of necrosis cause foci of moderate hypointensity on T1-weighted sequences, foci of hyperintensity on T2-weighted sequences, and heteroge- neous enhancement with gadolinium. Haemorrhage in the subacute or chronic phase shows high signal on T1-weighted images. On CT, microadenomas show little inherent contrast to the normal pituitary Box 13.2.1.3 Causes of hypopituitarism • Pituitary and nonpituitary tumours — Pituitary adenomas — Craniopharyngiomas — Meningiomas — Gliomas — Chordomas — Ependymomas — Primary or metastatic (especially lung and breast) cancer — Hamartomas — Germinomas — Optic gliomas •

Lymphocytic hypophysitis • Pituitary apoplexy • Sheehan’s syndrome (postpartum hypopituitarism) • Cranial irradiation • Pituitary surgery • Traumatic brain injury • Subarachnoid haemorrhage • Haemochromatosis • Granulomatous diseases — Sarcoidosis — Tuberculosis — Langerhans’ histiocytosis • Empty sella syndrome • Genetic causes Mutations of genes encoding transcription factors including HESX1 (homeobox gene expressed in embryonic stem cells 1), LHX3 (LIM-domain homeobox gene 3), LHX4 (LIM-domain homeobox gene 4), PROP1 (prophet of Pit1), POU1F1 (POU domain, class 1, transcription factor 1) • Infections • Abscess • Meningitis • Encephalitis

SECTION 13 Endocrine disorders 2274 tissue and intravenous contrast demonstrates nonenhancement against a background of normal gland enhancement. On MRI, they are hypointense on T1-weighted sequences and this contrast may or may not be amplified after gadolinium. The treatment of pituitary adenomas involves surgery, radio- therapy, or medical therapy and has been described in previous sections. Pituitary carcinomas Pituitary carcinomas are defined as pituitary tumours with sub- arachnoid, brain, or systemic metastasis. They account for less than 0.5% of symptomatic pituitary tumours. They mainly arise from the transformation of initially large, but benign, adenomas. Their pathogenetic mechanism remains unclear; it has been pro- posed that under the influence of unknown growth-enhancing stimuli, an early proliferative stage of polyclonality is followed by monoclonal or multiclonal mutations, leading to selective growth advantage and a state of invasiveness. Alterations in the function of oncogenes and/or tumour suppressor genes may also be impli- cated. Their malignant nature is not usually obvious in their micro- scopic appearance and the reliable distinction between carcinoma and adenoma is impossible on the basis of standard histological cri- teria. Their clinical manifestations are similar to invasive and non- invasive pituitary adenomas (pressure effects to the surrounding tissues and/or consequences of hormonal hypersecretion). The great majority of pituitary carcinomas are hormonally active, most commonly ACTH-secreting or PRL-secreting. No differ- ences in the hormone levels differentiating pituitary carcinomas from other invasive and/or noninvasive macroadenomas have been identified. Although on imaging pituitary carcinomas ap- pear as invasive macroadenomas, there are no reliable features distinguishing tumours that could behave in a malignant manner from other types of invasive adenomas. Metastases can occur in every part of the central nervous system (usually cortex, cere- bellum, and cerebellopontine angle) or in distant sites (usually liver, lymph nodes, bone, and lung). The treatment of pituitary carcinomas is similar to that of large and aggressive pituitary tumours and includes surgery, external beam radiotherapy, and adjuvant medical treatment (chemotherapy). In the last years, the alkylating agent temozolomide has been used for aggressive pituitary adenomas and carcinomas. The therapy of pitu- itary carcinoma is mainly palliative and may not prolong survival to any major extent (mean survival after the development of metastatic disease is reported to be less than 4 years). Pituitary apoplexy Pituitary apoplexy is a clinical syndrome resulting from acute haemorrhage or infarction of the pituitary gland. It is potentially life-threatening and is characterized by the sudden onset of head- ache, vomiting, visual disturbance, ophthalmoplegia, and altered consciousness. This constellation of findings occurs primarily in patients with pre- existing pituitary adenomas and can be due to ex- tensive tumour infarction or haemorrhage. The term has also been used to describe spontaneous infarction and haemorrhage within a nontumorous pituitary gland with similar clinical effects. The age range of occurrence is broad, from the first to the ninth decade. The incidence of pituitary apoplexy presenting with classic symptoms is reported to be in the order of 0.6 to 9.1% of surgically treated pi- tuitary adenomas. However, clinically silent pathological evidence of pituitary haemorrhage (‘subclinical pituitary

