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cortex Mark Sherlock and Mark Gurnell ESSENTIALS Three classes of steroid hormone are produced by the adrenal cortex after uptake of precursor cholesterol from the plasma— mineralocorticoids, glucocorticoids, and sex steroids—with classical endocrine feedback loops controlling their secretion. Adrenocortical diseases are relatively uncommon, but they have detrimental clinical consequences and can be treated effectively. Hormonal deficiency or excess is usually the result of abnormal secretion. Glucocorticoid excess Cushing's syndrome may be ACTH dependent (usually due to a pituitary adenoma, Cushing's disease) or ACTH independent (most often caused by an adrenal adenoma or exogenous glucocorticoid exposure). Clinical features—presentation may be with 'classical' manifestations of centripetal obesity, moon face, hirsutism, and plethora, with signs (when present) that best distinguish from simple obesity being bruising and muscle weakness (typically proximal), but cases may be more subtle. Diagnosis—the presence of Cushing's syndrome can be confirmed by finding one or more of elevated Urine free cortisol, elevated late-night salivary cortisol, or failure to suppress 09.00 h cortisol to less than 50 nmol/litre following a dexamethasone suppression test (1 mg overnight, or 2 mg/d for 48 h). ACTH-dependent causes can be distinguished from ACTH-independent causes by measurement of plasma ACTH (09.00 h sample). Determining whether elevated ACTH is coming from the pituitary (Cushing's disease) or from an ectopic source can be difficult, but may be achieved by consideration of plasma potassium, high-dose dexamethasone suppression test, a corticotropin-releasing factor test, and bilateral inferior petrosal sinus sampling/selective venous catheterization. Imaging—pituitary MRI is the investigation of choice once biochemical testing suggests Cushing's disease. In ectopic ACTH secretion, CT scanning of the neck, thorax, abdomen, and pelvis is required, often in

conjunction with isotope (functional) imaging. Adrenal CT scanning is required if biochemical testing suggests ACTH-independent Cushing's syndrome. Management—drugs that interfere with cortisol synthesis (e.g. metyrapone, ketoconazole) can lower cortisol levels, but definitive treatment depends on the cause: (1) adrenal adenomas—unilateral adrenalectomy; (2) Cushing's disease—trans-sphenoidal removal of the pituitary tumour; (3) ectopic ACTH—surgical removal of the tumour can lead to cure, but this is not always possible. Glucocorticoid deficiency
Glucocorticoid deficiency can be due to adrenal disease (primary, in which case mineralocorticoids and adrenal androgens are also deficient) or as a result of ACTH deficiency (secondary, in which case glucocorticoids and sex steroids are deficient). Aetiology—primary hypoadrenalism (Addison's disease) is most commonly caused by autoimmune disease (>70% cases in the Western world) or infection, for example, tuberculosis (the commonest cause worldwide). The commonest cause of secondary hypoadrenalism is stopping of exogenous glucocorticoid therapy or its inadequacy in stressful situations. Clinical features—primary adrenal failure may present (1) acutely—with hypotension and acute circulatory failure (Addisonian crisis); or (2) chronically—with vague features of ill health, sometimes including gastrointestinal symptoms, features suggestive of postural hypotension, and salt craving. Skin pigmentation is nearly always present in primary adrenal insufficiency (but not in secondary). 13.5 Adrenal disorders Acknowledgement: The chapter on disorders of the adrenal cortex in the fifth edition of this textbook was written by Professor P M Stewart. Some of his chapter is retained here.

SECTION 13 Endocrine disorders 2332 Biochemical diagnosis—this depends on an ACTH stimulation test: plasma cortisol should rise to over 450 nmol/litre (16.3µg/dl) in response to injection of tetracosactide (Synacthen, 250 µg) and failure to do so indicates adrenal insufficiency. Management—patients presenting acutely should be treated in a critical care setting with immediate intravenous hydrocortisone (100 mg, followed by 200 mg per 24 h). Appropriate fluid replacement and glucose/ electrolyte monitoring and treatment are also central to effective management, along with treatment of any precipitating condition. Long-term treatment requires glucocorticoid replacement in divided doses, with the largest dose on waking to mimic the circadian rhythm, and with the dose typically doubled in the event of intercurrent stress or illness. Patients should be supplied with, and trained in how to use, an emergency hydrocortisone injection. Mineralocorticoid replacement is usually required in primary adrenal failure. Every patient should be advised to wear a medical alert bracelet or necklace and to carry a 'steroid card'. Mineralocorticoid excess Primary aldosteronism (Conn's syndrome) accounts for between 5 and 10% of all hypertension and 20–25% of 'resistant hypertension'. The diagnosis is often challenging, but in the absence of confounding influences is suggested by a high random plasma aldosterone/renin ratio, especially if plasma aldosterone concentration is over 415 pmol/litre (15 ng/dl). The cause of primary aldosteronism can also be difficult to establish: adrenal MRI/CT scanning may demonstrate a unilateral adenoma but cannot exclude bilateral disease. Adrenal vein cannulation with sampling for estimation of aldosterone/cortisol ratio may be required to ensure appropriate lateralization. Treatment of a unilateral adrenal adenoma is by surgical excision and of bilateral adrenal hyperplasia is medical, usually with spironolactone. Several single gene defects can cause mineralocorticoid excess, including 17α-hydroxylase deficiency, 11β-hydroxylase deficiency, glucocorticoid-suppressible hyperaldosteronism, and apparent mineralocorticoid excess (mutations in 11β-hydroxysteroid dehydrogenase type 2 gene). Mineralocorticoid deficiency This is most commonly seen in the context of primary hypoadrenalism but is also caused (rarely) by conditions including primary

defects in aldosterone biosynthesis, defects in aldosterone action, and hyporeninaemic hypoaldosteronism (most commonly in the context of diabetic nephropathy or chronic interstitial nephritis). Introduction An initial rate-limiting step in adrenal steroidogenesis is the uptake of cholesterol from circulating cholesterol bound to low-density lipoprotein, by mitochondria in the adrenal cortex. This process is dependent upon steroidogenic acute regulatory (StAR) protein. Thereafter, the functional zonation of the adrenal cortex is in part achieved through the discrete expression and regulation of the genes for the final steroidogenic enzymes: aldosterone synthase (EC 1.14.15.5) in the zona glomerulosa, and 11 β -hydroxylase (EC 1.14.15.4) in the zona fasciculata (Fig. 13.5.1.1). Aldosterone acts physiologically to stimulate sodium transport across epithelial cells in the distal nephron, colon, and salivary gland. This involves the interaction of aldosterone with the mineralocorticoid receptor, and the induction of the expression of the genes for the basolateral Na⁺, K⁺ -ATPase pump and the apical sodium channel. This is mediated by the induction of SGK1, the gene for serum/glucocorticoid-regulated kinase 1. The mineralocorticoid receptor, however, is nonselective in vitro; paradoxically, cortisol and aldosterone have the same intrinsic affinity for the mineralocorticoid receptor, raising the question of why aldosterone is the preferred mineralocorticoid in vivo. This selectivity is achieved at a prereceptor level through the production of an enzyme, 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2; HSD11B2; EC 1.1.1.1.46), which efficiently inactivates cortisol to cortisone, allowing aldosterone to occupy the mineralocorticoid receptor. Inhibition of 11 β -HSD2 results in cortisol, conventionally regarded as a glucocorticoid, acting as a potent mineralocorticoid. Glucocorticoids have more diverse and extensive roles than mineralocorticoids, regulating sodium and water homeostasis, glucose and carbohydrate metabolism, inflammation, and stress. These effects are mediated by the interaction of cortisol with ubiquitous glucocorticoid receptors, and the induction or repression of target gene transcription (via glucocorticoid response elements, GREs). Adrenocortical diseases are most readily classified by whether they are characterized by hormone excess or deficiency (Table 13.5.1.1). Glucocorticoid excess: Cushing's syndrome Harvey Cushing first described a case of polyglandular syndrome secondary to pituitary basophilia in 1912, and several years later linked this to bilateral adrenal hyperplasia. The first case of an adrenal adenoma was probably reported by H G Turney in 1913 (Fig. 13.5.1.2). StAR Pregnenolone Cholesterol SCC Aldosterone ACTH Progesterone CYP 21 DOC 3 β -HSD CYP11 β 1 Corticosterone CYP11 β 2 Mineralocorticoid Zona Glomerulosa Zona Fasciculata Zona Reticularis CYP 17 17-OH-Pregnenolone 17-OH-Progesterone 11-Deoxycortisol Glucocorticoid DHEA A'dione Androgens CYP11 β 1 Cortisol CYP 17 Fig. 13.5.1.1 Pathways of adrenocortical steroid biosynthesis. Key: 3 β -HSD, 3 β -hydroxysteroid dehydrogenase; ACTH, adrenocorticotrophic hormone; CYP, cytochrome enzymes; DOC, deoxycorticosterone; SCC, side-chain cleavage enzyme; StAR, steroidogenic acute regulatory protein.

13.5.1 Disorders of the adrenal cortex 2333 Definition Cushing's syndrome comprises the symptoms and signs associated with prolonged exposure to inappropriately elevated levels of free plasma glucocorticoids. This definition thus takes into account the elevated corticosteroid levels that may be found in severely depressed patients, but which appear to be appropriate to the condition, and also the increased total (but normal free) glucocorticoid levels found when there is an increase in circulating cortisol-binding globulin (e.g. in patients on oral oestrogen therapy). The use of the term glucocorticoid in the definition covers both endogenous (cortisol) and exogenous steroid excess (e.g. prednisolone, fluticasone, budesonide, beclomethasone, dexamethasone, etc). The condition is most readily classified into ACTH-dependent and ACTH-independent causes (Table 13.5.1.2). The term 'Cushing's syndrome' is used to describe all causes, whereas 'Cushing's

disease' is reserved for cases of pituitary-dependent Cushing's syndrome. ACTH-dependent causes Cushing's disease. When iatrogenic causes are excluded, the most frequent cause of Cushing's syndrome is Cushing's disease, which accounts for approximately 70% of cases. The adrenal glands show bilateral adrenocortical hyperplasia, with widening of the zona fasciculata and zona reticularis. Nodules may form within the hyperplastic glands.

Table 13.5.1.1 Adrenocortical diseases

Glucocorticoid excess	Glucocorticoid deficiency
- Cushing's syndrome ACTH dependent - Cushing's disease (pituitary) - Ectopic ACTH production - ACTH independent - Exogenous glucocorticoid therapy - Adrenal tumours	- Primary Congenital adrenal hyperplasia (21-hydroxylase, P450 oxidoreductase, 3β-hydroxysteroid dehydrogenase, 17-hydroxylase, 11 β-hydroxylase, and StAR deficiencies) - Addison's disease - Hereditary adrenocortical unresponsiveness to ACTH - Secondary Postcorticosteroid therapy - Hypothalamic/pituitary disease
- Mineralocorticoids Excess - Primary aldosteronism (aldosterone) - Congenital adrenal hyperplasia (deoxycorticosterone) 11β-Hydroxylase deficiency 17α-Hydroxylase deficiency - Glucocorticoid receptor resistance (deoxycorticosterone) - Glucocorticoid receptor mutations - Metyrapone, RU486 ingestion - Deoxycorticosterone—secreting adrenal tumour - Liddle's syndrome 11 β-Hydroxysteroid dehydrogenase deficiency (apparent mineralocorticoid excess and liquorice and carbenoxolone ingestion) (cortisol) - Ectopic ACTH syndrome (cortisol) - Deficiency	- Addison's diseases - Congenital adrenal hyperplasia - Congenital adrenal hypoplasia - Disorders of terminal part of aldosterone biosynthetic pathway - Pseudohypoaldosteronism - Hyporeninaemia - Adrenal androgens Excess - Congenital adrenal hyperplasia (21-hydroxylase, 11 β-hydroxylase deficiency) - Polycystic ovary syndrome (PCOS) - Tumours - Deficiency - Congenital adrenal hyperplasia (17-hydroxylase, 3β-hydroxysteroid dehydrogenase deficiency) - Adrenal incidentalomas and carcinomas

Fig. 13.5.1.2 H.G. Turney's case of Cushing's syndrome before and after developing the condition.

SECTION 13 Endocrine disorders 2334 Cushing himself raised the question of whether his disease was a primary pituitary condition or secondary to an abnormality of the hypothalamus. There is abundant evidence to indicate that the condition is related to the pituitary rather than the hypothalamus. In over 90% of cases it is caused by a pituitary adenoma of monoclonal origin; basophilic hyperplasia is very rare, and selective surgical removal of the microadenoma usually results in remission. A somatic mutational hotspot is found in the USP8 gene in 30–60% of corticotrophinomas, resulting in impaired down regulation of the epidermal growth factor receptor (EGFR) which enables its constitutive signalling. Epidermal growth factor (EGF) is an important regulator of corticotroph function and its receptor is highly expressed in Cushing's pituitary tumours, where it leads to increased ACTH synthesis in vitro and in vivo. The mutational hotspot found in corticotrophinomas hyperactivates USP8, enabling it to rescue EGFR from lysosomal degradation and facilitate its stimulatory signalling.

Ectopic ACTH syndrome Cushing's syndrome may be caused by nonpituitary tumours producing ACTH, most commonly a malignant small-cell carcinoma of the bronchus (Table 13.5.1.3). However, the most challenging diagnostic problems relate to ACTH secretion from more benign and indolent neuroendocrine tumours (which may be very small), which may present with Cushing's syndrome many years before the occult tumour manifests, indeed in one large series 1 in 8 patients did not have identification of the source of ACTH secretion despite prolonged follow-up.

Ectopic production of corticotropin-releasing factor (CRF) This is a very rare cause of pituitary-dependent Cushing's disease. However, cases have been described in which a tumour (e.g. medullary thyroid, prostate carcinoma) has been shown to produce CRF.

ACTH-independent causes Iatrogenic Cushing's syndrome Estimates suggest that up to 3% of the population of the United Kingdom and United States are currently

taking glucocorticoid therapy. Long-term prescription rates for oral glucocorticoids have increased in recent decades, as has the use of inhaled, intranasal, and topical glucocorticoid therapy. In most cases, the doses of prescribed glucocorticoids are sufficient to cause hypothalamic–pituitary–adrenal (HPA) axis suppression (total daily doses >5 mg prednisolone or equivalent, Table 13.5.1.4). Glucocorticoid pre- scriptions are often extended for a sustained period of time; as a result, iatrogenic Cushing’s syndrome and subsequent suppression of the HPA axis may be frequent and potentially overlooked. In a recent study assessing rates of hypoadrenalism in patients receiving exogenous steroids there was a high percentage who failed a short Synacthen test, indicating suppression of endogenous cortisol se- cretion as one would see in patients who have iatrogenic Cushing’s syndrome. In patients who received oral or intravenous steroids the rate of failure on Synacthen testing was 44.3% and in those receiving inhaled, intranasal, or topical steroids 24.6%. While overt iatrogenic Cushing’s syndrome is clinically easy to diagnose, more subtle cases may often evade diagnosis. If left on long-term glucocorticoids, patients with ‘mild’ iatrogenic Cushing’s syndrome may develop all the adverse effects seen in patients with endogenous Cushing’s syndrome. Indeed, studies have shown that patients who receive exogenous glucocorticoids at doses 7.5 mg or more of prednisolone per day have increased cardiovascular mortality. Importantly other concomitant medications can increase the potency of exogenous glucocorticoids (e.g. drugs which inhibit glucocorticoid metabolism via cytochrome P450-3A4). Concomitant adrenal insufficiency is a clinically important factor in patients who develop iatrogenic Cushing’s syndrome. If these pa- tients have their steroids stopped abruptly, or if they are unwell and do not follow directions for stress dose steroids, they may develop an adrenal crisis. As such, if these patients are discontinuing their exogenous glucocorticoid therapy, they may require replacement doses of glucocorticoids until their hypothalamic–pituitary–adrenal axis recovers.

