17 Endocrine Disorders that Cause Diabetes

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Keypoints

- Endocrine causes of diabetes are mainly a result of an excess of hormones that are counter-regulatory to insulin, and act by inhibiting insulin secretion and/or action.
- Acromegaly is almost always secondary to growth hormone-secreting adenomas of the anterior pituitary somatotrophs and disturbs glucose homeostasis in up to approximately 50% of patients.
- Cushing syndrome is caused by excessive levels of glucocorticoids and disturbs glucose homeostasis to some degree in over 50% of cases.
- Pheochromocytoma is a tumor of the chromaffin cells, which in 90% of cases is located in the adrenal medulla and causes hyperglycemia in approximately 50% of cases.

- Glucagonoma and somatostatinoma are rare islet cell tumors that produce hormones that inhibit the secretion and action of insulin.
- Thyrotoxicosis commonly causes mild glucose intolerance, but overt diabetes only occurs in a tiny minority.
- Other endocrinopathies such as primary aldosteronism and primary hyperparathyroidism can disturb glucose homeostasis.
- Polycystic ovarian syndrome occurs in 5–10% of women of reproductive age and associates with some degree of glucose intolerance or diabetes resulting from insulin resistance in approximately 50% of cases.

Introduction

The primary focus of this chapter is on those endocrine disorders that cause hyperglycemia and where effective treatment of the endocrinopathy can be expected to normalize the blood glucose concentration. These conditions mostly reflect excessive secretion of "counter-regulatory" hormones, the metabolic actions of which oppose those of insulin by inhibiting its secretion, action, or both.

Acromegaly

### Etiology, incidence and clinical features of acromegaly

Acromegaly comprises a constellation of symptoms and signs caused by excessive growth hormone (GH) secretion that leads to bony and soft tissue overgrowth accompanied by cardiovascular and metabolic pathology (Figure 17.1a; Table 17.1) [1]. It affects approximately 60 people per million [2] and, in 99% of cases, is caused by a pituitary adenoma, most commonly larger than 1 cm in diameter (a "macroadenoma"; Figure 17.1b). A tiny minority of cases are caused by excessive secretion of GH-releasing hormone (GHRH) from a hypothalamic gangliocytoma

or a carcinoid tumor of the lung or pancreas [1]. A small percentage of acromegaly occurs within the wider endocrine syndrome of multiple endocrine neoplasia type 1 (MEN1) caused by mutations in the tumor suppressor gene, *MENIN* [3]. MEN1 can also include glucagonomas and somatostatinomas, both of which are separately capable of causing secondary diabetes. Commonly, acromegaly has been present for a decade prior to diagnosis [4]. This long-standing hypersecretion of GH provides the time necessary for the characteristic external features of the disorder to develop (Figure 17.1a; Table 17.1).

Features of disturbance to glucose tolerance in acromegaly

Glucose intolerance or overt diabetes is common in acromegaly because of the direct hyperglycemic effects of GH excess (Figure 17.2). Overt diabetes has been reported in a range of 19–56% of patients with acromegaly, while impaired glucose intolerance (IGT) affects 16–46% [5–8]. Diabetes is most frequent in patients with higher GH levels [9,10]. There is also a correlation between serum insulin-like growth factor I (IGF-I), and both fasting and post-prandial glucose. In fact, placing age-adjusted IGF-I values into rising quartiles correlated very accurately to decreasing insulin sensitivity such that serum IGF-I levels could predict insulin sensitivity more accurately than either random GH levels or the nadir value following glucose tolerance testing [11].

Clinically, diabetes in acromegaly usually resembles the type 2 form (T2DM), with most patients not needing insulin therapy but being maintained with oral hypoglycemic agents or diet alone

(a)