apoplexy') has been reported in up to 25% of surgically removed pituitary aden- omas. The clinical syndrome of pituitary apoplexy usually evolves fully within hours to 2 days and its pathophysiology remains un- certain. Predisposing factors for pituitary apoplexy include major surgery, warfarin, aspirin, arterial hypertension, oral contraceptive pill, gonadotropin-releasing hormone analogue, dynamic pituitary function tests, and head trauma. A variety of pituitary tumours, both endocrinologically active and inactive, have been documented in association with pituitary apoplexy, but opinions differ as to whether there is a predominance of a particular type of pituitary tu- mour. Following apoplexy, hypofunctioning (partial or complete) of normal pituitary tissue appears to be the rule. Hyponatraemia, noted in 44% of patients, may be caused either by inappropriate antidiur- etic hormone secretion, hypocortisolism, or hypothyroidism or by a combination of these. On pituitary MRI performed in the first 3 to 5 days, the haemorrhage within the sella is isointense or hypointense on T1-weighted images and hypointense on T2-weighted sequences. When pituitary apoplexy is suspected, the initial management con- sists of close monitoring of fluid and electrolyte balance coupled with immediate replacement of deficient hormones, in particular corticosteroids. Although not widely accepted, it has been suggested that in patients with visual field or visual acuity defects, surgical de- compression should be performed as soon as possible, preferably within the first week, as this appears to optimize visual outcome and to improve pituitary function. Following apoplexy, the risk of tu- mour recurrence is small, but careful follow-up initially with annual imaging is indicated. Craniopharyngiomas Craniopharyngiomas are epithelial tumours (grade I, World Health Organization classification) arising along the path of the craniopharyngeal duct (the canal connecting the stomodeal ectoderm with the evaginated Rathke's pouch). Their overall in- cidence is 0.13 per 100 000 person-years and they account for 2 to 5% of all the primary intracranial neoplasms (5.6–15% of the intracranial tumours in children). They may be diagnosed at any age (peak incidence rates between 5 and 14 years and 50 and 74 years). Histologically, two primary subtypes have been recog- nized, the adamantinomatous and the papillary, but transitional or mixed forms have also been described. The adamantinomatous craniopharyngioma is the most frequently reported and may be diagnosed at all ages. Macroscopically, it shows cystic and/or solid components, necrotic debris, fibrous tissue, and calcification. The liquid within the cysts ranges from 'machinery oil' to shimmering cholesterol-laden fluid and it is mostly composed of desquamated squamous epithelial cells, rich in membrane lipids and cytoskel- eton keratin. In this subtype, the flat squamous epithelial cells may be desquamated in distinctive stacked clusters forming the path- ognomonic nodules of 'wet' keratin. The papillary subtype has been almost exclusively found in adult patients. Macroscopically

 it is usually solid or mixed, calcification is rarely seen, and the cyst content is mostly viscous and yellow. Mutations in CTNNB1, encoding β-catenin and in the BRAF gene have been identified in craniopharyngiomas and their significance in the pathogenesis of these tumours remains to be established. Presentation Most of the craniopharyngiomas are detected in the sellar/parasellar region (a suprasellar component is present in 94–95% of cases). They may exert pressure effects to various brain structures resulting in multiple clinical features (neurological, visual, hypothalamo- pituitary); headaches, nausea/vomiting, visual disturbances, growth failure (in children), and hypogonadism (in adults) are the most frequently described symptoms. A substantial number of patients present with compromised hypothalamo-pituitary function; re- ported rates for pituitary hormone deficits include 35 to 95% for GH, 38 to 82% for FSH/LH, 21 to 62% for ACTH, 21 to 42% for TSH, and 6 to 38% for antidiuretic hormone. Useful imaging tools for the diagnosis of craniopharyngiomas include plain