Table 13.5.1.2 Classification of causes of Cushing’s syndrome

ACTH dependent	ACTH independent
Cushing’s disease (pituitary-dependent)	Ectopic ACTH syndrome
Ectopic corticotrophin-releasing factor syndrome	Iatrogenic (treatment with ACTH1–39 or Synacthen®, ACTH1–24)
Iatrogenic (such as pharmacological doses of prednisolone, fluticasone, budesonide, beclomethasone, or dexamethasone)	Adrenal adenoma
Adrenal carcinoma	Carney’s complex
McCune–Albright syndrome	Aberrant receptor expression

Table 13.5.1.3 Tumours associated with the ectopic ACTH syndrome

Tumour type	Approximate incidence (%)
Small-cell lung carcinoma	50
Non-small-cell lung carcinoma	5
Pancreatic neuroendocrine tumours (NETs)	10
Thymic NETs	5
Lung NETs	10
Other NETs	2
Medullary carcinoma of thyroid	5
Phaeochromocytoma and related tumours	3
Rare carcinomas of prostate, breast, ovary, gallbladder, colon	10

Table 13.5.1.4 Equivalent anti-inflammatory effects of commonly used glucocorticoids

Anti-inflammatory effects equivalent to 20 mg hydrocortisone
5 mg prednisolone
25 mg cortisone acetate
0.75 mg dexamethasone
0.75 mg beclomethasone
4 mg methylprednisolone
4 mg triamcinolone
6 mg deflazacort

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Adrenal adenoma and carcinoma With the exclusion of iatrogenic Cushing’s syndrome, a solitary cortisol-secreting adrenal adenoma is the cause in about 10% of cases. Adrenal carcinomas are rare, have a poor prognosis, and may be associated with the secretion of other hormones in addition to cortisol (usually adrenal androgens) or may be ‘endocrine inactive’ (although steroid profiling often reveals evidence of excess adrenal corticosteroid production even in the absence of overt clinical features). Carney’s complex Carney complex (CNC) is a rare multiple neoplasia syndrome, inherited in an autosomal-dominant manner or occurring sporadically as a result of a de novo genetic defect, and first de- scribed by J. Aidan

Carney as 'the complex of myxomas, spotting pigmentation and endocrine over-reactivity'. It is characterized by pigmented lesions of the skin and mucosae, cardiac, cutaneous, and other myxomatous tumours, and multiple other endocrine (pituitary, adrenal, thyroid, gonads) and nonendocrine neoplasms (eye, breast, uterus, liver, bone). In patients with Carney complex who develop Cushing's syndrome the adrenal glands contain multiple small, pigmented nodules (primary pigmented nodular adrenocortical disease (PPNAD), see Fig. 13.5.1.3). Carney complex is associated with mutations in the regulatory subunit R1A of protein kinase A, PRKAR1A gene. PRKAR1A, which is situated at the 24.2-24.3 locus of the long arm of chromosome 17 and has 11 (a) (b) (d) (f) (h) (g) (e) (i) (c) Fig. 13.5.1.3 Characteristics of patients with Carneys Complex. Characteristic distribution of the lentigines on the eyelids (a), the vermillion border of the lips and the cheeks (b), and the ears, including the ear canal (c) in patients with CNC; such typical pigmentation on the face is only present in less than one-third of the patients but it is rather diagnostic when present. (d) a pigmented macule (arrow) on the outer canthus of a patient with CNC who had minimal other pigmentation; inner or outer canthal pigmentation such as the one shown here is only seen in CNC and Peutz-Jeghers syndrome making it diagnostic for these two conditions. (e) Nipple myxoma in a female patient with CNC. (f) Ear myxoma complicated by chronic infection and tissue overgrowth in a toddler with CNC. (g and h) Large myxoma (circled) between the left atrium and ventricle detected by echocardiography in an adolescent with CNC (g) who had surgery immediately thereafter, and a much smaller myxoma (arrow) of the left ventricle originating from the cardiac diaphragm detected by cardiac MRI in an older patient with CNC (h); this myxoma was followed by serial echocardiogram and has yet to be operated, as it is not growing and poses no immediate risks. (i) 5× magnification haematoxylin and eosin staining of the adrenal gland of a patient with CNC: the characteristic nodules of PPNAD are shown by the arrows; the overall size of the gland is normal and the nodules may not be visible by imaging studies. From Correa R, Salpea P, Stratakis CA (2015). Carney complex: an update. *Eur J Endocrinol*, 173, M85-97.

SECTION 13 Endocrine disorders 2336 exons, of which exons 2-11 are protein-coding. More than 70% of the patients diagnosed with Carney complex carry mutations on the PRKAR1A gene (CNC1 locus) and this percentage increases to 80% for those with Cushing's syndrome due to PPNAD.

A second genetic locus is associated with Carney complex and is referred to as the 'CNC2' locus (CNC1 being the PRKAR1A gene 17q locus). CNC2 is a 10 Mb region in the 2p16 locus.

McCune-Albright syndrome In this condition, fibrous dysplasia and cutaneous pigmentation may be associated with pituitary, thyroid, gonadal, and adrenal hyperfunction, with the latter manifesting as Cushing's syndrome. McCune-Albright syndrome (MAS) is caused by mosaicism for a mutation in the guanine nucleotide-binding protein, α -stimulating activity polypeptide (GNAS) gene, which maps to chromosome 20q13, and encodes the ubiquitously expressed stimulatory subunit α of the G protein (Gsa). Gsa activates adenylyl cyclase and leads to the generation of cAMP. Causative mutations in GNAS result in the G protein being constitutively activated, which, in the adrenal gland, mimics constant ACTH stimulation leading to adrenal hypersecretion and nodule formation. Aberrant receptor expression Initially, patients were described with nodular hyperplasia, ACTH-independent Cushing's syndrome, and enhanced adrenal responsiveness to gastric inhibitory polypeptide (GIP). The biochemical clues were the presence of subnormal morning levels of plasma cortisol and a rise in cortisol after food. This food-dependent form of Cushing's syndrome results from the normal increase in GIP after eating. Not surprisingly, the clinical syndrome is related to food intake; fasting can produce adrenal insufficiency. More recently, several novel mechanisms

which regulate cortisol secretion from adrenal nodules have been uncovered. This includes constitutive activation of the cAMP system and steroidogenesis, or its regulation, as a consequence of aberrant adrenal expression of several hormone receptors, particularly G-protein coupled hormone receptors (GPCR) and their ligands. When surgical samples of patients with bilateral macronodular adrenal hyperplasia and unilateral adrenal tumours (with Cushing's syndrome) are analysed there are frequent aberrant expression of G-protein coupled receptors and frequent coexpression of several receptors. Aberrant hormone receptors can also exert their activity by regulating the paracrine secretion of ACTH or other ligands. The aberrant expression of hormone receptors is not limited to adrenal Cushing's syndrome but can be implicated in other endocrine tumours including primary aldosteronism and Cushing's disease. Alcohol-associated pseudo-Cushing's syndrome In the original description of this syndrome, urinary and plasma cortisol levels were elevated, but were not suppressed with dexamethasone. Plasma ACTH may be normal or suppressed. The frequency and pathogenesis of this condition remain unknown, but a two-hit hypothesis has been put forward to explain its aetiology. Chronic liver disease, irrespective of the cause, is associated with impaired cortisol metabolism, but in those consuming excess alcohol this is associated with an increase in the cortisol secretion rate, rather than concomitant suppression in the face of impaired metabolism. With abstinence from alcohol the biochemical abnormalities rapidly revert to normal. Micronodular and macronodular adrenal hyperplasia There is a spectrum of recently recognized bilateral hyperplasias including micronodular adrenal disease (and its pigmented variant, primary pigmented nodular adrenocortical disease, see Carney complex) and macronodular bilateral adrenal hyperplasia (ACTH-independent macronodular hyperplasia or massive macronodular adrenocortical disease). Micronodular hyperplasia is commonly due to a genetic defect (including PRKAR1A, PDE11A, PDE8B) and is associated with Cushing's syndrome in children and young adults. Macronodular adrenal hyperplasia is less frequently linked to a genetic cause (e.g. MENIN, APC (familial adenomatous polyposis coli), GNAS, FH (fumarate hydratase), ectopic G-protein coupled receptors, WNT (encoding Wnt (wingless-related integration site) and WISP-2 (Wnt-inducible signalling pathway protein 2)), and very rarely manifests in childhood, but rather presents with atypical Cushing's syndrome in middle-aged or elderly adults (for more details, see Table 13.5.1.5). Clinical features The classical features of Cushing's syndrome—centripetal obesity, moon face, hirsutism, and plethora—are well known following Cushing's initial description in 1912 (Fig. 13.5.1.2 and Fig. 13.5.1.4), but this gross clinical picture is not always present. The signs and symptoms in patients with Cushing's syndrome are listed in Table 13.5.1.6, together with the most discriminatory features distinguishing Cushing's syndrome from simple obesity. Weight gain and obesity are the most common symptom and sign, but the distribution of fat is not invariably centripetal—a 'buffalo hump' or cervicodorsal fat pad is present in about one-half of patients. Gonadal dysfunction is very common, with menstrual irregularity in females and loss of libido in males, resulting from a suppressive effect of cortisol on gonadotropin secretion. Hirsutism is frequently found in female patients, as is acne, and typically reflects ACTH-stimulated hyperandrogenism, but may also be seen in the context of an adrenal carcinoma cosecreting cortisol and androgens. Psychiatric abnormalities have been reported in all series of patients with Cushing's syndrome, regardless of cause. Depression and lethargy are among the most common problems, but poor concentration, paranoia, and overt psychosis are also well recognized. Lowering of plasma cortisol by medical or surgical therapy usually results in a rapid improvement in the psychiatric state. Many patients with long-standing Cushing's syndrome have lost height because of osteoporotic vertebral collapse. Pathological fractures, either spontaneous or after minor trauma, are not uncommon. Rib fractures, by contrast with those of the vertebrae,

are often painless. The radiographic appearance is typical, with exuberant callus formation at the site of the healing fracture. The plethoric appearance of the patient with Cushing's syndrome results from thinning of the skin, not true polycythaemia. The typical red-purple livid striae of the syndrome are found most frequently on the abdomen, but may also be present on the upper thighs and axilla. They are very common in younger patients, and less so in those over 50 years of age. Myopathy and bruising are two of the most discriminatory features of the syndrome. The myopathy involves the proximal muscles

13.5.1 Disorders of the adrenal cortex 2337 of the lower limbs and the shoulder girdle. Complaints of weakness, such as an inability to climb stairs or get up from a deep chair, are relatively uncommon, but observation of whether the patient can rise from a crouching position often reveals the problem. Bruising of the skin may be extensive and occurs with unknown or trivial trauma. Hypertension is another prominent feature. Even though epidemiological data show a strong association between blood pressure and obesity, hypertension is much more common in patients with Cushing's syndrome than in those with simple obesity due to several factors including action on angiotensin II, catecholamine sensitivity, and cortisol action at the mineralocorticoid receptor. Pigmentation is rare in Cushing's disease, but common in ectopic ACTH syndrome. However, in some pituitary tumours there is abnormal processing of the pro-opiomelanocortin (POMC) precursor molecule, with resulting pigmentation. Infections are more common in patients with Cushing's syndrome than in unaffected individuals. In many instances these are asymptomatic, as the normal inflammatory response may be suppressed. Reactivation of tuberculosis has been reported. Fungal infection of the skin is frequently found. Glucose intolerance may be a predisposing factor, with overt diabetes being present in up to one-third of patients in some series. Ocular effects may include raised intraocular pressure, chemosis, and exophthalmos (present in up to one-third of patients in Cushing's original series). Cataracts, a well-recognized complication of exogenous corticosteroid therapy, seem to be uncommon, except as a complication of diabetes. In patients with ectopic ACTH syndrome caused by small-cell lung carcinoma, the clinical presentation more commonly resembles Addison's disease than Cushing's syndrome. The patients are commonly pigmented (associated with high ACTH concentrations) and have lost weight, but the association of these with hypokalaemic alkalosis and alterations in glucose homeostasis should alert the clinician to the diagnosis. Patients with more indolent causes, such as bronchial carcinoids, present with the more typical features of Cushing's syndrome. Patients with Cushing's syndrome have increased rates of venous thromboembolic disease. As with all cases of thromboembolic disease there are alterations in one or more of Virchow's triad (endothelial dysfunction, hypercoagulability, and venous stasis). Patients with Cushing's syndrome have abnormalities in

Table 13.5.1.5 Adrenocortical causes of Cushing's syndrome

Type of lesion	Frequency (percentage of cases of Cushing's syndrome)	Age group	Condition (gene/protein)
Benign	Common	Adenoma	10%
All ages	MEN 1 (menin)	FAP (APC)	MAS (GNAS)
HLRCS (FH)	CNC (PRKAR1A, 2p16)	Others	Primary macronodular adrenal hyperplasia (PMAH, nodules

10 mm diameter) <1% 40–60 yr MEN 1 (menin) FAP (APC) MAS (GNAS) HLRCS (FH) (ARMC5) (MC2R) (PDE11A) Micronodular hyperplasias (nodules <10 mm diameter) <1% Isolated primary pigmented nodular adrenocortical disease (i-PPNAD) Children and young adults (PRKAR1A) (PDE11A) (2p16) CNC-

associated PPNAD (c-PPNAD) CNC (PRKAR1A, 2p16) Isolated micronodular adrenocortical disease (i-MAD) (PDE11A) (PDE8B) Malignant Cancer (sporadic) 8% All ages (TP53) (Wnt/ β -catenin) (INHA) Others Cancer (syndromic) Children and young adults Li-Fraumeni (TP53, CHEK2) Beckwith–Wiedemann syndrome (chromosome 11 abnormalities, IGF2, H19) Rubenstein–Taybi syndrome (CREBBP, EP300) Brazil variant Children and young adults MEN 1, multiple endocrine neoplasia type 1; FAP, familial adenomatous polyposis (polyposis coli); MAS, McCune–Albright syndrome; HLRCs, hereditary leiomyomatosis and renal cancer syndrome; FH, fumarate hydratase; AD, autosomal dominant; CNC, Carney complex; GPCR, G-protein-coupled receptors; LFS, Li-Fraumeni syndrome; BWS, Beckwith–Wiedemann syndrome; RTS, Rubinstein–Taybi syndrome; AD, autosomal dominant; PMAH is also known as ACTH-independent macronodular adrenocortical hyperplasia (AIMAH); PPNAD, primary pigmented nodular adrenocortical disease.

SECTION 13 Endocrine disorders 2338 the coagulation cascade such that pro-coagulant factors are increased (factors VIII, IX, and von Willebrand factor) and fibrinolytic ability is decreased (elevation in plasminogen activator inhibitor 1). There may also be a rise in platelets, thromboxane B2, and fibrinogen. The result of the aforementioned abnormalities is a reduction of activated partial thromboplastin time and increased thrombin generation. Therefore, these patients are at high risk of thromboembolic disease and should be treated with prophylactic anticoagulation in keeping with guidance for high-risk patients. Special features Cyclical Cushing's syndrome Of particular clinical interest has been a group of patients with cyclical Cushing's syndrome, characterized by periods of excess cortisol production, followed by intervals of normal (or decreased) (a) (b) (c) (d) Fig. 13.5.1.4 Clinical features of a patient with Cushing syndrome before (a and b) and after (c and d) treatment. From Jolly E, Fry A, Chaudry A (eds) (2016). Training in medicine. By permission of Oxford University Press.