(b)
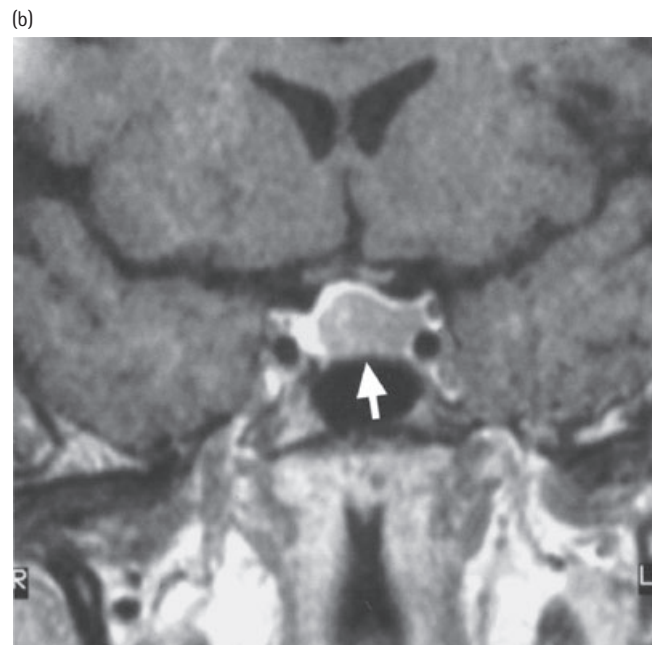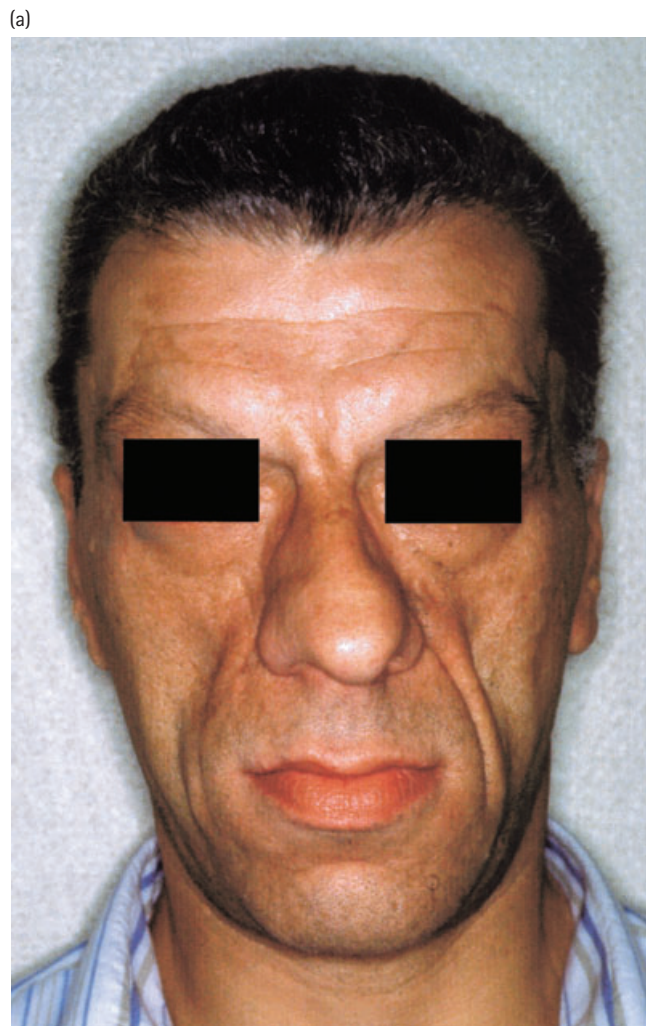
Figure 17.1 Acromegaly in a patient found to have a random blood glucose level of 13 mmol/L during preparation for sinus surgery. Features included: (a) the characteristic facial appearance; (b) a large adenoma (arrow) extending up to but not in contact with the optic chiasm demonstrated by magnetic resonance imaging (R, right; L, left). Following successful trans-sphenoidal removal of the tumor, glucose tolerance returned to normal.

[9]. GH can induce insulin resistance when infused into normal subjects [12,13], and insulin resistance is a consistent feature of people with acromegaly [14,15]. Insulin action is impaired in both the liver and extrahepatic tissues, with decreases in both the suppression of hepatic glucose production and in insulin-dependent glucose disposal [13,15]. For instance, impairment of insulin-mediated activation of glycogen synthase has been demonstrated in skeletal muscle [16–18]. Insulin resistance may also be exacerbated by the lipolytic action of GH, generating non-esterified fatty acids (NEFAs) which act on the liver to increase glucose production and in muscle to inhibit glucose utilization (via the "glucose–fatty acid" cycle) (Figure 17.2). Where pancreatic compensation is adequate, an exaggerated insulin secretory response creating hyperinsulinemia can counterbalance the insulin resistance and maintain euglycemia. Similar to the natural history of deteriorating blood glucose control in T2DM, eventually β-cell compensation fails, the insulin response is impaired and hypergylcemia ensues [14]. This has been termed the Starling curve of the pancreas (see Figure 11.1).

Diagnosis and treatment of acromegaly

GH release is normally pulsatile with intervening periods of low level or undetectable hormone, whereas secretion from pituitary adenomas is autonomous. Therefore, the diagnosis can be deduced from a series of random serum measurements where GH is consistently detected. An alternative, better diagnostic test takes advantage of the negative feedback on GH secretion by glucose. A failure of serum GH to suppress to below 2 mU/L (approximately 1 μg/L) within 3 hours of 75 g oral glucose is diagnostic of acromegaly. A further option, particularly suited as the initial screening test of outpatients, is measurement of serum IGF-I, which if raised above sex- and age-matched controls is diagnostic of acromegaly, unless there is a possibility of GH abuse [1]. It is noteworthy that the diagnosis of acromegaly can be difficult in patients with type 1 diabetes mellitus (T1DM) where GH hypersecretion is observed. Whereas this might compromise the use of serum GH as a diagnostic biomarker of a somatotroph adenoma, IGF-I values tend to be low in poorly controlled T1DM indicative of the state of GH resistance. Thus, raised serum IGF-I values

Table 17.1 Clinical features of acromegaly.