skull radio- graphs, CT, MRI, and, occasionally, cerebral angiography. The con- sistency of the tumours is purely or predominantly cystic in 46% to 64%, purely or predominantly solid in 18% to 39%, and mixed in 8% to 36%. Calcification is present in 45% to 57% and is probably more common in children (78–100%). Hydrocephalus has been re- ported in 20% to 38% and is probably more often seen in childhood populations (41–54%). Plain skull radiographs may show calcifica- tion and an abnormal sella. CT is helpful for the evaluation of the bony anatomy, the identification of calcifications, and the discrim- ination of the solid and the cystic components (the cystic fluid is hypodense and the solid portions, as well as the cyst capsule show enhancement following contrast administration). The MRI is useful for the topographic and structural analysis of the tumour. A solid lesion appears isointense or hypointense relative to the brain on precontrast T1-weighted images, shows enhancement following gadolinium administration, and is usually of mixed hypointensity or hyperintensity on T2-weighted sequences. Large amounts of cal- cification present as areas of low signal on both T1-weighted and T2-weighted images. A cystic element is usually hypointense on T1- weighted sequences and hyperintense on T2-weighted sequences. On T1-weighted images a thin peripheral contrast-enhancing rim of the cyst is demonstrated. Protein, cholesterol, and methaemo- globin may cause high signal on T1-weighted images. The differen- tial diagnosis includes several sellar or parasellar lesions, including Rathke's cleft cyst, dermoid cyst, epidermoid cyst, pituitary ad- enoma, germinoma, hamartoma, suprasellar aneurysm, arachnoid cyst, suprasellar abscess, glioma, meningioma, sarcoidosis, tubercu- losis, and Langerhans cell histiocytosis. Treatment Surgery combined or not with adjuvant external beam irradiation is currently the most widely used first therapeutic approach for these tumours. Craniopharyngiomas remain challenging tumours, even in the era of modern neurosurgery. This is mainly attributed to their sharp, irregular borders and to their tendency to adhere to vital neurovascular structures making surgical manipulations potentially hazardous to vital brain areas. Consequently, the at- tempted degree of excision has been a subject of long-standing debate. The advances in neuroimaging, microsurgical techniques, perioperative care, and hormone replacement therapy have signifi- cantly improved the perioperative mortality, which according to recent reports is between 1.7 and 5.4% for the primary operations. The mean interval for the diagnosis of recurrence following various primary treatment modalities ranges between 1 and 4.3 years. The recurrence rates following gross total removal range between 0 and 62% at 10 years follow-up and are significantly lower than those after partial or subtotal resection (25–100% at 10 years follow- up). In cases of limited surgery, adjuvant radiotherapy significantly im- proves the local control rates (recurrence rates 10–63% at 10 years follow-up). Finally, radiotherapy alone provides 10-year recur- rence rates ranging between 0 and 23%. For predominantly cystic tumours, fluid aspiration provides relief of the obstructive mani- festations and facilitates the consecutive removal of the solid tu- mour portion; the latter should not be delayed for more than a few weeks due to the significant risk of the cyst refilling. The man- agement of recurrent tumours remains difficult, as scarring and/ or adhesions from previous operations or irradiation decrease the chances of successful excision. In such cases, total removal is achieved at a substantially lower rate when compared with pri- mary surgery (0–25%) and is associated with increased periopera- tive morbidity and mortality (10.5–24%). The beneficial effect of radiotherapy (preceded or not by second surgery) in recurrent lesions is well established. Other treatment modalities include brachytherapy (stereotactically guided instillation of β-emitting isotopes into cystic craniopharyngiomas), intracystic installation of the antineoplastic agent bleomycin, stereotactic radiosurgery or radiotherapy, and systemic chemotherapy. Morbidity and mortality Craniopharyngiomas are associated with significant long-term mor- bidity (mainly endocrine,