13.5.1 Disorders of the adrenal cortex 2339 cortisol production. The length of each cycle, and the intervening period between episodes, can vary markedly from days to months and even years. Some of these patients demonstrate a paradoxical rise in plasma ACTH and cortisol when treated with dexamethasone. Most patients have been thought to have pituitary-dependent disease, and in many instances, basophil adenomas have been removed, some with long-term cure. However, cortisol secretion may show cyclicity in other causes of Cushing's syndrome, notably ectopic ACTH syndrome. Children All the aforementioned features occur in children, but growth arrest is almost invariable. The dissociation between height and weight on the growth chart is obvious. If the child is growing along the same centile lines, then the diagnosis of Cushing's syndrome is highly unlikely. In addition to glucocorticoid-induced growth arrest, androgen excess may result in precocious puberty. Pregnancy Pregnancy is rare in women with Cushing's syndrome because of associated amenorrhoea resulting from androgen excess or hypercortisolism. However, several cases have been reported, 50% of which resulted from adrenal adenomas. A few cases of true pregnancy-induced Cushing's syndrome have been reported, with postpartum regression. In these cases, the aetiology is unknown. Establishing a diagnosis and cause can be difficult; normal pregnancy is associated with a threefold increase in plasma cortisol caused by increased

production rates and increases in cortisol-binding globulin. Urinary free cortisol also rises, and dexamethasone does not suppress plasma cortisol to the same degree as in the nonpregnant state. However, salivary cortisol levels/profiles are potentially helpful (as they reflect unbound free cortisol levels). Untreated, the condition has high maternal and fetal morbidity and mortality. Adrenal and/or pituitary adenomas should be excised (most frequently performed in the second trimester). Metyrapone has been effective in controlling the hypercortisolism in many cases, but a risk benefit discussion regarding possible fetal toxicity is required (there is limited data available and hence it is not recommended during pregnancy for the management of endogenous Cushing's syndrome unless clearly necessary). Metyrapone is excreted in breast milk.

Adrenocortical carcinomas In addition to features of glucocorticoid excess the patient may present with other problems relating to: (1), the tumour (e.g. abdominal pain from the primary tumour or secondary deposits), or (2), the secretion of other steroids such as androgens or mineralocorticoids. Thus, in addition to hirsutism, there may be other features of virilization in females, including clitoromegaly, breast atrophy, deepening of the voice, temporal recession, and severe acne. Men can present with gynaecomastia due to increased oestrogen synthesis.

Adrenocortical carcinomas are discussed later in the chapter in more detail. **Investigation** There are two stages in the investigation of a patient with suspected Cushing's syndrome: (1) Does the patient have Cushing's syndrome? (2) If the answer to (1) is yes, what is the cause? Many investigators fail to make this distinction and ill-advisedly use tests that are relevant to question (2) to try to answer question (1), this leads to difficulties when trying to appropriately interpret the results of investigations. Accurate diagnosis can be challenging as no single test confers 100% sensitivity and specificity. However, because of the potential seriousness of untreated Cushing's syndrome, highly sensitive tests are recommended to avoid missing the diagnosis. In all cases this brings with it a high prevalence of false positives, and the clinical pretest probability of the patient having Cushing's syndrome, based on clinical symptoms and signs, remains of paramount importance. In particular, it is essential that appropriate radiological investigations are not undertaken until Cushing's syndrome has been confirmed biochemically (given the high rate of incidentalomas reported in pituitary and adrenal imaging). **Diagnostic tests** Four screening tests with high sensitivity can be used to confirm Cushing's syndrome. Depending on the index of clinical suspicion these can be performed in isolation or combination. 1. Urine free cortisol (UFC; at least two/three measurements) 2. Late-night salivary cortisol (at least two measurements)

Table 13.5.1.6 Prevalence of symptoms and signs in Cushing's syndrome and discriminant index compared with prevalence of features in patients with simple obesity % Discriminant index Weight gain 91 Menstrual irregularity 84 1.6 Hirsutism 81 2.8 Psychiatric 62 Backache 43 Muscle weakness 29 8.0 Fractures 19 Loss of scalp hair 13 Obesity Truncal Generalized 97 46 55 1.6 0.8 Plethora 94 3.0 Moon face 88 Hypertension 74 4.4 Bruising 62 10.3 Red/purple striae 56 2.5 Muscle weakness 56 Ankle oedema 50 Pigmentation 4 Other findings Hypertension Diabetes Overt Impaired GTT Osteoporosis Renal calculi 74 50 13 37 50 15 Data from Ross EJ, Linch DC (1982). Cushing's syndrome—killing disease: discriminatory value of signs and symptoms aiding early diagnosis. *Lancet*, 2, 646–9.

SECTION 13 Endocrine disorders 2340 3. 1 mg overnight dexamethasone suppression test (DST) 4. 48-hour low-dose DST (LDDST) (2 mg/day for 48 hours) **Urinary free cortisol** For many years, the diagnosis of Cushing's syndrome was based on the measurement of urinary metabolites of cortisol (24-h urinary 17-hydroxycorticosteroid or 17-oxogenic steroid excretion, depending on the method used). However, the sensitivity and specificity of these methods is poor, and these assays have

now been replaced with the much more sensitive measurement of urinary free cortisol excretion. Urinary free cortisol is an integrated measure of plasma- free cortisol. As cortisol secretion increases, the binding capacity of cortisol-binding globulin is exceeded, resulting in a disproportionate rise in urinary free cortisol. This is a useful screening test, but even so, it is accepted that urinary free cortisol may be normal in 7 to 10% of patients with Cushing's syndrome. False positives may occur with high urine volumes, and certain medications may increase urinary free cortisol including carbamazepine, liquorice, carbenoxolone, fenofibrate (if measured by HPLC), and some synthetic glucocorticoids (if measured by immunoassays). False negative results may occur in renal impairment when the creatinine clearance falls to less than 60 ml/min, if the patient has cyclical disease, or if the patient has mild Cushing's syndrome. Because UFC levels in a patient with Cushing's syndrome are variable at least two/ three collections should be performed. Measurement of the cortisol:creatinine ratio in the first urine specimen passed on waking obviates the need for a timed collection, and has been used by some as a sensitive screening test, particularly if multiple assessments are needed, for example if cyclical Cushing's syndrome is suspected. However, this test has largely been replaced by midnight salivary cortisol for this indication.

Late-night plasma/salivary cortisol In normal subjects, plasma cortisol concentrations are at their highest first thing in the morning and reach a nadir at around midnight (with plasma cortisol <50 nmol/litre at midnight effectively excluding Cushing's syndrome). This circadian rhythm is lost in patients with Cushing's syndrome, such that in most patients the 09.00 level of plasma cortisol is normal, but nocturnal levels are raised. Random morning levels of plasma cortisol are therefore of little value in making the diagnosis. In addition, various factors, such as the stress of venepuncture, intercurrent illness, and admission to hospital, may result in normal subjects losing their circadian rhythm. It is therefore good practice not to measure plasma cortisol until the patient has been in hospital for 48 hours. For practical reasons midnight plasma cortisol is not routinely used as a first-line screening test. By contrast, midnight salivary cortisol can be collected at home and offers greater accuracy. The most commonly accepted salivary cortisol cut-off is less than 4 nmol/litre at midnight. Using a range of cut-offs, the midnight salivary cortisol test has 92–100% sensitivity and 93–100% specificity in diagnosing Cushing's syndrome. Other screening and confirmatory tests may be required to evaluate false-positive results. The performance and reliability of immunoassays at these levels of cortisol may limit their interpretation and therefore liquid chromatography-tandem mass spectrometry (LC-MS/MS) is the preferred analytical method if available.

Overnight dexamethasone suppression test In normal subjects, administration of a supraphysiological dose of a glucocorticoid results in suppression of ACTH and hence reduction in cortisol secretion. In Cushing's syndrome of whatever cause there is failure of this suppression when low doses of the synthetic glucocorticoid dexamethasone are given. The overnight test is often used as an outpatient screening test. Various doses of dexamethasone have been used, usually given at 23:00 h, but most experience is with a dose of 1 mg. A plasma cortisol of less than 50 nmol/litre (1.8µg/dl) between 08.00 and 09.00 the following morning has a sensitivity of 95% and specificity of 80% in excluding Cushing's syndrome. Thus, the outpatient 1 mg dexamethasone suppression test has high sensitivity but low specificity, and further investigation is often required.

Low-dose dexamethasone suppression test (LDDST) The LDDST may require inpatient admission, although with clear instructions this can be performed reliably as an outpatient. Here, plasma cortisol is measured at 09.00 on day 0 and 48 h later, following dexamethasone given at a dose of 0.5 mg every 6 h for 48 h; a result less than 50 nmol/litre (1.8µg/dl) is normal. This test is reported as having a sensitivity of 96% and a specificity of between 70 and 80%. There are some medications which may interfere with the dexamethasone

suppression test by either accelerating dexamethasone metabolism or impairing dexamethasone metabolism via their interaction with CYP 3A4. Drugs which accelerate dexamethasone metabolism include phenobarbital, phenytoin, carbamazepine, primidone, rifampicin, rifapentine, ethosuximide, pioglitazone. Drugs which impair dexamethasone metabolism include itraconazole, ritonavir, fluoxetine, diltiazem, cimetidine, and aprepitant/fosaprepitant. Healthy women who receive oral oestrogen therapy will often fail the dexamethasone suppression test (50% false-positive rate) due to elevated levels of cortisol-binding globulin. Therefore, oral oestrogens should be discontinued for six weeks prior to assessment with DST. Other tests Occasionally, other (second line) screening tests (e.g. the dexamethasone suppressed corticotrophin-releasing hormone (CRH) test or the desmopressin stimulation test) may be used to try and discriminate true Cushing's syndrome from unaffected subjects or pseudo-Cushing's states—however, these tests are less well validated than their more commonly employed counterparts and clinicians may be less familiar with interpretation, which can therefore add to diagnostic uncertainty. Differential diagnostic tests Once the biochemical diagnosis has been made, other investigations are required to determine the cause of the Cushing's syndrome. Plasma ACTH at 09.00 h This will differentiate ACTH-dependent from ACTH-independent causes. ACTH is either within the normal reference range (50% of cases) or elevated in patients with Cushing's disease. ACTH levels in ectopic ACTH syndrome are typically high, but overlap the values

13.5.1 Disorders of the adrenal cortex 2341 seen in Cushing's disease in 30% of cases and cannot therefore be used to differentiate these two conditions (Fig. 13.5.1.5). The measurement of ACTH precursors (pro-ACTH, POMC) is not routinely available, but may be more useful in detecting an ectopic source of ACTH. In patients with autonomous adrenal tumours, plasma ACTH is invariably undetectable. This can also occur with degradation of ACTH; consequently, nonhaemolysed blood samples should be taken on ice and immediately separated. Diagnosis is a problem in those patients whose plasma ACTH levels are in the low normal range or intermittently detectable. This may occur in macronodular hyperplasia. The danger is that in some patients with ACTH-dependent disease the asymmetry of the nodular hyperplasia may lead to a diagnosis of adrenal adenoma, the plasma ACTH is ignored, and an inappropriate adrenalectomy is performed. Conversely, in some patients with this syndrome an autonomous adrenal tumour develops and, despite detectable ACTH, unilateral adrenalectomy is required. Plasma potassium Hypokalaemic alkalosis is a marker of severity of hypercortisolaemia as it reflects the overwhelming of the protective effect of 11 β -HSD2 at the level of the mineralocorticoid receptor, resulting in cortisol-induced mineralocorticoid hypertension (see 'Apparent mineralocorticoid excess syndrome' later). Hypokalaemic alkalosis is present in many patients with ectopic ACTH syndrome, but in fewer than 10% of patients with Cushing's disease. In addition, these patients have higher levels of the ACTH-dependent mineralocorticoid deoxycorticosterone. High-dose dexamethasone suppression test The rationale for this test is that in Cushing's disease there is negative feedback control of ACTH but set at a higher level than normal. Thus, in Cushing's disease, cortisol levels are not suppressed with a low dose of dexamethasone, but are suppressed with a higher dose. The original test introduced by Liddle was based on giving dexamethasone at a dose of 2 mg every 6 h for 48 h and measuring urinary 17-oxogenic steroids. Suppression was defined as a greater than 50% fall in 24-h urinary 17-oxogenic steroids. In the modern test, plasma cortisol is measured at 0 and 48 h or, less commonly, plasma cortisol is measured at 08.00 (basal sample), 8 mg dexamethasone is given orally at 23.00 on the same day, and plasma cortisol is measured again at 08.00 on the following morning. In both these tests, greater than 50% suppression of plasma cortisol in

comparison with the basal sample has been used to define a positive response. In Cushing's disease about 90% of patients have a positive 48-h test, compared with 10% with ectopic ACTH syndrome. With overnight 8 mg DST testing, 89% sensitivity and 100% specificity has been reported for Cushing's disease. Corticotrophin-releasing factor (CRF) test CRF is a peptide of 41 amino acids, identified by Vale in 1981 from ovine hypothalamus. The ovine sequence differs by seven amino acid residues from that of the human peptide, but despite this stimulates the release of ACTH in humans. The test involves the intravenous injection of either ovine or human CRF at a dose of 1 µg/kg body weight (or a single dose of 100 µg). The test can be performed in the morning or afternoon, and—after basal sampling—blood samples for ACTH and cortisol are taken every 15 min for 1 to 2 hours after administering CRF. There are differences in the performance of the CRF test depending on whether ovine or recombinant human CRF are used and this needs to be taken into account when interpreting the test results. In normal subjects CRF elicits a rise in ACTH and cortisol, and this response is exaggerated in Cushing's disease. It is typically absent in ectopic ACTH syndrome and patients with adrenal tumours. In distinguishing pituitary-dependent Cushing's disease from ectopic ACTH syndrome, the response of ACTH to CRF has a specificity of 90%, and with cortisol as the endpoint, 95%, using as endpoints an ACTH increase of 100% over basal or a cortisol rise of 50%. Inferior petrosal sinus sampling/selective venous catheterization This is the most robust test for distinguishing Cushing's disease from ectopic ACTH syndrome, but also the most costly and technically demanding. As blood from each half of the pituitary drains

Condition	Normal range
Untreated Adrenal tumour	110000
Ectopic ACTH	4000–12000
Cushing's disease	2000–4000
Post-adrenal-ectomy	1000–2000
	900
	700
	500
	300
	250
	200
	150
	100
	50
	0
	37
	49
	9
	42

08.00–10.00 Plasma immunoreactive ACTH (ng/litre) Fig. 13.5.1.5 Immunoreactive N-terminal ACTH levels in plasma samples taken between 08.00 and 10.00 in normal subjects (hatched area), and patients with Cushing's disease (either untreated or postadrenalectomy), adrenal tumours, or ectopic ACTH syndrome. Courtesy of Professor LH Rees.