Musculoskeletal
Protruding mandible (prognathia) with lower teeth separation
Big tongue (macroglossia)
Enlarged forehead (frontal bossing)
Large hands and feet (carpal tunnel syndrome, tight rings, increasing shoe
    size)
Osteoarthritis from abnormal joint loading
Increased stature (gigantism; if GH excess occurs prior to epiphyseal closure)

Skin
Irritating, thickened, greasy (increased sebum production)
Excessive sweating

Cardiovascular
Dilated cardiomyopathy causing cardiomegaly and cardiac failure
Hypertension

Metabolic
Impaired glucose tolerance or potentially diabetes

General
Headaches
Tiredness, often very disabling and lowers quality of life/ability to work
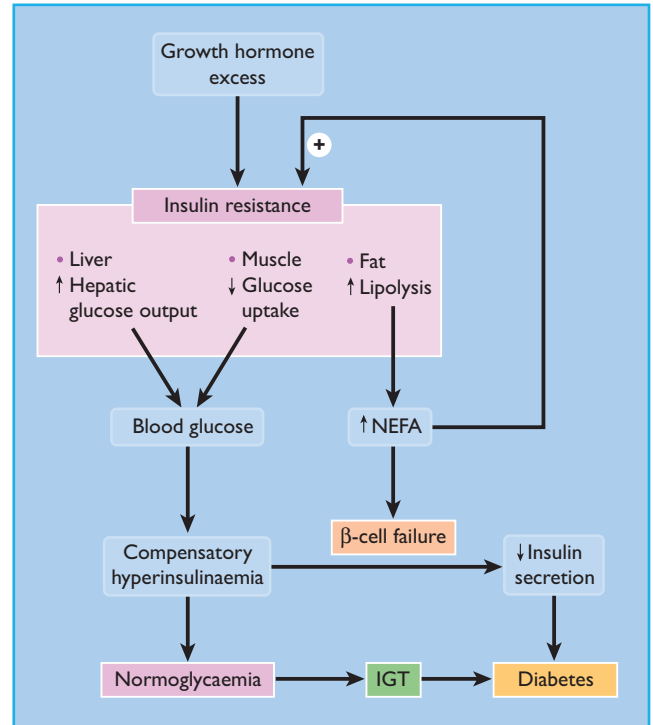
Local tumor effects
Compression of the optic chiasm (superior tumor growth) or cranial nerves
    III, IV and/ or VI (lateral tumor growth into cavernous sinus)

GH, growth hormone.

Figure 17.2 Mechanisms of hyperglycemia and diabetes in acromegaly. Diabetes develops if β-cells fail to compensate for the increased demand for insulin. IGT, impaired glucose tolerance; NEFA, non-esterified fatty acid.

remain a confident predictor for a diagnosis of acromegaly in people with T1DM. Having diagnosed acromegaly, magnetic resonance imaging (MRI) of the anterior pituitary defines the extent of the adenoma (Figure 17.1b).

Based on this investigation, symptoms, patient wishes and co-morbidity, and GH levels, treatment can be either surgical, medical or radiotherapy (Table 17.2) [1,19]. When the tumor is a macroadenoma, especially if it extends beyond the pituitary fossa, curative surgery becomes unlikely or impossible; however, surgery can be useful for "debulking" and rapid lowering of serum GH levels in patients who are highly symptomatic, or where the tumor has encroached upon the optic chiasm and affected visual fields. The standard approach is trans-sphenoidal, either via the nostril or from behind the upper lip. Once the sphenoid sinus has been traversed and midline access to the sella turcica gained, tumor is removed from the anteroinferior aspect causing the residual tissue to drop back down into or towards the pituitary fossa. Tumor beyond the fossa, in locations such as the cavernous sinus, cannot be approached directly, hence the reason why surgery for large tumors is not anticipated to be curative [19]. Conversely, cure can be commonly achieved for over 50% of microadenomas (<1 cm diameter). The reported ranges vary widely according to expertise.

Medical therapy, most commonly using somatostatin analogs, is effective at both lowering GH levels and shrinking the tumor volume [1,20,21]. Approximately 60% of patients respond to somatostatin analogs because of the presence of predominantly

Table 17.2 Treatment of acromegaly (Adapted from Holt and Hanley [130].)