visual, hypothalamic, neurobehavioural, and cognitive sequelae), which compromise normal psychosocial integration and quality of life. These complications are attributed to the damage to critical structures by the primary or recurrent tu- mour and/or to the adverse effects of the therapeutic interventions. In studies with variable follow-up periods and after different treat- ment modalities, the rates of individual hormone deficits range from 88 to 100% for GH, 80 to 95% for FSH/LH, 55 to 88% for ACTH, 39 to 95% for TSH, and 25 to 86% for ADH. Compromised vision has been reported in up to 62.5% of the patients treated by surgery combined or not with radiotherapy during observation periods of 10 years. Hypothalamic damage may result in hyperphagia and un- controllable obesity, disorders of thirst and water/electrolyte balance, behavioural and cognitive impairment, loss of temperature control, and disorders in the sleep pattern. Among these, obesity is the most frequent (affecting 26–61% of the patients treated by surgery com- bined or not with radiotherapy) and is a consequence of the dis- ruption of the mechanisms controlling satiety, hunger, and energy balance. Other rare long-term irradiation-attributed morbidities include vasculopathy and second brain tumours. The overall mor- tality rates of patients with craniopharyngioma have been reported to be 3 to 6 times higher than that of the general population. The 10- year survival rates range between 83 and 92.7% and are significantly lower in cases of recurrent disease. Apart from the deaths directly attributed to the tumour (pressure effects to critical structures) and to the surgical interventions, the risk of cardiovascular/cerebrovas- cular and respiratory mortality is increased.

 Hypophysitis Inflammatory processes of the hypophysis are classified as pri- mary, when the inflammation is confined to the pituitary gland with no identifiable aetiological association, and secondary, when the inflammatory pituitary reaction is triggered by a def- inite aetiological agent or a known systemic disease (local lesions such as germinomas, Rathke’s cleft cysts, craniopharyngiomas, or pituitary adenomas, or systemic diseases such as sarcoidosis, Langerhans cell histiocytosis, or tuberculosis). In the latter cases, the infiltrate is mainly lymphocytic or xanthogranulomatous and focuses around the lesion rather than diffusing to the entire gland. Drug-related autoimmune hypophysitis (e.g. after immune modulation using anticytotoxic T-lymphocyte-associated antigen 4 biological therapy) is a new form of hypophysitis being increas- ingly recognized under a spectrum of immune-related adverse events. Recently, IgG4-related hypophysitis has emerged as a part of IgG4-related disease with multiple coexisting organ involve- ment. Anti-PIT-1 hypophysitis is a newly described condition associated with a thymoma or other neoplasm that ectopically ex- presses PIT-1 protein. Primary hypophysitis is histologically classified into three types: granulomatous, xanthomatous, and lymphocytic. Granulomatous hypophysitis has an unclear pathogenesis, affects men and women in equal proportions, and presents with nausea, vomiting, dia- betes insipidus, and hyperprolactinaemia. It is characterized by diffuse collections of multinucleated giant cells and histiocytes with surrounding lymphocytes and plasma cells. Xanthomatous hypophysitis is an infiltrating process of the pituitary of unclear cause; it consists of cystic-like areas of liquefaction infiltrated by lipid-rich foamy histiocytes and lymphocytes. Lymphocytic hypophysitis is a rare condition, but insufficient population-based data exist to estimate its real incidence. Based on the published cases, women are affected more frequently than men in a ratio of about 5 to 1 or 8 to 1. It shows a striking temporal association with pregnancy, with most of these patients presenting in the last month of pregnancy (without causing complications to the fetus or the outcome of pregnancy) or in the first 2 months after delivery. Its clinical presentation is variable and comprises four categories of symptoms: sellar compression (headaches, visual disturbances, diplopia), hypopituitarism (mainly ACTH followed by TSH, gonadotropins, and PRL—it should be noted that the usual order of loss of