SECTION 13 Endocrine disorders 2342 into the ipsilateral inferior petrosal sinus (in most cases), catheter-ization of both sinuses with simultaneous sampling of venous blood can distinguish a pituitary from an ectopic source, and aid in the lateralization of a pituitary microadenoma (Fig. 13.5.1.6). The re-sults for lateralization are not as robust as the results for determining whether the ACTH comes from a pituitary versus ectopic sources, as many patients have anatomical variations in drainage. However, because of the problem of intermittent ACTH secretion, it is useful to make measurements before and at intervals (e.g. 2, 5, and 10 min) after intravenous injection of 100 µg of CRF. If the pituitary-to-peripheral ratio of ACTH is greater than 2 the patient has Cushing's disease, with a sensitivity and specificity of up to 100%. In Cushing's disease an ipsilateral:contralateral ACTH more than 1.4 may be helpful in localizing the adenoma to an individual side, however this is far from 100% accurate and an experi-enced surgeon on review may find an adenoma on the opposite side. If the pituitary-to-peripheral ratio of ACTH is less than 1.5 the patient has ectopic Cushing's syndrome. Rarely, selective catheter-ization of vascular beds may be required to identify the source of ectopic ACTH secretion (e.g. from a small pulmonary or thymic neuroendocrine tumour). Tumour markers Many tumours responsible for ectopic ACTH syndrome also produce peptide hormones other than ACTH or its precursors. Calcitonin, chromogranin A, and gut hormones such as gastrin and vasoactive intestinal polypeptide should be measured for assess-ment of secretion from neuroendocrine tumours. Imaging High-resolution contrast-enhanced imaging of thin sections of the pituitary by MRI and adrenals by either CT or MRI has revolution-ized the investigation of Cushing's syndrome. However, if mistakes are to be

avoided it is essential that full biochemical assessment takes place prior to imaging and the results of any imaging technique must always be interpreted in the light of the biochemical results. In Cushing's disease imaging, the adrenals often reveal asymmetrical nodular hyperplasia which may lead to a false diagnosis of adrenal adenoma (Fig. 13.5.1.7) and inappropriate adrenal resection. Similarly, in patients with Cushing's syndrome secondary to an adrenal lesion there may be a pituitary incidentaloma on MRI. Thus, assessment of biochemistry and in particular ACTH is key to directing and interpreting imaging. Pituitary MRI is the investigation of choice if the biochemical tests suggest Cushing's disease, and has a sensitivity of 70% and specificity of 87% (Fig. 13.5.1.8). Approximately 90% of ACTH-secreting pituitary tumours are microadenomas (i.e. less than 10 mm in diameter). The classical features of a pituitary microadenoma are a hypodense lesion after contrast and a convex upper surface of the pituitary gland (Fig. 13.5.1.8). With such small tumours it is not surprising that the sensitivity of CT scanning is relatively low (20–60%), with a similar specificity, and therefore CT scanning of the pituitary should not be used unless MRI is contraindicated. By contrast, CT scanning is the investigation of choice for adrenal imaging and affords good spatial resolution (Fig. 13.5.1.9), with MRI serving as an alternative. Once again, adrenal incidentalomas are present in up to 5% of normal subjects (this number increases with age), and thus adrenal imaging should not be performed unless biochemical investigation suggests a primary adrenal cause. Adrenal carcinomas are large and often associated with metastatic spread at presentation (Fig. 13.5.1.10). Cavernous sinus Inferior petrosal sinus Pituitary veins Jugular vein Fig. 13.5.1.6 Positions of bilateral catheters in inferior petrosal sinus sampling. Fig. 13.5.1.7 CT scan of patient with Cushing's disease with asymmetrical nodular hyperplasia (right > left).

13.5.1 Disorders of the adrenal cortex 2343 In patients with occult ectopic ACTH syndrome, high-definition MRI/CT scanning of the neck, thorax, and abdomen/pelvis, with images every 0.5 cm, may be required to detect small ACTH-secreting carcinoid (NET) tumours. Functional imaging (e.g. with 18F-fluorodeoxyglucose (18F-FDG) or 68Gallium DOTATATE (68Ga-DOTATATE) positron emission tomography (PET)/CT may aid localization of small neuroendocrine tumours or confirm sites of metastatic disease. 11C-methionine PET/CT coregistered with MRI has also been proposed as a method for localizing small corticotroph adenomas not readily visualized on MRI. Management Studies carried out before the introduction of effective therapy suggested that 50% of patients with untreated Cushing's syndrome died within 5 years, causing some physicians to label this the 'killing disease'. Even with modern management, an increased prevalence of cardiovascular risk factors persists for many years after an apparent remission. Close follow-up of all patients is recommended. Adrenal causes Adrenal adenomas should be removed by unilateral adrenalectomy, which has a 100% cure rate. Laparoscopic adrenalectomy is now the surgical treatment of choice for unilateral adenomas as it reduces surgical morbidity and postoperative hospital stay compared with open approaches. After surgery it may take many months or even years for the contralateral suppressed adrenal to recover (due to chronic lack of stimulation as a result of low ACTH levels). Patients who undergo a unilateral adrenalectomy for Cushing's syndrome secondary to an adrenal adenoma will require hydrocortisone replacement peri- and postoperatively. To assess if the contralateral adrenal gland has recovered from suppression intermittent measurement of the 08.00 level of plasma cortisol after having omitted therapy the evening before and morning of test is advised. When the morning plasma cortisol is above 180 nmol/litre a stimulation test such as the Synacthen test (250 mcg), may then demonstrate whether the contralateral adrenal gland has recovered from its suppression. Adrenocortical carcinomas have a very poor prognosis. It is usual

practice to try to remove the primary tumour, even though metastases may be present, so as to enhance the response to the adrenolytic agent mitotane (see 'Medical treatment of Cushing's syndrome' later). Radiotherapy to the tumour bed and to some metastases, such as those in the spine, may be of limited value (see the 'Adrenocortical carcinomas' section). Pituitary-dependent Cushing's disease In most cases, the treatment of Cushing's disease involves transsphenoidal surgery. Before the selective removal of a pituitary microadenoma became routine, the treatment of choice was bilateral adrenalectomy. This had an appreciable mortality, even in the best centres (c.4%), as well as postoperative morbidity. The main risk was the subsequent development of Nelson's syndrome (postadrenalectomy hyperpigmentation with locally aggressive pituitary tumour) (Fig. 13.5.1.11). To avoid this, pituitary Fig. 13.5.1.8 MRI scan of pituitary demonstrating the typical appearance of a pituitary microadenoma. A hypodense lesion is seen in the centre of the gland. Following a biochemical diagnosis of Cushing's disease, this patient was cured following transsphenoidal hypophysectomy. Fig. 13.5.1.9 Typical solitary left-sided nonsecretory adrenal adenoma with low HU on noncontrast adrenal CT scanning.

SECTION 13 Endocrine disorders 2344 irradiation is often carried out in patients who have undergone bilateral adrenalectomy. These patients required lifelong replacement therapy with hydrocortisone and fludrocortisone. Today, bilateral adrenalectomy is reserved for patients with Cushing's disease in whom no pituitary tumour can be found, or when pituitary surgery has failed to control hormone hypersecretion, or the condition has recurred or is life-threatening. After selective removal of a microadenoma, the surrounding corticotrophs are normally suppressed (Fig. 13.5.1.12). In these cases, plasma cortisol concentrations are also suppressed postoperatively, and glucocorticoid replacement therapy is required, but gradual recovery of the HPA axis can be anticipated (Figs 13.5.1.12(c) and 13.5.1.13), particularly in patients with normal pituitary function as it relates to other endocrine axes. There is no consensus on the criteria for defining remission after resection of an ACTH producing tumour. However, remission is generally considered likely if morning serum/plasma cortisol is less than 138 nmol/litre (5µg/dl) and/or urinary free cortisol less than 28–56 nmol/24 hours (<10–20 µg/24 hours) within 7 days of surgery, but a number of alternative cut-offs have been suggested. Patients who are eucortisolaemic following surgery may still have residual tumours, even though cortisol secretion may have fallen to normal or subnormal values. These patients are at high risk of recurrence. An important caveat to this relates to patients with mild or cyclical Cushing's disease and those rendered eucortisolaemic prior to surgery (following treatment with medical therapy), who may not have suppressed corticotropes in the pituitary. In this situation their 24-hour urinary free cortisol assessments and morning cortisol may be nonsuppressed, but they may be in true remission from their Cushing's disease. In such patients the return of a normal circadian rhythm (as demonstrated by the finding of low midnight salivary cortisol levels) is helpful in assessing disease control. In the past, pituitary irradiation was often used in the treatment of Cushing's disease. However, improvements in pituitary surgery have resulted in far fewer patients receiving radiotherapy. Radiotherapy is not recommended as a primary treatment, but is reserved for patients not responding to pituitary surgery (e.g. when bilateral adrenalectomy has been performed), or in those with established Nelson's syndrome. Conventional pituitary radiotherapy has been associated with increased risk of stroke in patients with nonfunctioning adenomas and acromegaly. Conventional radiotherapy has also been associated with development of hypopituitarism and rarely secondary intracranial malignancies and damage to the optic apparatus. There is increasing data relating to radiosurgery techniques in

the management of Cushing's disease, which appear to show favourable results when compared with fractionated conventional radiotherapy. Radiosurgery may offer more rapid biochemical response and less risk of radiation damage to surrounding brain structures, but careful case selection is paramount, and more data is required in this area. Ectopic ACTH syndrome Treatment of ectopic ACTH syndrome depends on the cause. If the tumour can be found and has not spread, then its removal can lead to cure (e.g. bronchial carcinoid tumours, or thymomas). However, the prognosis for small-cell lung cancer associated with ectopic ACTH syndrome is poor. The cortisol excess and associated hypokalaemic alkalosis and diabetes mellitus can be ameliorated by medical therapy (see later). Treatment of the small-cell tumour itself will also, at least initially, produce improvement (see Chapter 18.19.1). Sometimes, if the ectopic source of ACTH cannot be found, it may be necessary to perform bilateral adrenalectomy and then follow the patient carefully clinically and with directed imaging (sometimes for several years) to find the primary tumour.

Medical treatment of Cushing's syndrome Several drugs have been used in the treatment of Cushing's syndrome. Most commonly, metyrapone or ketoconazole has been given, often to lower cortisol concentrations before definitive therapy, or while awaiting benefit from pituitary irradiation. The daily dose has to be determined by measuring either plasma or urinary free cortisol to guide dose titration. Metyrapone Metyrapone inhibits 11- β hydroxylase which catalyses the conversion of 11-deoxycortisol to cortisol. Metyrapone is usually given in doses ranging from 250 mg twice daily to 1.5 g every 6 h (due to its short half-life of 2 hours). Nausea is a common side effect and can be alleviated (if not caused by adrenal insufficiency) by giving the drug with milk. Adverse effects of metyrapone include gastrointestinal disturbances (need to ensure not related to unrecognized hypoadrenalism), hirsutism, acne (due to stimulation of androgenic precursors) and hypertension, hypokalaemia, and oedema (due to accumulation of mineralocorticoid precursors). Importantly when assessing response of cortisol hypersecretion to metyrapone it is best to use a

Fig. 13.5.1.10 CT scan of a patient with rapidly progressing Cushing's syndrome and virilization as a result of a left-sided adrenal carcinoma. An irregular left adrenal mass is shown.

13.5.1 Disorders of the adrenal cortex 2345 LC-MS/MS assay rather than an immunoassay as significant levels of 11-deoxycortisol can accumulate while on metyrapone, which can cross react with immunoassays for cortisol. In a recent study there was a significant difference in cortisol concentrations reported in the same sample between the two methods. The difference between LC-MS/MS versus immunoassay in the metyrapone therapy group positively correlated with metyrapone dose and serum 11-deoxycortisol concentrations. The immunoassay read higher cortisol concentrations than LC-MS/MS due to interference from 11 deoxycortisol—if not recognized, this may lead to an increase in dose of metyrapone with subsequent unrecognized adrenal insufficiency. A recent large study of metyrapone use in clinical practice showed higher doses were required to control patients with adrenocortical cancer, Cushing's disease, and ectopic ACTH syndromes than benign adrenal nodules. Several approaches may be used to assess the (a) (b) (c) Fig. 13.5.1.11 A young woman with Cushing's disease, photographed initially alongside her identical twin sister (a). In this case treatment with bilateral adrenalectomy was undertaken and several years later the patient re-presented with Nelson's syndrome and right third cranial nerve palsy (b) following cavernous sinus infiltration from a locally invasive corticotropinoma (c). (a) +++ Secretion above normal (c) (b)

- Secretion is detectable

–ve Secretion suppressed ND not detectable ACTH secreting tumour ACTH Cortisol ND ACTH–ve ACTH+ Cortisol+ ACTH–ve ACTH–ve ACTH+++ Cortisol+++ Fig. 13.5.1.12 Selective removal of a microadenoma and its effect on the hypothalamic–pituitary–adrenal axis. Because the surrounding normal pituitary corticotrophs are suppressed in a patient with an ACTH- secreting pituitary adenoma (a), successful removal of the tumour results in ACTH and hence adrenocortical deficiency with an undetectable (<50 nmol/litre) level of plasma cortisol (b). With time the HPA axis can recover (c). Courtesy of Professor P Trainer. I.H.T. Trans-sphenoidal microadenomectomy 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0 5 10 15 20 25 Weeks 0900h Plasma cortisol (μmol/litre) I.H.T. Insulin hypoglycaemia test Fig. 13.5.1.13 Gradual recovery of function of the hypothalamic–pituitary–adrenal axis after removal of a pituitary ACTH-secreting microadenoma. The insulin hypoglycaemia test eventually demonstrated the return of a normal stress response.

SECTION 13 Endocrine disorders 2346 degree of control in patients receiving metyrapone, and include cortisol day profiles and measurement of 24-hour urinary free cortisol. A second 11β-hydroxylase inhibitor (LCI699) is currently in development. Ketoconazole Ketoconazole (an imidazole previously used as an antifungal agent) blocks a variety of steroidogenic cytochrome P450-dependent enzymes (in both the adrenal gland and gonads), and thus lowers plasma cortisol levels. Its main effect is via inhibiting side-chain cleavage, 17,20-lyase, and 11-β hydroxylase enzymes. For effective control of Cushing's syndrome, 400 to 800 mg ketoconazole daily is typically required, but liver function tests must be monitored closely since hepatic failure is a potentially serious complication. Normalization of cortisol hypersecretion is seen in between 25 and 93% of cases depending on the study reviewed. Abnormal liver function tests occur in 10 to 15% of patients and a severe idiosyncratic hepatic reaction in 1 in 15 000 exposed individuals. The Food and Drug Administration (FDA) issued a black box warning and the European Medicines Agency has restricted access to the agent to physicians specialized in treating Cushing's syndrome. Levoketoconazole (the pure 2 S,4R enantiomer of ketoconazole) is currently undergoing phase 3 studies, and may show a more favourable efficacy, safety, and tolerability profile. Mitotane Mitotane is an adrenolytic drug that is taken up by both normal and malignant adrenal tissue, causing adrenal atrophy and necrosis. Because of its toxicity, it has been used mainly in the management of adrenal carcinoma. Doses of up to 8 g/day are required to control glucocorticoid excess. The drug will also produce mineralocorticoid deficiency, and both glucocorticoid and mineralocorticoid replacement therapy may be required. Importantly, mitotane increases the levels of cortisol-binding globulin within serum and also increases the metabolism of cortisol in the liver and therefore higher doses of glucocorticoid replacement (e.g. hydrocortisone 20 mg thrice daily) are required to avoid hypoadrenalism. Mitotane can cause several biochemical and endocrine abnormalities, including thyroid dysfunction (a mixed picture of primary and secondary thyroid dysfunction) that may require replacement. Abnormalities in liver function, in particular raised γ-glutamyl transferase and hyperlipidaemia, are frequently seen. Clinical side effects are common and include fatigue, skin rashes, and gastrointestinal disturbance. Levels of mitotane need to be closely monitored as the drug has a narrow therapeutic window in the treatment of adrenocortical carcinoma. Mitotane toxicity is associated predominantly with gastrointestinal and neurological symptoms, which are reversible on discontinuation of the drug. Mitotane doses at levels below the