Advantages	Disadvantages
Trans-sphenoidal surgery	
Rapid effect	Invasive and requires general anesthetic
Can restore vision in optic nerve compression	Non-curative for large extrasellar tumors
Might be curative if complete resection	
Somatostatin analog drugs	
Non-invasive	Monthly intramuscular injection
May shrink tumor	Expensive
Decreases GH in ~60% of patients	Gastrointestinal side effects (commonly diarrhea)
	Unlikely to be curative (i.e. continuous therapy needed)
Pegvisomant	
Non-invasive	Expensive
Blocks GH action	GH concentrations remain elevated
Radiotherapy	
Non-invasive	Slow to act – may take up to 10 years
Likely to shrink tumor	Standard external three-beam radiotherapy likely to cause hypopituitarism by destroying other pituitary cell types
Likely to reduce GH levels	
Might be curative	

GH, growth hormone.

type 2 and type 5 somatostatin receptors on the tumor cell surface [1,21]. The analogs can be administered subcutaneously; however, once it is clear that they are tolerated, the most common formulation is month-long intramuscular depot preparations. They can be used either prior to surgery, with the goal of operating on a shrunken tumor, on a long-term basis in place of surgery or post-surgery where GH levels have not been normalized.

Some GH-secreting adenomas co-express dopamine receptors more characteristic of prolactinomas [21]. Indeed, 25% of cases of acromegaly show raised levels of both prolactin and GH possibly indicating a tumor cell phenotype more consistent with the somatomammotroph from which it is thought that somatotrophs (GH secretion) and lactotrophs (prolactin secretion) terminally differentiate. In these instances, dopamine agonists, as used in hyperprolactinemia, can be useful, especially as they can be administered orally, and allow reduction in dosage of the more expensive intramuscular depot somatostatin analogs. This opportunity to use lower doses of somatostatin analogs may also lessen their side-effects, such as gastrointestinal disturbance (most commonly diarrhea) and gallstones. It has recently been questioned, however, whether commonly used ergot alkaloid derived dopamine agonists, such as cabergoline, cause fibrotic side-effects, especially involving heart valves [22,23]. Despite concerns from regulatory agencies, the prevailing view from endocrinologists is that the doses of these agents used to treat endocrine disorders (compared with the therapeutic regimens in Parkinson disease) are not problematic. In any case, alternative non-ergot derived agents, such as quinagolide, are available. Bromocriptine is less commonly used because of the almost inevitable side-effects of nausea. Responsiveness to both dopamine and somatostatin analog therapy can be easily assessed at the start of treatment by hourly measurement of serum GH over 8 hours following the administration of a test dose of each agent given sequentially on two consecutive days.

The last decade has seen the appearance of a new clinical agent that blocks GH action. GH induces signal transduction via binding to its receptor as a dimer. Pegvisomant has been developed as a GH antagonist by preventing this dimerization and thus inhibiting GH action. This leaves elevated GH levels from the somatotroph adenoma but, nevertheless, pegvisomant is effective at reversing the clinical features of acromegaly [1,24]. The major problem with its use in many countries has been its prohibitive cost. Concern over tumor growth because of loss of negative feedback (a scenario akin to Nelson syndrome following bilateral adrenalectomy in Cushing disease) seems unfounded [1,24].

Radiation therapy is most commonly administered as conventional three-field external beam radiotherapy [1]. It is effective at lowering GH and IGF-I levels [25]. This approach delivers approximately 4500 Gy to the pituitary region with the total dose calculated such that the optic chiasm receives less than 8 Gy. An alternative is stereotactic radiotherapy (also known as γ-knife therapy or radiosurgery), which by using more sources can focus a higher concentration of radiation to a defined area of tumor. Whereas the latter modality allows greater preservation of adja-cent normal pituitary tissue, the former approach is a more all-encompassing strategy to ensure tumor destruction, albeit with a higher post-therapy incidence of hypopituitarism. The choice is important as there is evidence that pituitary radiotherapy is associated with increased morbidity and mortality from subsequent cerebrovascular disease meaning that repeat therapy is not undertaken lightly [26].

Outcome of acromegaly and disturbance to glucose tolerance

Unless there are cogent reasons against, attempts should be made to normalize GH excess in acromegaly to decrease the morbidity and mortality associated with the disorder [1,26]. Curative treatment is best defined by a nadir serum GH of less than 2 mU/L upon 75 g oral glucose challenge. Glucose tolerance improves and insulin levels decrease after successful treatment by pituitary surgery and irradiation [27,28]. Hyperglycemia may worsen in a few patients, presumably those with a stronger underlying tendency to T2DM, when treated with somatostatin analogs because these drugs also suppress insulin secretion [29,30]. In the longer term, somatostatin analogs tend to improve glucose tolerance [31,32]. Insulin sensitivity is also improved with pegvisomant therapy in patients with both glucose intolerance and diabetes [33–36]. If hyperglycemia persists after serum GH levels have been normalized then the patient should be considered as having T2DM. One caveat to this is the possibility of GH deficiency as part of hypopituitarism post-surgery or radiotherapy [14]. GH deficiency causes centripetal fat deposition, which would itself cause or accentuate insulin resistance and potential loss of euglycemia.