anterior pituitary hormones does not occur in patients with hypophysitis), diabetes insipidus, and hyperprolactinaemia. The defining pathological feature is the infiltration of the pituitary gland with lymphocytes. The immune infiltrate also contains other cells including plasma cells, eosinophils, macrophages, histiocytes, and neutrophils. The role of antipituitary antibodies remains to be established but their detection has amplified the diagnostic criteria, also suggesting a possible pathogenetic role. The mechanisms by which the infiltrate causes loss of function/destruction of the endo- crine cells or impairment of vasopressin release are not clear. It has been suggested that the disease progresses through various stages. Initially, the pituitary gland is inflamed, infiltrated by lymphocytes, and oedematous, causing mass effect symptoms; subclinical hypo- pituitarism may be present. If the inflammation resolves and the pituitary parenchyma is not destroyed, remission occurs. If the inflammation continues, the pituitary is replaced by fibrotic tissue, becomes atrophic, and loses its function. Even when using modern MRI studies, nearly 40% of the cases are misdiagnosed as pituitary adenomas. The typical precontrast MRI findings include a symmetrical enlargement of the pituitary gland, a thickened but rarely displaced stalk, and a usually intact sellar floor. The pattern of signal enhancement after gadolinium may be helpful in differentiating hypophysitis from macroadenoma. A strong and homogenous enhancement of the anterior pituitary gland is more suggestive of an inflammatory infiltrative process. A strip of enhanced tissue along the dura mater (‘dural tail’) has also been described. Macroadenomas enhance less or more slowly than the normal pi- tuitary on dynamic MRI. If the infundibuloneurohypophysitis is in- volved, there is the loss of T1 hyperintensity in the neurohypophysis, swelling of the posterior pituitary, and thickening of the pituitary stalk of more than 3 mm at the level of the median eminence of the hypothalamus. The treatment of this condition is controversial and includes re- placing the defective endocrine function and/or reducing the size of the pituitary mass. The role of surgery remains controversial; it should be performed only in the presence of serious and progressive deficits of visual fields, visual acuity, or ocular movements. It is also performed when a pituitary adenoma is suspected and the diagnosis is subsequently made by histology. Cases of spontaneous resolution without any treatment have been reported. Rathke’s cleft cysts Rathke’s cleft cysts are common benign sellar and/or suprasellar le- sions, found in 13 to 33% of routine autopsies. Symptomatic cases are rare and they probably arise from remnants of Rathke’s pouch, a structure apparent during the third week of gestation and formed by the infolding of the simple ciliated columnar epithelium lining the roof of the stomodeum. Rathke’s cleft cysts are smoothly marginated cysts with size usually ranging from a few millimetres to 1 to 2 cm. Their contents vary from a clear cerebrospinal fluid-like liquid to a thick mucoid material made up of cholesterol and protein. They are lined by single or pseudostratified cuboidal or columnar epithelium with or without cilia and with goblet cells. The presenting mani- festations are the result of compression to adjacent structures. The most frequent ones include headaches, hypopituitarism of varying degrees, hyperprolactinaemia, visual disturbance, and diabetes insipidus. Their imaging features are highly variable. Forty per cent are completely intrasellar, whereas 60% have some suprasellar ex- tension. On CT, the cyst density ranges from hypodense to isodense or is mixed. On MRI, they have a variable T1 signal (hyperintense, hypointense, or isointense) depending on their biochemical content. Cysts with high protein concentration show high T1 signal intensity and usually have a low intracystic water content leading to T2 signal decrease. Small intracystic nodules corresponding to proteinaceous concentrations may be demonstrated presenting with lower T2 and higher T1 signal intensity than the rest of the cyst. The nodules do not enhance and are virtually pathognomonic for Rathke’s cleft cysts. Symptomatic cases are managed by surgery. The risk of recur- rence following evacuation and biopsy ranges between 8 and 33%. Although not widely accepted, the extent of

removal (gross total vs. partial) may predict relapse.

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