therapeutic window may be beneficial in controlling hypercortisolaemia, but will not have an impact on growth of adrenocortical cancers. Glucocorticoid receptor antagonist (mifepristone) Mifepristone works by blocking the glucocorticoid receptor, therefore ACTH or cortisol estimation cannot be used to assess disease control, indeed ACTH levels increased twofold in 31/44 patients in one study due to the loss of negative feedback. Assessment of disease control in patients on mifepristone include clinical measures such as improvement in hypertension, hyperglycaemia, weight, quality of life, clinical appearance, and symptoms. As it is difficult to assess efficacy, it is generally recommended to start at a low dose of 300 mg per day and titrate up as clinically indicated (max dose of 1200 mg/day). Adverse effects include those associated with adrenal insufficiency (fatigue, nausea, vomiting, arthralgias and headache), antiprogesterin (endometrial thickening) and mineralocorticoid excess (hypertension, oedema, hypokalaemia). Given the blockade of the glucocorticoid receptor, treatment of adrenal crisis can be challenging; mifepristone should be held, haemodynamic support given, and one study reported the use of high-dose dexamethasone. Etomidate Etomidate (an anaesthetic agent) can be used in patients with severe Cushing's syndrome who cannot take oral medications or are critically unwell due to their Cushing's syndrome. It is an imidazole derivative (similar to ketoconazole) which can be given at subhypnotic doses to rapidly decrease cortisol levels by inhibiting side-chain cleavage, 17,20-lyase and 11- β hydroxylase enzymes. Etomidate should only be given under careful monitoring conditions such as is possible in an intensive care unit because of its potential hypnotic properties. A loading dose of 3–5 mg can be followed by a continuous infusion of 0.03–0.1 mg/kg/hr (this may need to be adjusted in patients with renal impairment as etomidate is renally excreted). During treatment, cortisol should be measured 4–6 hourly and the etomidate infusion titrated to achieve a serum cortisol level between 280 and 560 nmol/litre (10–20 μ g/dl). Pasireotide Pasireotide is a second-generation somatostatin receptor ligand (SRL) with a different receptor subtype affinity to octreotide or lanreotide. Pasireotide has a much stronger affinity to SSTR1 and SSTR5 than SSTR2 (unlike octreotide and lanreotide). Corticotroph tumours have a high expression of SSTR5. A phase 3 trial of twice daily subcutaneous pasireotide in patients with Cushing's disease in whom surgery had failed (or who were not suitable for surgery) reported that 20% of treated patients had a normal 24-hour urinary free cortisol and 44% had a reduction in tumour size. Adverse effects were similar to those seen in patients receiving first generation SRL's, with the exception of hyperglycaemia which was significantly more frequent in patients treated with pasireotide than is seen in patients treated with octreotide or lanreotide, hence close monitoring of glycaemic control is required in patients receiving pasireotide. Studies investigating the use of a long acting pasireotide LAR in Cushing's disease are underway. Cabergoline Cabergoline is a long acting agonist of the D2 dopamine receptor (which is frequently expressed on corticotroph adenomas). There is limited data regarding its efficacy in Cushing's disease, with reports of between 30 and 40% of patients responding with lowering of cortisol levels; however, in some of these patients the initial response did not persist despite high doses of cabergoline therapy. Adverse effects of cabergoline (less frequent than in patients receiving older dopamine agonists such as bromocriptine) include nausea, dizziness, constipation, and there has recently been a concern regarding valvular fibrosis in patients who receive a high cumulative dose of cabergoline for Parkinson's disease (although the data in patients receiving cabergoline at doses used for the treatment for prolactinoma are reassuring). Cabergoline is also under investigation in combination with some of the other agents discussed.

13.5.1 Disorders of the adrenal cortex 2347 Aminoglutethimide Aminoglutethimide is a more toxic drug that in high doses blocks the initial steps in the biosynthetic pathway, and thus affects the secretion of steroids other than cortisol. In doses of 1.5 to 3 g daily (starting with 250 mg every 8 h) it commonly produces nausea, marked lethargy, and a skin rash. Trilostane Trilostane, a 3 β -hydroxysteroid dehydrogenase inhibitor, is ineffective in Cushing's disease since the block in steroidogenesis is overcome by the rise in ACTH. However, it can be effective in patients with adrenal adenomas. Targeted therapies in ectopic ACTH production Neuroendocrine tumours which secrete ectopic ACTH may express SSTR2 and D2 receptors and may therefore be responsive to SRL (octreotide and lanreotide) therapy or cabergoline. The use of these agents may decrease ACTH secretion, but typically has little effect on tumour growth rates. Glucocorticoid deficiency: Primary and secondary hypoadrenalism Primary hypoadrenalism refers to glucocorticoid deficiency occurring in the setting of adrenal disease, whereas secondary hypoadrenalism arises from a deficiency of ACTH (due to hypothalamic/pituitary dysfunction), the major trophic hormone controlling cortisol secretion. The principal distinction between these two conditions is that mineralocorticoid deficiency invariably accompanies primary hypoadrenalism, but this does not occur in secondary hypoadrenalism because only ACTH is deficient; the renin-angiotensin-aldosterone axis is intact. Primary hypoadrenalism Congenital adrenal hyperplasia Various inherited enzyme defects have been identified in the synthetic pathway of adrenocortical hormones, which cause a spectrum of glucocorticoid and/or mineralocorticoid deficiency. Adrenal androgens may be increased or decreased, depending upon the underlying enzyme block. This group of conditions is addressed in Chapter 13.5.2.

Addison's disease Thomas Addison described this condition in his classic monograph published in 1855. Addison worked with Bateman, a dermatologist who produced one of the first classifications of skin disease. It seems likely that this stimulated Addison's interest in the skin pigmentation that is so characteristic of this disease. Addison's disease is a rare condition, with an estimated incidence in the developed world of 0.8 cases per 100 000 population. The causes of primary adrenal insufficiency are listed in Table 13.5.1.7. Table 13.5.1.7 Aetiology of adrenocortical insufficiency Primary adrenal insufficiency Secondary adrenal insufficiency Addison's disease Tuberculosis Autoimmune: Sporadic Polyglandular deficiency type I (Addison's disease, chronic mucocutaneous candidiasis hypoparathyroidism, dental enamel hypoplasia, alopecia, primary gonadal failure) Polyglandular deficiency type II (Schmidt's syndrome) (Addison's disease, primary hypothyroidism, primary hypogonadism, insulin-dependent diabetes, pernicious anaemia, vitiligo) Bilateral adrenalectomy Metastatic tumour Lymphoma Amyloid Haemochromatosis Intra-adrenal haemorrhage (Waterhouse-Friderichsen syndrome) following meningococcal septicaemia Adrenal infarction or infection other than tuberculosis (especially AIDS) also Ebola and other haemorrhagic fevers Adrenoleukodystrophies Congenital adrenal hypoplasia (DAX-1 mutations) Hereditary adrenocortical unresponsiveness to ACTH Type 1: ACTH receptor, melanocortin 2 receptor gene MC2R Type 2: MRAP Familial glucocorticoid deficiency (MCM4, NNT, TXNRD2) Triple A (Allgrove's) syndrome, achalasia, Addison's disease, alacrima, AAAS gene mutation Drug-induced adrenal enzyme inhibitors: mitotane, ketoconazole, metyrapone, etomidate, aminoglutethimide, drugs that may accelerate cortisol metabolism and induce adrenal insufficiency CTLA-4 inhibitors may enhance autoimmunity and cause PAI Other metabolic disorders Mitochondrial disease (rare) Wolman's disease Adrenal hypoplasia Congenita—X-linked NROB1, Xp21 deletion (with Duchenne's muscular deficiency), SF-1 mutations (XY sex reversal), IMAGE syndrome Exogenous glucocorticoid therapy Hypopituitarism: Selective removal of ACTH-secreting pituitary adenoma Pituitary tumours and pituitary surgery, craniopharyngiomas Pituitary apoplexy Granulomatous disease (tuberculosis,

sarcoid, eosinophilic granuloma) Secondary tumour deposits (breast, bronchus) Postpartum pituitary infarction (Sheehan's syndrome) Pituitary irradiation (effect usually delayed for several years) Isolated ACTH deficiency

SECTION 13 Endocrine disorders 2348 Infectious causes Worldwide, infectious diseases are the most common cause of primary adrenal insufficiency. Leading causes include tuberculosis, fungal infections (histoplasmosis, cryptococcosis), and cytomegalovirus. Adrenal failure may occur in AIDS and has been reported in haemorrhagic fevers such as Ebola. In tuberculous Addison's disease the adrenals are initially enlarged, with extensive epithelioid granulomas and caseation. Chronic atrophy can occur, and calcification eventually ensues in most cases (Fig. 13.5.1.14): both the cortex and the medulla are affected. Autoimmune causes In the Western world, autoimmune adrenalitis accounts for over 70% of all cases of Addison's disease. Pathologically, the adrenal glands are atrophic, with loss of most of the cortical cells, but the adrenal medulla is usually intact. However, catecholamine synthesis may be impaired due to the need for intra-adrenal cortisol to regulate catecholamine synthesis (norepinephrine to epinephrine by phenylethanolamine N-methyltransferase). Adrenal autoantibodies can be detected in up to 75% of newly diagnosed cases and have helped elucidate the cause of the disease. Fifty per cent (50%) of patients with Addison's disease have an associated autoimmune disease, and these polyglandular autoimmune syndromes have been classified into two distinct variants: Type I is inherited as an autosomal recessive condition and comprises Addison's disease, chronic mucocutaneous candidiasis, and hypoparathyroidism. The condition is rare and usually presents in childhood with either candidiasis or hypoparathyroidism. Other autoimmune conditions, such as pernicious anaemia, thyroid disease, chronic active hepatitis, and gonadal failure may occur, but are rare. Autoantibodies to the cholesterol side-chain cleavage enzyme and 17 α -hydroxylase may be detected, but not to 21-hydroxylase. The condition occurs because of mutations in the autoimmune regulator gene, AIRE. Type II polyglandular autoimmune syndrome is more common, comprising Addison's disease, autoimmune thyroid disease, diabetes mellitus, and hypogonadism. The condition has an inherited basis, with linkage to the HLA major histocompatibility complex, notably HLA DR3 and DR4. Autoantibodies to 21-hydroxylase are usually present and are predictive for the development of adrenal destruction. Other causes With the exception of tuberculosis and autoimmune adrenal failure, other causes of Addison's disease are rare (Table 13.5.1.7). Adrenal metastases (most commonly from primary lung and breast tumours) are often found at post-mortem examinations, but adrenal insufficiency from these is uncommon (unless associated with adrenal haemorrhage). Necrosis of the adrenals following intra-adrenal haemorrhage should be considered in any severely ill patient, and may result from infection, trauma, or hypercoagulability. Intra-adrenal bleeding may be found in severe septicaemia of any cause, particularly in children. When this is caused by meningococci, the association with adrenal insufficiency is known as Waterhouse-Friderichsen syndrome. Adrenal infiltration/ replacement leading to glandular failure may also occur with amyloidosis and haemochromatosis. Congenital adrenal hypoplasia is an X-linked disorder comprising congenital adrenal insufficiency and hypogonadotropic hypogonadism. The condition is caused by mutations in the DAX1 (NR0B1) gene, a member of the nuclear receptor family that is expressed in the adrenal cortex, gonads, and hypothalamus. X-linked adrenoleukodystrophy causes adrenal insufficiency in association with demyelination within the nervous system, and results from a failure of β -oxidation of fatty acids within peroxisomes. Increased accumulation of very long-chain fatty acids (VLCFA) occurs in many tissues, and serum measurement can be used diagnostically. Male patients have the fully expressed condition, and female carriers are

increasingly recognized to be affected by it (albeit with different timings of symptom development). X-linked adrenoleukodystrophy (X-ALD), which accounts for about 10% of cases of adrenocortical failure in boys and men, is clinically characterized by two main phenotypes: adrenomyeloneuropathy (AMN) and the cerebral demyelinating form of X-ALD (cerebral ALD). AMN and cerebral ALD occur frequently within the same family and there is no correlation between X-ALD phenotype and mutations in the ABCD1 gene. Cerebral ALD presents usually with a rapidly progressive inflammatory demyelination within the brain resulting in severe cognitive and neurologic disability, a vegetative state within two to five years of clinical symptom onset, and death thereafter. This phenotype is most common during childhood and adolescence, but up to 20% of adult males initially presenting with AMN will develop cerebral ALD later in life. The pathology of AMN is fundamentally different from that of cerebral ALD and is characterized predominantly by a noninflammatory distal axonopathy involving mostly the long tracts of the spinal cord that results in a progressive spastic paraplegia. Adrenal insufficiency is usually present, but does not appear to correlate with the neurological deficit. Both the childhood and adult conditions result from mutations in the ABCD1 gene on chromosome Xq28, which encodes an ATP-binding cassette peroxisomal membrane protein involved in the import of VLCFA into the peroxisome. Monounsaturated fatty acids that block the synthesis of saturated VLCFA have been used for treatment. A combination of erucic acid and oleic acid (Lorenzo's oil) has led to normal levels of VLCFA, but this has not altered the rate of neurological deterioration. Bone marrow transplantation appears to be more effective if undertaken in the early stages of the disease. Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive cause of hypoadrenalism that usually presents in childhood. Fig. 13.5.1.14 Plain radiograph of the abdomen showing adrenal calcification in a patient with tuberculous Addison's disease.

13.5.1 Disorders of the adrenal cortex 2349 The renin-angiotensin-aldosterone axis is intact, and children usually present either with neonatal hypoglycaemia, or later with increasing pigmentation, often with enhanced growth velocity. Patients have glucocorticoid deficiency with very high plasma ACTH levels; this occurs because of mutations in the melanocortin 2 receptor (MC2R; ACTH receptor) or an accessory protein involved in the cellular trafficking of MC2R (MRAP). Mutations in mini chromosome maintenance-deficient 4 homologue (MCM4) and nicotinamide nucleotide transhydrogenase (NNT), genes involved in DNA replication and antioxidant defence respectively, have been recognized in FGD cohorts. A variant syndrome is called the triple A or Allgrove's syndrome, and refers to a triad of adrenal insufficiency, namely ACTH resistance, achalasia, and alacrima. Allgrove syndrome is characterized by mutation(s) in the AAAS gene, located on chromosome 12q13, that codes for ALADIN protein. Secondary hypoadrenalism (ACTH deficiency) This is a common clinical problem and most often results from a sudden cessation of exogenous glucocorticoid therapy, or a failure to give adequate glucocorticoid cover for intercurrent stress in a patient who has been on long-term glucocorticoid therapy. Such therapy suppresses the hypothalamic-pituitary-adrenal axis, with consequent adrenal atrophy that may last for months to years after stopping glucocorticoid treatment. Adrenal atrophy and subsequent deficiency should be anticipated in any subject who has taken more than the equivalent of 30 mg of oral hydrocortisone per day (approximately 7.5 mg/day prednisolone or 0.75 mg/day dexamethasone) for longer than 1 month. In addition to the magnitude of the dose of glucocorticoid, the timing of administration may affect the degree of adrenal suppression. Thus, prednisolone in a dose of 5 mg at night and 2.5 mg in the morning will produce more marked suppression of the hypothalamic-pituitary-adrenal axis than 2.5 mg at night and 5 mg in the morning because the

larger evening dose blocks the early morning surge of ACTH. Other causes of secondary adrenal insufficiency are rare (Table 13.5.1.7), and reflect inadequate ACTH production from the anterior pituitary gland. In many of these, other pituitary hormones are deficient in addition to ACTH, so that the patient presents with partial or complete hypopituitarism. However, if there is isolated ACTH deficiency this diagnosis may be readily missed. Lymphocytic hypophysitis and mutations in a transcription factor gene, *Tpit* (*TBX19*), involved in dictating the corticotroph lineage within the anterior pituitary, are rare diseases that may cause isolated ACTH deficiency. Hypoadrenalism may also complicate critical illness, even in individuals with a previously intact hypothalamic–pituitary–adrenal axis. This functional adrenal insufficiency is usually transient and not caused by a structural lesion. This is a controversial area and debate continues regarding its diagnosis, aetiology, and treatment. This is beyond the scope of this chapter (for further information, see suggested reading). Clinical features The most obvious feature differentiating primary from secondary hypoadrenalism is skin pigmentation (Fig. 13.5.1.15), which is nearly always present in primary adrenal insufficiency (unless of short duration) and absent in secondary. The pigmentation is seen in sun-exposed areas, recent rather than old scars, axillae, nipples, palmar creases, pressure points, and in mucous membranes (buccal, vaginal, vulval, anal). The pigmentation reflects increased melanocyte activity induced by POMC-related peptides acting via the melanocortin 1 receptor (*MC1R*). In autoimmune Addison's disease there may be associated vitiligo (Fig. 13.5.1.16). Patients with primary adrenal failure usually have both glucocorticoid and mineralocorticoid deficiency. By contrast, those with secondary adrenal insufficiency have an intact renin–angiotensin–aldosterone system. This accounts for differences in salt and water balance in the two groups of patients, which in turn result in different clinical presentations. (a) (b)

Fig. 13.5.1.15 Pigmentation in a patient with Addison's disease. This is increased in sun-exposed areas (panel (a)) and in the palmar creases (panel (b), where the patient's hand is on the right side of the image, compared to an unaffected control subject's hand on the left side). With permission from Medical Masterclass, 3rd edition, RCP London.