Generally, diabetic complications are considered rare in acromegaly. Nevertheless, it is worth considering GH action in the context of both macrovascular and microvascular diabetic complications. Untreated GH excess increases cardiovascular morbidity and mortality and, potentially, abnormalities of glucose metabolism occurring in acromegaly could contribute to hypertension which affects over 50% of patients with acromegaly [5]. GH has been linked to proliferative diabetic retinopathy ever since resolution of diabetic retinopathy was noted in a woman who developed rapid-onset pan-hypopituitarism [37,38], so much so that hypophysectomy was used as treatment prior to the advent of laser photocoagulation [38]. This view is supported by the observations that patients with diabetes who are GH-deficient rarely develop retinopathy [39], and an experimental study in mice demonstrated that inhibition of GH secretion ameliorated diabetic retinopathy [40]. Patients with diabetes who are acromegalic, however, do not show an increased incidence of diabetic retinopathy [41,42]. Data on the progression of diabetic retinopathy treated with either pegvisomant or somatostatin analog are contradictory, and the outcome of larger trials are awaited [38].

Effects of diabetes on GH–IGF-I axis

Dysregulation of the GH–IGF-I axis has been well documented in T1DM. The main disturbances include increased GH secretion (Figure 17.3), paradoxically associated with decreased serum
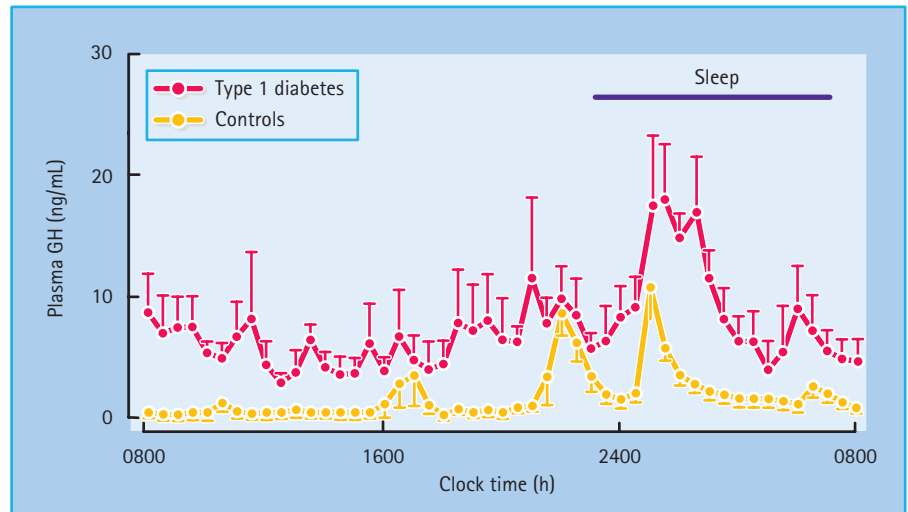
Figure 17.3 Increased growth hormone (GH) secretion in type 1 diabetes. Note the marked hypersecretion during sleep in the early hours of the morning. Reproduced from Hansen *et al.* [127], with permission from Wiley-Blackwell.

IGF-I levels [43]. GH secretory pulses are larger and more frequent and total 24 hour serum and urinary GH levels are elevated. High circulating GH levels are most obvious during periods of poor diabetic control, and return towards normal with improved control. Pulses of GH secretion during sleep in the early hours of the morning lead to insulin resistance, which manifests itself before breakfast and is largely responsible for the "dawn phenomenon" of fasting hyperglycemia [44]. This physiologic effect, along with that caused by exercise and GHRH, is exaggerated in patients with T1DM, especially those who are poorly controlled. GH secretion accounts for much of the decreased insulin sensitivity observed during normal puberty, as well as the deterioration in glycemic control at this time in adolescents with T1DM. Despite GH hypersecretion, levels of IGF-I – the principal mediator of GH activity – are inappropriately low, indicating a state of GH resistance (Figure 17.4). Hepatic resistance to GH has been attributed both to decreased number of GH receptors and to post-receptor defects [43]. Circulating levels of GH-binding protein (GHBP) are also decreased in T1DM. Administration of recombinant human IGF-I (rhIGF-I) as an adjunct to insulin has been demonstrated to reverse GH hypersecretion and improve glycemic control, while reducing insulin requirements. Co-administration of IGF-binding protein 3 (IGFBP-3) with IGF-I has similar beneficial effects on carbohydrate metabolism, and also avoids side effects of IGF-I, notably edema, headache, retinal edema and jaw pain [45]. Recombinant IGF-I has also been used to treat states of severe insulin resistance in which the insulin receptor is functionally impaired, such as the spectrum from Donohue to Rabson–Mendenhall syndrome (see Chapter 15) [46]. In such patients, rhIGF-I can be used to treat ketoacidosis, which is the major cause of death and may fail to respond even to massive doses of insulin.

Abnormalities of IGFBP may also alter the regulation of the GH–IGF-I axis in diabetes (Figure 17.4). Six IGFBPs have been identified in humans, the two most relevant being IGFBP-1 (molecular weight 25 kDa), whose synthesis by hepatocytes is
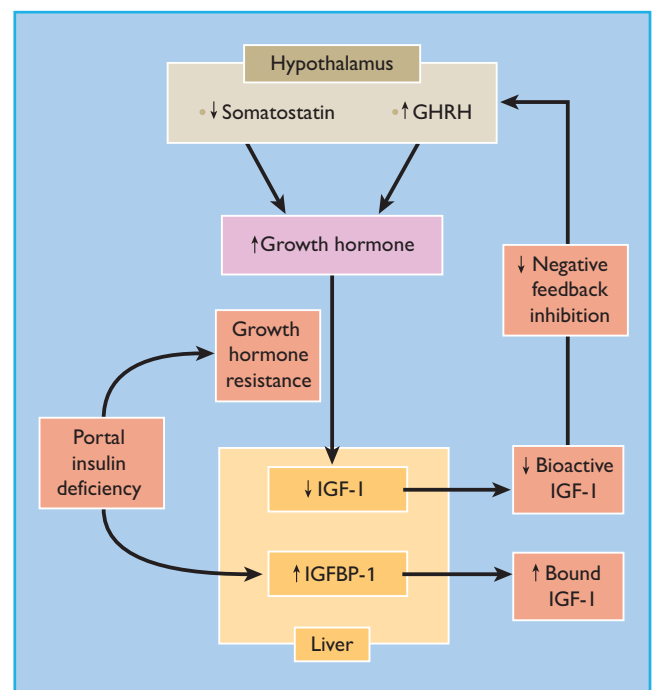
Figure 17.4 Mechanisms of growth hormone (GH) hypersecretion in diabetes. Insulin-like growth factor 1 binding protein 1 (IGFBP-1) binds and reduces the bioavailability of insulin-like growth factor I (IGF-I), which normally decreases GH secretion by negative feedback inhibition on the hypothalamus and pituitary; IGFBP-1 expression is inhibited by insulin.

inhibited by insulin but independently of GH, and IGFBP-3 (molecular weight 44 kDa), which is GH-dependent [47]. IGFBP-1 levels are increased in T1DM as a result of portal and hepatic insulin deficiency (Figure 17.4) [43], and increase with worsening insulin deficiency and rising HbA$_{1c}$ concentrations (Figure 17.5). Increased IGFBP-1 levels have been shown to inhibit IGF-I bioactivity. Portal insulin deficiency in T1DM can thus account for
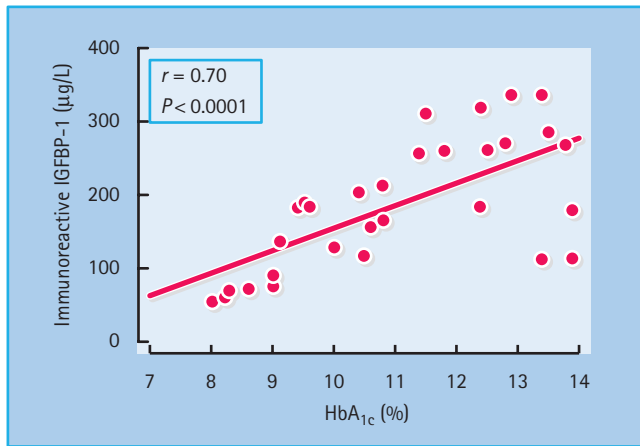
Figure 17.5 Correlation between serum immunoreactive insulin-like growth factor 1 binding protein 1 (IGFBP-1) and glycated hemoglobin (HbA$_{1c}$) concentrations in 48 patients with type 1 diabetes mellitus. Reproduced from Langford and Miell [128], with permission from the *European Journal of Clinical Investigation*.

Figure 17.6 Growth failure in a boy with diabetes. Height fell progressively below the centiles (97th centile at diagnosis) and the pubertal growth spurt was delayed, resulting in a lower final height than predicted.