SECTION 13 Endocrine disorders 2350 Primary adrenal failure may present with hypotension and acute circulatory failure (Addisonian crisis). Anorexia may be an early feature that progresses to nausea, vomiting, diarrhoea, and sometimes, abdominal pain. These crises may be precipitated by intercurrent infection or by stress, such as surgery. Alternatively, the patient may present with vague features of chronic adrenal insufficiency—weakness, tiredness, weight loss, nausea, intermittent vomiting, abdominal pain, diarrhoea or constipation, general malaise, muscle cramps, and symptoms suggestive of postural hypotension. Salt craving may be a feature, and there may be a low-grade fever. The lying blood pressure is usually normal, but almost invariably there is a fall in blood pressure on standing. In adrenal insufficiency secondary to hypopituitarism, the presentation may relate to deficiency of hormones other than ACTH, notably luteinizing hormone/follicle-stimulating hormone (infertility, oligo-/amenorrhoea, poor libido), thyroid-stimulating hormone (weight gain, cold intolerance), and growth hormone (hypoglycaemia). Patients with isolated ACTH deficiency present with malaise, weight loss, and other features of chronic adrenal insufficiency. By contrast with primary adrenal failure, patients are usually pale. Investigation Routine biochemical profile In established primary adrenal insufficiency, hyponatraemia is present in about 90% of cases and hyperkalaemia in 65%. The blood urea concentration is usually elevated. In secondary adrenal failure there may be dilutional hyponatraemia, with normal or low blood urea, because glucocorticoids are required to maintain the glomerular filtration rate and excrete a water load. Therefore, patients with secondary adrenal

failure (glucocorticoid deficiency only) may be misdiagnosed as having the syndrome of inappropriate ADH secretion (SIADH). Hypoglycaemia has been found in up to 50% of patients with chronic adrenal insufficiency. Plasma cortisol/ACTH Clinical suspicion of the diagnosis should be confirmed with definitive diagnostic tests. Basal plasma cortisol concentrations are often in the low normal range and cannot be used to exclude the diagnosis. In primary adrenal insufficiency the simultaneous measurement of plasma cortisol and plasma ACTH reveals an ACTH level that is disproportionately elevated in comparison with plasma cortisol (Fig. 13.5.1.17). A plasma ACTH concentration exceeding 66 pmol/litre (300 ng/litre) provides maximum stimulation of glucocorticoid synthesis, hence in the setting of a low cortisol a level of ACTH more than 66 pmol/litre indicates the inability of the adrenal cortex to respond to ACTH stimulation.

Mineralocorticoid status In primary hypoadrenalism there is usually mineralocorticoid deficiency, with elevated plasma renin activity or concentration and either low or low-normal plasma aldosterone. This aspect of investigation is all too frequently ignored in patients with Addison's disease. By contrast, in secondary adrenal failure, only ACTH drive to the adrenal cortex is lacking; the renin-angiotensin-aldosterone axis is intact. **Stimulation tests** In practice, all patients suspected of having adrenal insufficiency should have an ACTH stimulation test. This involves the intramuscular or intravenous administration of 250 µg of tetracosactide (Synacthen, cosyntropin), a peptide comprising the first 24 amino acids of normally secreted 1–39 ACTH. Plasma cortisol levels are measured at 0 and 30 min after tetracosactide administration, and a normal response is defined by a peak plasma cortisol of more than 450–500 nmol/litre (the exact threshold is assay dependent). Levels less than this in response to tetracosactide are found in both primary and secondary adrenal insufficiency. False-positive results have occasionally been reported, particularly in cases of sudden-onset secondary hypoadrenalism. For example, in patients following pituitary surgery or apoplexy assessment of ACTH reserve indirectly by ACTH stimulation test should be delayed for six weeks postoperatively to allow adrenal atrophy to occur in patients with ACTH deficiency (glucocorticoid cover may of course be required in the intervening period). Fig. 13.5.1.16 Vitiligo: smooth depigmented patches. From Barge S, Matin R, Wallis D (eds). Oxford handbook of medical dermatology, 2nd edition. By permission of Oxford University Press. **PRIMARY SECONDARY Addison's Congenital adrenal hyperplasia Organic Iatrogenic** 15 000 1000 500 100 Plasma ACTH (ng/litre) Fig. 13.5.1.17 Morning immunoreactive ACTH values in patients with hypoadrenalism. The reference range is indicated by the shaded bar. Courtesy of Professor LH Rees.

13.5.1 Disorders of the adrenal cortex 2351 A low-dose ACTH stimulation test giving only 1 µg ACTH has been proposed to screen for adequate function of the hypothalamic–pituitary–adrenal axis, with the suggestion that it may be more sensitive than the conventional 250 µg test. At present there are insufficient data to support this. A prolonged ACTH stimulation test, involving the administration of depot tetracosactide in a dose of 1 mg by intramuscular injection, with measurement of plasma cortisol at 0, 4, and 24 h, will differentiate primary from secondary hypoadrenalism, but this test is now rarely required if plasma ACTH has been appropriately measured at baseline. The insulin-induced hypoglycaemia or insulin tolerance test remains one of the most useful in assessing ACTH and growth hormone reserves. It should not be performed in patients with ischaemic heart disease (check ECG before test), epilepsy, or severe hypopituitarism (i.e. plasma cortisol at 09.00 <100 nmol/litre). The test involves the intravenous administration of soluble insulin in a dose of 0.1 to 0.15 U/kg body weight, with measurement of plasma cortisol at 0, 30, 45, 60, 90, and 120 min. Adequate hypoglycaemia (blood glucose <2.2

mmol/litre, with signs of neuroglycopenia—sweating and tachycardia) is essential. In normal subjects the peak plasma cortisol exceeds 500 nmol/litre. However, the response to hypoglycaemia can be reasonably reliably predicted by the response to acute ACTH stimulation (see earlier); a safer, cheaper, and quicker test. If the ACTH test is normal, insulin-induced hypoglycaemia testing is not necessary in the vast majority of cases, unless there is a need to document endogenous growth hormone reserve in a patient with pituitary disease. Other tests

Radioimmunoassays to detect autoantibodies, such as those against the 21-hydroxylase antigen, are available and should be undertaken in patients with primary adrenal failure. In autoimmune Addison's disease it is also important to look for evidence of other organ-specific autoimmune disease (e.g. thyroid dysfunction, pernicious anaemia, coeliac disease, and premature ovarian failure). In long-standing tuberculous adrenal disease there may be adrenal atrophy with calcification on plain radiographs or CT scanning. Early morning urine samples should be cultured for mycobacteria or QuantiFERON checked if tuberculosis is suspected.

Management Acute adrenal insufficiency This is an emergency and treatment should not be delayed while waiting for definitive proof of diagnosis. However, in addition to the measurement of plasma electrolytes and blood glucose, appropriate samples for ACTH and cortisol determination should be taken before giving corticosteroid therapy. If the patient is not critically ill, an acute ACTH stimulation test can be performed, but if necessary this can be delayed and carried out with the patient on corticosteroid therapy. Once the patient has been stabilized, the patient can have a Synacthen test (with omission of evening and morning dose of hydrocortisone prior to test; once the test is complete the patient can receive their usual morning dose of hydrocortisone). In the acute setting, patients should be treated in a critical care setting and intravenous hydrocortisone should be given immediately at a dose of 100 mg, followed by 200 mg of hydrocortisone per 24 hours (either as a continuous infusion or 50 mg by injection every 6 hours). If this is not possible then the intramuscular route should be used. In the patient with shock, 1 litre of 0.9% sodium chloride should be given intravenously over the first hour. Because of possible hypoglycaemia, 5% dextrose is often also required. Subsequent intravenous fluid replacement will depend on biochemical monitoring and the patient's condition. Inotropic support may be required initially until the patient's condition is improved. Clinical improvement, especially in blood pressure, should be seen within 4 to 6 h if the diagnosis is correct. It is important to recognize and treat any associated condition, such as an infection that may have precipitated the acute adrenal crisis.

Table 13.5.1.8 Management of primary adrenal insufficiency

Condition	Suggested action
Home management of illness with fever	Hydrocortisone replacement doses doubled ($>38^{\circ}\text{C}$) or tripled ($>39^{\circ}\text{C}$) until recovery (usually 2 to 3 d); increased consumption of electrolyte-containing fluids as tolerated
Unable to tolerate oral medication due to gastroenteritis or trauma	Adults, IM or SC hydrocortisone 100 mg; children, IM hydrocortisone 50 mg/m ² or estimate; infants, 25 mg; school-age children, 50 mg; adolescents, 100 mg
Minor to moderate surgical stress	Hydrocortisone, 25–75 mg/24 h (usually 1 to 2 d)
Major surgery with general anaesthesia, trauma, delivery, or disease that requires intensive care	Hydrocortisone, 100 mg per IV injection followed by continuous iv infusion of 200 mg hydrocortisone/24 h (alternatively 50 mg every 6 h IV or IM)
Children	hydrocortisone 50 mg/m ² iv followed by hydrocortisone 50–100 mg/m ² /d divided q 6 h
Weight-appropriate continuous iv fluids	with 5% dextrose and 0.2 or 0.45% NaCl
Rapid tapering and switch to oral regimen	depending on clinical state
Acute adrenal crisis	Rapid infusion of 1000 ml isotonic saline within the first hour or 5% glucose in isotonic saline, followed by continuous iv isotonic saline guided by individual patient needs
Hydrocortisone	100 mg IV immediately followed by hydrocortisone 200 mg/d as a continuous infusion for 24 h, reduced to hydrocortisone 100 mg/d the following day

Children, rapid bolus of normal saline (0.9%) 20 ml/kg. Can repeat up to a total of 60 ml/kg within 1 h for shock. Children, hydrocortisone 50–100 mg/m² bolus followed by hydrocortisone 50–100 mg/m²/d divided q 6 h For hypoglycaemia: dextrose 0.5–1 g/kg of dextrose or 2–4 ml/kg of D25W (maximum single dose 25 g) infused slowly at rate of 2–3 ml/min. Alternatively, 5–10 ml/kg of D10W for children <12 years old Cardiac monitoring: rapid tapering and switch to oral regimen depending on clinical state Abbreviation: D10W, 10 % dextrose solution; D25W, 25% dextrose solution. From Bornstein SR, et al. (2016). Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab, 101, 364–89. By permission of Oxford University Press.

SECTION 13 Endocrine disorders 2352 After 24 hours of clinical improvement (and if there is no ongoing precipitant) the dose of hydrocortisone can be reduced, usually to 100 mg per 24 h (either by continuous infusion or 25 mg every 6 hours). If the patient continues to recover and the precipitant has been treated then, if the patient can take by mouth, hydrocortisone can be switched to the oral route, 40 mg in the morning and 20 mg at 18.00. This can then be rapidly reduced to the normal replacement dose. Some patients will require more than 30 mg/day, but most patients require less than this (usually 15–25 mg/day). Chronic adrenal insufficiency Glucocorticoid replacement Long-term treatment requires glucocorticoid replacement; doses vary between 15 and 25 mg hydrocortisone (or 20–35 mg cortisone acetate) in divided doses (either twice or thrice daily), with the largest dose on waking to mimic the circadian rhythm. Hydrocortisone is to be doubled or trebled in the event of intercurrent stress or illness. Higher doses may be required in some patients but there needs to be caution in using higher doses for prolonged periods due to the potential of chronic glucocorticoid overexposure. Monitoring of glucocorticoid replacement should be performed by clinical assessment including body weight, postural blood pressure, energy levels, and signs of frank glucocorticoid excess. A newly marketed modified release hydrocortisone preparation can be administered once/ twice daily and other slow release preparations are in development. Patients receiving glucocorticoid replacement therapy should be advised to double/treble the dose in the event of an intercurrent febrile illness, accident, or in some cases of psychological stress. If the patient is vomiting and cannot take by mouth, parenteral hydrocortisone must be given urgently, as indicated earlier. For minor surgery, 50 to 100 mg of hydrocortisone is given with the premedication. For major procedures this is then followed by the same regimen as for acute adrenal insufficiency. Every patient on glucocorticoid therapy should be advised to register for an alert bracelet or necklace and to carry a steroid card giving information on the treatment being given. Many patients also carry hydrocortisone emergency kits for self-injection in case immediate access to medical care is not possible, and all patients should be trained in giving themselves hydrocortisone injections. The hydrocortisone emergency kit should only be used as a stopgap in order to allow the patient to get to hospital for urgent medical attention. Mineralocorticoid replacement In primary adrenal failure, mineralocorticoid replacement is usually also required in the form of fludrocortisone at a dose of 50 to 100 µg/day. After the acute phase has passed, the adequacy of mineralocorticoid replacement can be assessed by measuring electrolytes, supine and erect blood pressure, and plasma renin activity; too little fludrocortisone may cause postural hypotension with elevated plasma renin activity, and too much causes the converse. If patients develop hypertension while receiving fludrocortisone an initial dose reduction may be helpful; equally a dose reduction of hydrocortisone replacement may be required. If hypertension persists, fludrocortisone should not be discontinued but rather an antihypertensive agent added. If the patient is euvolaemic the

antihypertensive of choice is an angiotensin II receptor blocker. If these cannot be used or tolerated, then a dihydropyridine calcium channel blocker can be used, but diuretics should be avoided and eplerenone and spironolactone are contraindicated. Adrenal androgen replacement For patients with both primary and secondary adrenal failure, beneficial effects have been reported for adrenal androgen replacement therapy with 25 to 50 mg/day dehydroepiandrosterone (DHEA). Benefit is principally confined to female patients and includes improvement in sexual function and well-being, hence those who have low libido, depressive symptoms, and low energy levels despite optimized glucocorticoid and mineralocorticoid replacement may be helped by DHEA. If there are no improvements in symptoms after six months the treatment should be discontinued. Morning dehydroepiandrosterone sulphate (DHEAS) levels before the ingestion of DHEA dose can be used for monitoring with a target DHEAS in the mid-normal range.

Mineralocorticoid excess Blood pressure is a quantitative trait that significantly affects cardiovascular and cerebrovascular risk and mortality. Based on this, arbitrary cut-offs define a hypertensive population that, depending on age, constitutes 10 to 25% of the population. In most cases, no underlying cause for the patient's raised blood pressure can be found, and they are given a diagnosis of essential hypertension. However, mineralocorticoid-based hypertension may account for a significant proportion of secondary causes of hypertension, and classically refers to hypertension caused by increased sodium and water retention by the kidney, and expansion of the extracellular fluid compartment, resulting in suppression of endogenous plasma renin activity. The implicated mineralocorticoid is most commonly aldosterone. Mineralocorticoid production and action Several key steps govern the production and action of mineralocorticoids:

- Angiotensinogen is converted to Angiotensin I under the control of renin (produced in the juxtaglomerular apparatus in response to reduced plasma volume and renal perfusion);
- Angiotensin I is, in turn, converted to angiotensin II by the action of Angiotensin Converting Enzyme (ACE).
- Aldosterone is synthesized in the zona glomerulosa of the adrenal cortex from corticosterone by aldosterone synthase (CYP11B2), which is regulated by serum potassium and angiotensin II (with ACTH having a lesser effect).
- Aldosterone binds to its (mineralocorticoid) receptor in the distal renal tubules and results in increased activity of the α subunit of the epithelial sodium channel, Na/K ATPase, and Aquaporin 2, which increase retention of salt and water and excretion of potassium and hydrogen ions.

Aetiology Mineralocorticoid excess may be seen in several contexts:

- Primary (hyper)aldosteronism
- Secondary (hyper)aldosteronism (e.g. due to renovascular disease)

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- Nonaldosterone mediated (e.g. some types of congenital adrenal hyperplasia; syndrome of apparent mineralocorticoid excess; excess liquorice or carbenoxolone ingestion; Cushing's syndrome; glucocorticoid resistance; deoxycorticosterone-producing adrenal tumour)

A comprehensive list of the causes of mineralocorticoid hypertension is given in Table 13.5.1.9. For a perspective from a specialist in hypertension, see Chapter 16.17.3 for further information.

Primary aldosteronism Epidemiology and aetiopathogenesis First described by Jerome Conn in 1955, primary aldosteronism was for a long time considered to account for only a small proportion of cases of hypertension. However, it has become clear in recent years that this classical teaching no longer holds true, with recent studies demonstrating a much higher prevalence of primary aldosteronism (5–10% of all patients), especially among those with resistant hypertension (up to 25%). Aldosterone-producing adenomas (APA, also known as Conn's adenomas) and bilateral idiopathic hyperaldosteronism (IHA, also known as bilateral adrenal hyperplasia) account for most cases. Rarer causes include unilateral hyperplasia, adrenal

carcinoma, ectopic aldosterone production, and familial/inherited syndromes. Several inherited and acquired forms of primary aldosteronism are now recognized. Familial (hyper)aldosteronism (FH) Type I: fusion of the CYP11B1 (11- β hydroxylase) and CYP11B2 (aldosterone synthase) genes creates a chimera in which the ACTH-responsive 11- β -hydroxylase promoter drives expression of aldosterone synthase; autosomal dominant (AD) inheritance, with early-onset severe hypertension; responds to glucocorticoid treatment [to suppress ACTH = glucocorticoid-remediable (suppressible) aldosteronism (GRA)]. Type II: aetiology remains unknown, although linkage has been shown to chromosome 7p22; AD inheritance with variable phenotype. Type III: caused by germline mutations in the KCNJ5 gene (encoding a subunit for an inwardly rectifying potassium channel GIRK4), which reduces potassium channel selectivity, and thus facilitates enhanced aldosterone production/secretion and possibly cell proliferation; AD. Type IV: caused by germline mutations in the CACNA1H gene, which encodes the α subunit of an L-type voltage-gated calcium channel (Cav3.2). Sporadic primary aldosteronism Somatic mutations in several genes have recently been identified in patients with sporadically-occurring APAs. These include: KCNJ5: the same gene as implicated in FH type III; mutations result in chronic depolarization and Ca^{2+} influx; estimated to be present in up to 40% of all APAs (but with a particular predominance in young females with APAs). ATP1A1: encodes the α subunit of the $\text{Na}^{+}/\text{K}^{+}$ -ATPase 1; mutations result in chronic depolarization, with opening of voltage-gated calcium channels leading to aldosterone production/secretion; estimated to be present in c.5% of APAs. ATP2B3: encodes the plasma membrane Ca^{2+} -ATPase 3; estimated to be present in c.1–2% of APAs. CACNA1D: encodes an L-type voltage-gated calcium channel (Cav1.3); mutations result in channel activation at less depolarized potentials and may in some instances impair channel inactivation; estimated to be present in c.10% of APAs. CTNNB1: activating mutations of CTNNB1 gene (β -catenin) in the Wnt signalling pathway. Clinical features Symptoms are often absent or nonspecific, but include tiredness, muscle weakness, thirst, polyuria, and nocturia resulting from hypokalaemia. Spontaneous hypokalaemia (<3.5 mmol/litre) is rare in untreated hypertension; when it is found in a patient on diuretics these should be withdrawn, and potassium stores replenished and Table 13.5.1.9 Differential diagnosis of mineralocorticoid excess Cause Offending mineralocorticoid Primary aldosteronism Aldosterone Congenital adrenal hyperplasia Deoxycorticosterone 11 β -Hydroxylase deficiency 17 α -Hydroxylase deficiency Glucocorticoid receptor resistance Deoxycorticosterone Glucocorticoid receptor mutations Metyrapone, RU486 ingestion Deoxycorticosterone-secreting adrenal tumour Deoxycorticosterone Liddle's syndrome None 11 β -Hydroxysteroid dehydrogenase deficiency Cortisol Apparent mineralocorticoid excess Liquorice and carbenoxolone ingestion Ectopic ACTH syndrome Liddle's syndrome is caused by a gain-of-function mutation in the epithelial sodium channel (ENaC) and is therefore strictly speaking independent of mineralocorticoid.

SECTION 13 Endocrine disorders 2354 remeasured 2 weeks later. Despite this, it is now accepted that most patients with confirmed primary aldosteronism have normal serum potassium concentrations. Screening for primary aldosteronism Screening for primary aldosteronism should be considered in the following circumstances: • Hypertension and hypokalaemia (especially unprovoked) • Young age of onset of hypertension and/or severe hypertension • Treatment-resistant hypertension (≥ 3 antihypertensive agents and poor control) • Hypertension in the setting of an incidental adrenal mass • Whenever secondary causes of hypertension are being considered. Case detection can be performed by measuring ambulatory, paired random plasma renin activity (PRA) (or plasma renin mass/ concentration—PRC) and plasma aldosterone concentration (PAC), to

yield an aldosterone-renin-ratio. It has been suggested that screening should preferably be performed using an early morning sample, but testing at other times of day is acceptable and often more practical. Interpretation of PRA and PAC measurements is laboratory and assay dependent and, wherever possible, locally derived PRA/PAC cut-offs should be defined (similarly, centres using plasma renin mass/concentration assays will need to determine thresholds for triggering further investigation). With a few notable exceptions including mineralocorticoid receptor antagonists, amiloride, renin inhibitors (which should be discontinued for at least 4–6 weeks before testing), and possibly β -adrenergic blockers (which require discontinuation for at least two weeks—although see comments to follow), PRA and PAC can be measured while the patient is taking antihypertensive therapy. However, careful interpretation underpinned by a clear understanding of the effects of different agents on the renin–angiotensin system (RAA) system is required if ‘false positives’ and ‘false negatives’ are to be avoided. ACE-inhibitors (ACE-I), angiotensin receptor antagonists/blockers, and nonpotassium-sparing diuretics can all elevate PRA/renin mass, thereby masking a diagnosis of primary aldosteronism (false negative screen). By contrast, the finding of a low/suppressed PRA/renin mass in this treatment context is very strongly suggestive of PA. β -adrenergic blockers (and centrally acting α -2-agonists) suppress renin and aldosterone secretion in subjects without primary aldosteronism, but the fall in aldosterone is typically less marked, resulting in an increase in the PAC/PRA ratio, although absolute aldosterone levels do not usually exceed 415 pmol/litre. It is important to note, however, that uncorrected hypokalaemia and/or calcium antagonist therapy (see later) may confound interpretation of absolute aldosterone levels. Dihydropyridine calcium antagonists/blockers can suppress aldosterone secretion, resulting in a false negative test. Some calcium channel antagonists (e.g. verapamil, diltiazem), α 1-adrenergic blockers (e.g. doxazosin) and the direct-acting smooth muscle relaxant hydralazine appear to have little effect on PRA and PAC and hence remain the ‘agents of choice’ when screening for primary aldosteronism in patients requiring antihypertensive therapy, but not all patients can be satisfactorily controlled on these drugs alone. It is also important to correct hypokalaemia before measuring PAC as a low serum potassium level can impair aldosterone secretion and, if left uncorrected, can result in false negative screening in milder cases of primary aldosteronism. Other (non-antihypertensive) agents may also interfere with measurement of PRA and PAC, most notably nonsteroidal anti-inflammatory drugs (NSAIDs), which lower renin and aldosterone levels. Patients should also be advised to avoid ingestion of liquorice-containing products given the potential to cause confusion by inducing a state of apparent mineralocorticoid excess (see next).

Confirmatory testing for primary aldosteronism

Several different tests have been proposed to confirm autonomous aldosterone secretion.

Oral sodium loading test Sodium (>200 mmol per day, equivalent to c.12 g of sodium chloride) is administered for three days, with potassium supplementation as required to prevent exacerbation of hypokalaemia. At completion of the test a 24 h urine specimen is collected (from the morning of day 3 to the morning of day 4) for estimation of sodium, creatinine, and aldosterone to confirm (i) adequate sodium loading, (ii) ongoing inappropriate/autonomous aldosterone secretion. This is more time-consuming than the intravenous saline infusion test and relies on ability of laboratory to accurately measure urinary aldosterone. It should be avoided in patients with severe uncontrolled hypertension, cardiac failure, arrhythmias, or renal impairment.

Intravenous saline infusion test Two litres of 0.9% saline is infused over 4 h with measurement of PAC before and after the infusion to demonstrate failure of suppression of aldosterone secretion. Hypokalaemia should be corrected, and blood pressure and heart rate must be monitored during the test, which is normally performed in the morning. It should be avoided in patients with severe uncontrolled hypertension, cardiac failure, arrhythmias,

or renal impairment. False negative results (i.e. apparent normal suppression) have been described in some patients with primary aldosteronism. Fludrocortisone suppression test 0.1 mg of oral fludrocortisone is given every 6 h for 4 days, with oral sodium supplementation as required and potassium replacement sufficient to avoid hypokalaemia. Caution must be exercised in patients with severe hypertension and in those with a history of cardiac or renal impairment. Captopril test This is possibly less reliable than the other tests described, with false negative or equivocal results reported. Distinguishing unilateral and bilateral (sporadic) primary aldosteronism In patients with unilateral primary aldosteronism (40–50% of cases) due to an APA or unilateral hyperplasia, adrenalectomy offers the potential for biochemical cure, and resolution/improvement of hypertension; by contrast, IHA is most appropriately treated with medical therapy, hence it is extremely important to achieve a correct diagnosis.

13.5.1 Disorders of the adrenal cortex 2355 Investigations used to establish laterality in primary aldosteronism include: Cross-sectional imaging Thin slice adrenal CT or MRI are the standard techniques (Fig. 13.5.1.18). Although the finding in a young patient (<35 y) of a classical solitary Conn's adenoma (1–2 cm diameter lesion) with an entirely normal contralateral gland may be sufficient to proceed directly to surgery, CT or MRI alone are generally considered insufficient to lateralize primary aldosteronism in most patients. Adrenal vein sampling This remains the gold-standard for distinguishing unilateral and bilateral primary aldosteronism, but is technically challenging and in many centres the right adrenal vein (which drains directly into the inferior vena cava) is successfully cannulated in only 50–80% of cases. Matters are further complicated by the fact that there are several different sets of criteria for defining successful adrenal vein cannulation and lateralization based on measurement of plasma cortisol and aldosterone levels in both adrenal veins and in the inferior vena cava (IVC). In recognition that both cortisol and aldosterone secretion can be pulsatile, many centres advocate performing adrenal vein sampling with tetracosactide (Synachen, cosyntropin) stimulation (either bolus or continuous infusion) and/or simultaneous (as opposed to sequential) adrenal vein sampling. These modifications minimize the chance of creating artificial gradients, and cosyntropin infusion can increase confidence that both adrenal veins have been successfully cannulated by enhancing the plasma cortisol gradients between adrenal veins and IVC. However, simultaneous sampling (at least theoretically) increases the risk of adrenal vein thrombosis due to longer catheter occupancy of the vein on the side catheterized first. A recently published expert consensus statement offers a detailed summary of the literature and makes helpful recommendations regarding how to perform and interpret adrenal vein sampling, although a recent study (SPARTACUS trial) has questioned the assumption that adrenal vein sampling is superior to cross-sectional imaging with respect to guiding management and yielding favourable outcomes, but these findings remain strongly debated. ¹¹C-metomidate PET-CT Emerging data suggests that functional adrenal imaging may offer a noninferior alternative to adrenal vein sampling for distinguishing unilateral and bilateral primary aldosteronism. An immediate attraction of this technique is its noninvasive nature, but further studies are awaited to confirm early findings. Clinical prediction score The inherent difficulties associated with performing adrenal vein sampling stimulated Kupers and colleagues to assess the potential utility of a clinical scoring system in predicting unilateral disease. In 87 patients with primary aldosteronism and successful adrenal vein sampling, lateralization was demonstrated in 49 patients. All 26 patients with a typical Conn's adenoma and serum potassium level less than 3.5 mmol/litre or estimated glomerular filtration rate (eGFR) at least 100 ml/min/1.73 m² (or both) had unilateral primary aldosteronism; this rule had 100% specificity and 53% sensitivity.

However, in two follow-up studies by independent workers, neither group was able to reproduce the 100% specificity (88.5% and 80%, respectively). Management Unilateral laparoscopic adrenalectomy remains the preferred treatment option for patients with an APA or unilateral hyperplasia. It offers the potential to ameliorate/correct hypertension, abolish hypokalaemia, and correct hyperaldosteronism. However, patients must be carefully counselled that successful surgery (as judged by the correction of biochemical hyperaldosteronism) does not translate into normalization of blood pressure in some cases, although the number of antihypertensive agents required is usually reduced postoperatively. Two potential complications must be looked out for following unilateral adrenalectomy: hypocortisolism secondary to cortisol cosecretion by an aldosterone-producing adenoma with suppression of the hypothalamic-pituitary-contralateral adrenal gland, and hypoaldosteronism manifest as hypotension (especially postural) and hyperkalaemia due to persistent suppression of the RAA system. Recovery of normal endogenous function is recognized in both contexts and should be checked for periodically. Hyperaldosteronism per se is associated with excess cardiovascular morbidity and mortality independent of its effects on blood pressure. (a) (b) Fig. 13.5.1.18 (a) Adrenal CT scan demonstrating a solitary adrenal adenoma in a patient with Conn's syndrome and (b) the characteristic yellow appearance of the cut surface of the excised tumour reflecting the high cholesterol content of these tumours.