GH resistance, through downregulation of hepatic GH receptors and increased IGFBP-1 levels, both reducing IGF-I production and bioactivity [48]. Decreased IGF-I levels in turn cause GH hypersecretion via reduced negative feedback at the hypothalamus and pituitary, and this exacerbates insulin resistance, thus establishing a vicious circle of raised GH and poor glycemic control (Figures 17.2 and 17.3).

Another consequence of IGF-I deficiency is impaired growth at puberty [48]. Paradoxically, children with new-onset diabetes tend to be taller, especially if the disease develops several years before puberty; increased GH and insulin levels during the preclinical evolution of the disease are a possible explanation. Once diabetes is established, growth may slow, particularly before the age of 10 years and if glycemia is poorly controlled (Figure 17.6). The pubertal growth spurt may be blunted and/or delayed, especially in girls, and this may lead to a reduction in final height [48]. Growth failure in adolescents with T1DM is rare nowadays, possibly because of improved management and monitoring of diabetes. Indeed, intensified insulin treatment has been shown to raise IGF-I levels, in parallel with an increase in growth velocity [48]. Finally, growth failure may be associated with truncal obesity, hepatomegaly (secondary to glycogen and/or triglyceride deposition) and sexual infantilism in the Mauriac syndrome [49]. This condition was reported in children with poor glycemic control and excessively high insulin dosages, but is now rare.

Cushing syndrome

Etiology, incidence and clinical features of Cushing syndrome

Cushing syndrome comprises a constellation of symptoms and signs caused by excessive levels of glucocorticoid that leads to a characteristic appearance accompanied by metabolic and cardio-
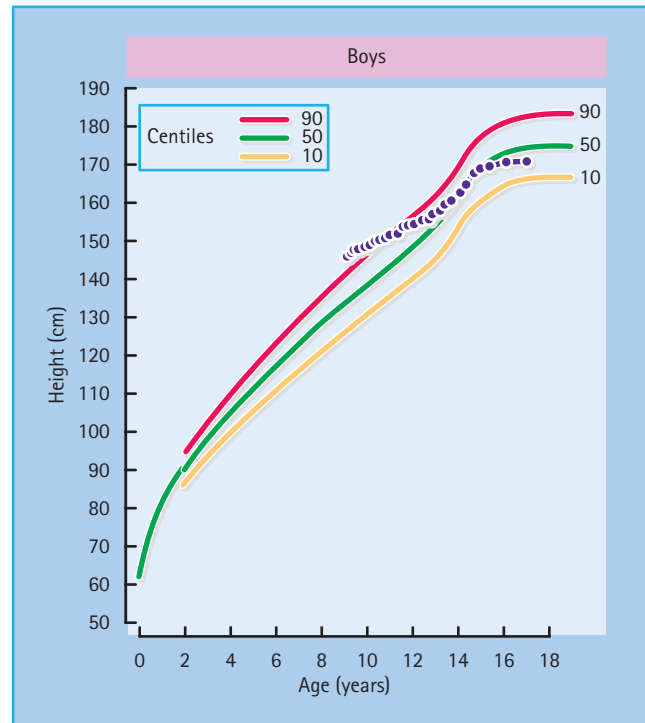
Table 17.3 Clinical features of Cushing syndrome.

Easily bruised, thin skin; poor wound healing
Striae (purple or "violaceous" rather than white)
Thin (osteoporotic) bones that easily fracture
Glucose intolerance/diabetes mellitus
Central obesity, characteristic rounded facies, "buffalo" hump
Susceptibility to infection
Predisposition to gastric ulcer
Hypertension
Disturbance of menstrual cycle; symptoms overlap with PCOS
Mood disturbance (depression, psychosis)

PCOS, polycystic ovarian syndrome.

vascular pathology (Figure 17.7; Table 17.3) [50–52]. It occurs most commonly as a side effect of synthetic glucocorticoids administered exogenously for conditions such as rheumatoid arthritis or reversible airways disease. Endogenous Cushing syndrome arises in approximately two-thirds of cases from adrenocorticotropin (ACTH) secreting corticotroph adenomas of the anterior pituitary which affect 5–10 individuals per million. In one-fifth of cases, the cause is a glucocorticoid-secreting tumor of the adrenal cortex and in one-tenth of cases is secondary to syndromes of ectopic ACTH secretion, most commonly from small cell carcinoma of the lung or, more rarely, carcinoid tumors [50–52]. Cushing syndrome is more common in women than

(a)

(b)