SECTION 13 Endocrine disorders 2356 pressure (e.g. through promoting myocardial fibrosis). Accordingly, mineralocorticoid receptor antagonist therapy is the treatment of choice when preparing patients for adrenalectomy and as long-term primary medical therapy in those unfit/unwilling to consider surgery or in whom there is evidence of bilateral disease. Spironolactone remains the mineralocorticoid receptor antagonist of choice in many centres, but side effects (gynaecomastia in males; menstrual irregularity in females) may limit its use. Eplerenone, a competitive and selective mineralocorticoid receptor antagonist, is a useful alternative, although its use in this context remains off-licence in most countries and its potency appears to be less than that of spironolactone. Combination with amiloride (to block the epithelial sodium channel) increases the efficacy of mineralocorticoid antagonism. Calcium antagonists are a useful adjunct for controlling hypertension in primary aldosteronism. Single gene defects resulting in mineralocorticoid excess Hypertension is a phenotype of some well-documented gene mutations; 17α -hydroxylase deficiency and 11β -hydroxylase deficiency cause forms of congenital adrenal hyperplasia in which mineralocorticoid excess occurs because of ACTH-driven deoxycorticosterone excess. A similar process is thought to explain the hypertension seen in patients with glucocorticoid resistance resulting from mutations in the glucocorticoid receptor gene. A significant advance in our understanding of the molecular basis of cardiovascular disease has been the elucidation of other single gene defects causing mineralocorticoid hypertension (Fig. 13.5.1.19). Glucocorticoid-suppressible hyperaldosteronism (See Chapter 16.17.4.) Liddle's syndrome (See Chapter 16.17.4.) Apparent mineralocorticoid excess and abnormalities of 11β -hydroxysteroid dehydrogenase type 2 (See Chapter 16.17.4 for discussion of apparent mineralocorticoid excess.) Liquorice has been associated with a mineralocorticoid excess state since the late 1940s, when Reeves, a Dutch physician, used a liquorice preparation, *succus liquoritiae*, to treat patients with dyspepsia. This was the origin of the antiulcer drug, carbenoxolone, which also results in mineralocorticoid side effects in up to 50% of patients. The active 'mineralocorticoids' in both cases are glycyrrhizic acid and its hydrolytic product, glycyrrhetinic acid, which themselves have little inherent mineralocorticoid activity, but cause

hyper-tension and hypokalaemia by inhibiting 11β -HSD2 (Fig. 13.5.1.20). Such patients will also have an increase in the urinary ratio of cortisol to cortisone metabolites (THF+allo-THF/THE), although not to the same extent as patients with apparent mineralocorticoid excess. Cortisol is also the offending mineralocorticoid in patients with some forms of Cushing's syndrome. In ectopic ACTH syndrome, for example, the high cortisol secretion rate overwhelms renal 11β -HSD2, resulting in spillover to the mineralocorticoid receptor. A high THF+allo-THF/THE ratio is also observed in some patients with pituitary-dependent Cushing's syndrome, and this may explain the hypertension in these cases. Activating mutations in the mineralocorticoid receptor One kindred has been reported with a homozygous point mutation in the mineralocorticoid receptor that results in a serine to leucine change at amino acid 810, with severe hypertension at a young age. An interesting facet of this mutation is that the mutated receptor is induced by progesterone and some of its hydroxylated derivatives, thereby explaining pregnancy-induced hypertension in affected female members of the kindred. Glucocorticoid resistance A few patients have been described who have increased cortisol secretion, but none of the stigmas of Cushing's syndrome. These patients are resistant to the suppression of cortisol with low-dose dexamethasone but respond to high doses. ACTH levels are elevated and lead to increased adrenal production of androgens and deoxy-corticosterone, hence patients may present with the features of androgen and/or mineralocorticoid excess. Treatment with a dose of dexamethasone adequate to suppress ACTH (usually 3 mg/day) results in a fall in adrenal androgens and often the return of plasma potassium and blood pressure to normal levels. Many of these patients have been found to have point mutations in the steroid-binding Na⁺ Apparent mineralocorticoid excess Liddle's syndrome Cortisone Apical Na channel Mineralocorticoid receptor Type 2 11β -HSD Cortisol Basolateral Na/K ATPase Target gene transcription Cortisol Aldosterone Aldosterone Aldosterone excess Glucocorticoid-suppressible hyperaldosteronism Na⁺ α β γ Fig. 13.5.1.19 A schematic diagram representing an epithelial cell in the distal colon or distal nephron. In normal physiology, aldosterone interacts with the mineralocorticoid receptor (MR) to stimulate sodium reabsorption via induction of the apical sodium channel and serosal Na⁺,K⁺-ATPase pump. GSH (glucocorticoid-suppressible hyperaldosteronism) is a cause of aldosterone excess that results from the production of a chimaeric gene, 11β -hydroxylase/aldosterone synthase, within the adrenal cortex. Apparent mineralocorticoid excess results because cortisol cannot be inactivated to cortisone by the type 2 isoform of 11β -hydroxysteroid dehydrogenase (11β -HSD2); cortisol can then act as a potent mineralocorticoid. Liddle's syndrome occurs because of constitutively active mutations in the β - or γ -subunits of the apical sodium channel. Activating mutations in the MR can also lead to inappropriate sodium retention.

13.5.1 Disorders of the adrenal cortex 2357 domain of the glucocorticoid receptor, with consequent reduction of glucocorticoid-binding affinity. Mineralocorticoid deficiency These syndromes are listed in Table 13.5.1.10. They can be divided into those that are congenital and others that are acquired. Adrenal insufficiency Mineralocorticoid deficiency may occur in some forms of congenital adrenal hyperplasia and these are discussed elsewhere (see Chapter 13.5.2). Similarly, other causes of adrenal insufficiency (e.g. Addison's disease and congenital adrenal hypoplasia) are discussed earlier. Primary defects in aldosterone biosynthesis Before the characterization of the CYP11B2 gene, the disease was termed corticosterone methyl oxidase type I (CMO I) deficiency and corticosterone methyl oxidase type II (CMO II) deficiency. Subsequently, both variants were shown to be secondary to mutations in aldosterone synthase and are now termed type I and type II aldosterone synthase deficiency. Both variants are rare and inherited as autosomal recessive

traits. The type II deficiency is found most frequently among Jews of Iranian origin. Presentation is usually in neonatal life as a salt-wasting crisis with severe dehydration, vomiting, and failure to grow and thrive. Hyperkalaemia, metabolic acidosis, dehydration, and hyponatraemia are found. Plasma renin activity is elevated, and plasma aldosterone levels are low. Plasma 18-hydroxycorticosterone levels and the ratio of plasma 18-hydroxycorticosterone to aldosterone and their urinary metabolites are used to differentiate the type I and II variants. In most infants the disorders become less severe as the child ages; in older children, adolescents, and adults, the abnormal steroid pattern described may be present and may persist throughout life without clinical manifestations. Mineralocorticoids (fludrocortisone) are given during infancy and early childhood, but this therapy can be discontinued in most adults. Spontaneous normalization of growth can occur in untreated patients. Rarely, presentation can be in adulthood. Defects in aldosterone action: Pseudohypoaldosteronism (See Chapter 16.17.4.) Hyporeninaemic hypoaldosteronism Angiotensin II is a key stimulus for aldosterone secretion, and damage or blockade of the renin-angiotensin system may result in mineralocorticoid deficiency. Various renal diseases have been associated with damage to the juxtaglomerular apparatus and hence renin deficiency. These include systemic lupus erythematosus, myeloma, amyloidosis, AIDS, and the use of NSAIDs, but the most common (>75% of cases) is diabetic nephropathy. The usual picture is of an older patient with hyperkalaemia, acidosis, and mild to moderate impairment of renal function. Plasma renin activity and aldosterone are low and fail to respond to sodium depletion, erect posture, or furosemide administration. By contrast with adrenal insufficiency, patients have normal or elevated blood pressure and no postural hypotension. Muscle weakness and cardiac arrhythmias may also occur. Other factors may contribute to the hyperkalaemia, including the use of potassium-sparing diuretics, potassium supplementation, insulin deficiency, and β -adrenoceptor blockers and prostaglandin synthase inhibitors that inhibit renin release. The treatment of primary renin deficiency is with fludrocortisone in the first instance, together with dietary potassium restriction. However, these patients are not salt depleted and may become MR F (a) (b) Kidney, colon, salivary gland MR AME 11 β -HSD2 F MR aldo MR aldo MR aldo MR aldo MR aldo MR aldo MR aldo F E F Kidney, colon, salivary gland MR F MR aldo MR F MR F MR F MR F MR F MR F E Fig. 13.5.1.20 (a) The role of 11 β -hydroxysteroid dehydrogenase (11 β -HSD2) in protecting the nonspecific mineralocorticoid receptor (MR) from cortisol, and (b) with congenital or acquired deficiency of the enzyme, F (cortisol) cannot be inactivated to E (cortisone) and acts as a potent mineralocorticoid. Table 13.5.1.10 Causes of mineralocorticoid deficiency Addison's disease Adrenal hypoplasia Congenital adrenal hyperplasia: 17-hydroxylase 3 β -hydroxysteroid dehydrogenase deficiencies Pseudohypoaldosteronism types I and II Hyporeninaemic hypoaldosteronism Aldosterone biosynthetic defects Drug induced

SECTION 13 Endocrine disorders 2358 hypertensive with fludrocortisone. In such a scenario the addition of a loop-acting diuretic such as furosemide is appropriate. This will increase acid excretion and improve the metabolic acidosis. Adrenal incidentalomas An adrenal incidentaloma is an adrenal mass detected on imaging not performed for suspected adrenal disease. With the more widespread use of high-resolution cross-sectional imaging procedures (CT and MRI), incidentally discovered adrenal masses have become common, being uncovered in 4 to 7% of patients over the age of 40 years who are imaged for nonadrenal pathology. Over 80% of cases are nonfunctioning, with pheochromocytomas and cortisol or aldosterone secreting adenomas making up most of the remainder. A few incidentalomas will be adrenocortical carcinomas or rarer causes such as lymphangioma or primary adrenal lymphoma. Importantly, in patients with prior

history of malignancy, an adrenal incidentaloma may reflect a metastatic deposit (e.g. up to 20% of patients with lung cancer have adrenal metastases on CT scanning). The data regarding relative frequency of different underlying tumour type is variable depending whether the series is surgical or one which takes all patients with an adrenal mass. Investigation In general, when an adrenal lesion is discovered, two questions need to be addressed: is this lesion malignant? And is this lesion secretory? These questions are answered by a combination of endocrinological and radiological tests.

Endocrinological tests Some incidentalomas may cause abnormal hormone secretion without obvious clinical manifestations of a hormone excess state, the best example of which relates to autonomous cortisol secretion (often without any clinical evidence of Cushing's syndrome) that may occur in up to 10% of all cases. As a result, all patients with incidentally discovered adrenal masses should undergo appropriate endocrine screening tests: plasma or urine metanephrines and normetanephrines to exclude a pheochromocytoma; overnight dexamethasone suppression test/late-night salivary cortisol/ 9am ACTH/DHEAS (low levels are suggestive of a lack of ACTH) to exclude autonomous hypercortisolism; plasma aldosterone:renin ratio to screen for primary aldosteronism; and adrenal androgens if hyperandrogenism is suspected.

Adrenal imaging There are three main radiological techniques that can help determine whether an adrenal lesion is benign or malignant: CT, MRI, and FDG-PET/CT.

CT scanning CT scanning has high spatial and quantitative contrast resolution, which allows assessment of tissue density as measured by Hounsfield units (HU—the HU value of water is 0 and tissues are compared to this). An adrenal lesion on a noncontrast CT with a density less than 10 HU is strongly suggestive of a lipid rich benign adenoma (Fig. 13.5.1.9), but 30% of benign adenomas will have a HU more than 10 which overlaps with more malignant lesions and pheochromocytomas. In an attempt to further characterize these lesions (with HU >10) a contrast-enhanced washout CT can be performed. Benign adenomas take up intravenous contrast rapidly, but also exhibit a rapid loss (washout) of contrast; malignant lesions are described as having slower contrast washout. During a contrast-enhanced washout scan, a measure of HU is taken at baseline before contrast injection (HUnative), 60 seconds following contrast injection (HUmax), and then 10 or 15 minutes postcontrast injection (HU 10/15). This allows calculation of the relative contrast enhancement washout ($=100 \times (HU_{max} - HU_{10/15 \text{ min}})/HU_{max}$) and absolute contrast enhancement washout ($=100 \times (HU_{max} - HU_{10/15 \text{ min}})/(HU_{max} - HU_{native})$). A relative washout more than 40% and an absolute washout more than 60% is suggestive that an adrenal lesion is benign.

MRI imaging This has the advantage of not exposing the patient to ionizing radiation and not requiring iodinated contrast. To differentiate between benign and malignant adrenal lesions the technique of chemical shift is utilized. This allows separate images to be generated, with fat and water oscillating in phase or out of phase with each other (Fig. 13.5.1.21). Adrenal adenomas, which are lipid rich, show signal dropout on the out of phase sequence (compare the grey and black appearances of the adrenal nodule during the in and out of phase images, respectively).

13.5.1 Disorders of the adrenal cortex 2359 have high intracellular lipid content usually, lose signal intensity on out of phase images compared with in phase images. Pheochromocytoma or malignant lesions which are lipid poor do not have this characteristic.

FDG-PET/CT This nuclear medicine modality provides quantitative tomography images after intravenous injection of 18F-fluorodeoxyglucose (18F-FDG-PET/CT). Positivity is not specific for cancer but rather a marker of cells which have increased requirement for glucose/ glucose metabolism. Quantitative measures of 18F concentrations within tissues can be determined by using the standardized uptake value,

which compares the intensity of uptake of ^{18}F in the adrenal lesion to the average of the whole body. Lesions which can be ^{18}F -FDG-PET/CT avid include pheochromocytomas/paragangliomas, adrenocortical carcinomas and metastases from nonadrenal primaries (Fig. 13.5.1.22).

Other investigations Despite the aforementioned imaging modalities there may still be some lesions which are indeterminate. In this setting there are three options: 1. Consider further imaging using a different modality 2. Interval imaging in 6–12 months (using noncontrast CT or MRI) 3. Surgical resection without further delay

The choice of the best approach for each individual patient should be made in a multidisciplinary team environment.

Biopsy of adrenal lesions In general, biopsy of an adrenal lesion should be avoided. This is important in patients who have an adrenocortical carcinoma as a biopsy breaches the tumour capsule, which can lead to seeding of the tumour and a poorer outcome. Similarly, a biopsy should not be undertaken until a thorough endocrine work up has been performed: most notably pheochromocytoma should be excluded given the risk of inducing a pheochromocytoma crisis. Adrenal biopsy should only be performed if the result of the biopsy will significantly alter the management of the patient, for example in assessment of someone with other malignant disease (e.g. lung cancer), in order to allow accurate staging. An adrenal resection rather than biopsy is often a more appropriate method of assessment.

Adrenocortical carcinoma Adrenocortical carcinoma is a rare and highly aggressive malignancy with an annual incidence of 0.7–2.0 cases per million population. Alterations have been found in several genes in this condition, including TP53, CTNNB1, SF1, 11p15 locus, mismatch repair genes, microRNAs, and Jag1. Autonomous hormone secretion is reported in more than 80% of cases. Detailed analysis of urinary corticosteroid metabolites by Gas Chromatography/ Mass Spectrometry reveals characteristic abnormalities of metabolites which may serve as a ‘fingerprint’ for malignancy and may in future be used as a potential biomarker. Imaging of adrenocortical carcinomas often show large heterogeneous tumours with central necrosis and in many cases metastatic disease at time of diagnosis (Fig. 13.5.1.10). All adrenocortical carcinomas show elevated Hounsfield units more than 10 on noncontrast imaging. On surgical resection specimens the diagnosis is made based on the Weiss score, comprised of certain histopathological features. The higher the score the more likely a diagnosis of adrenocortical carcinomas, a score of more than 3 particularly predicting increased risk of malignant behaviour. Treatment of adrenocortical carcinomas involves radical resection where possible, with or without irradiation to the tumour bed as adjuvant therapy. Other adjuvant therapies include mitotane and cytotoxic chemotherapy. In recurrent, metastatic, or advanced disease the treatment options include repeat surgery (limited to isolated disease) and mitotane with the addition of cytotoxic chemotherapy (FIRM-ACT protocol etoposide, doxorubicin, cisplatin, and mitotane). This treatment regimen has been shown to have a greater survival in a randomized control trial compared to streptozotocin and mitotane.

FURTHER READING Cushing’s syndrome Correa R, Salpea P, Stratakis CA (2015). Carney complex: an update. *Eur J Endocrinol*, 173, M85–M97. Daniel E, et al. (2015). Effectiveness of metyrapone in treating Cushing’s syndrome: a retrospective multicenter study in 195 patients. *J Clin Endocrinol Metab*, 100, 4146–54. El Ghorayeb N, Bourdeau I, Lacroix A (2015). Multiple aberrant hormone receptors in Cushing’s syndrome. *Eur J Endocrinol*, 173, M45–60. Fig. 13.5.1.22 ^{18}F -FDG-PET/CT scan of large right sided adrenocortical carcinoma.