(c)
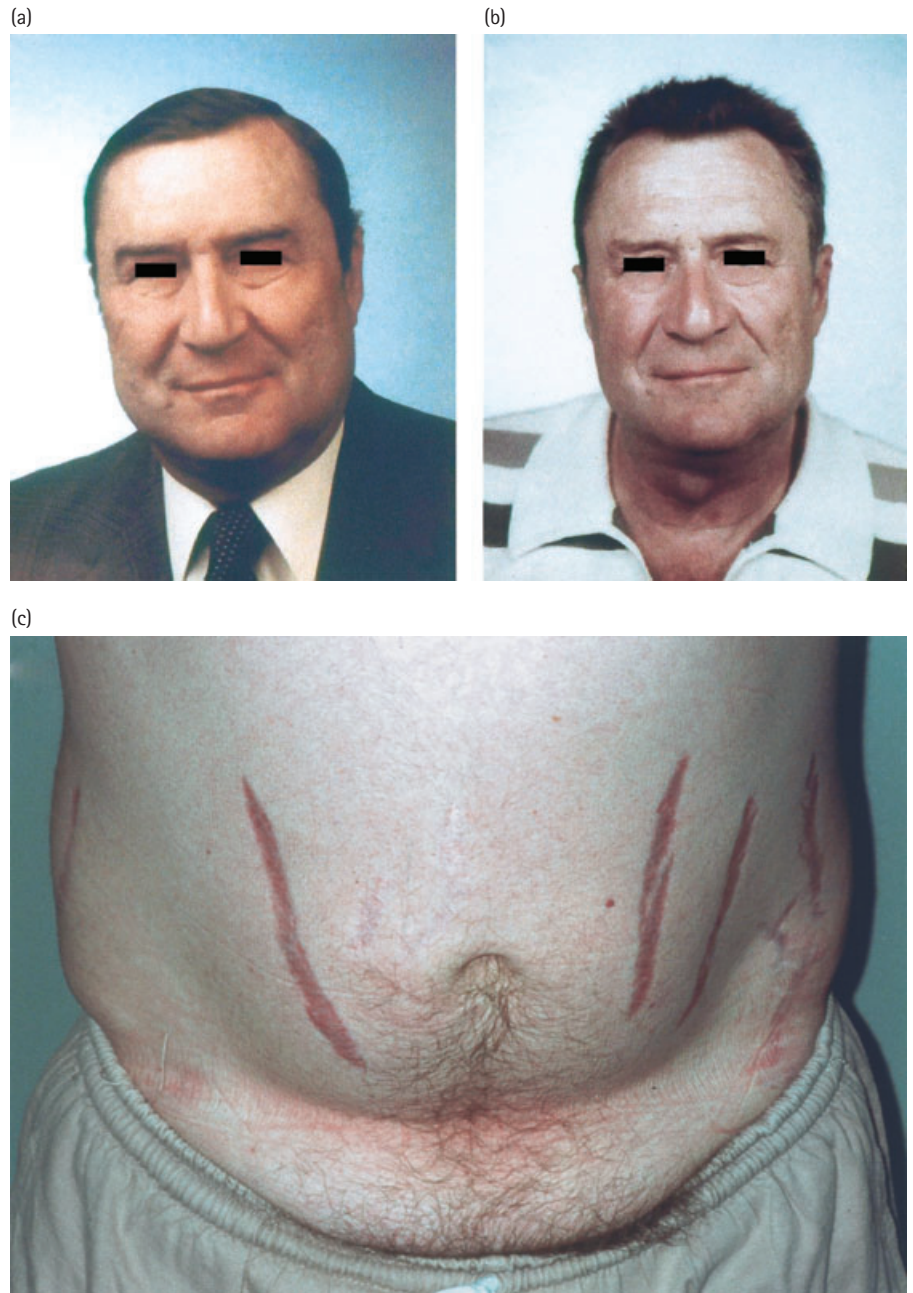
Figure 17.7 Cushing syndrome in a 53-year-old hypertensive man presenting with diabetes that required insulin to control hyperglycemia. Features included back pain from osteoporotic vertebral collapse, proximal myopathy that prevented him from climbing stairs, characteristic rounded facies (a) and truncal obesity with violaceous striae (c). After removal of the 10-mm corticotroph pituitary adenoma, his facial appearance returned to normal (b), as did blood pressure and blood glucose.

men, with a greater predilection for corticotroph adenomas as the underlying pathology. Prolonged excessive levels of cortisol, the major glucocorticoid in humans, either directly from an adrenocortical tumor or from excessive ACTH causing bilateral hyperfunctional adrenal cortices, causes the characteristic external features of the disorder to develop and results in excess cardiovascular morbidity and mortality (Fig. 17.7a; Table 17.3) [50–52].

Features of disturbance to glucose tolerance in Cushing syndrome

Impairment of glucose tolerance is observed in 30–60% of cases [7,50,53]. Overt diabetes occurs in 20–50%, arguably in patients predisposed to diabetes (e.g. those with a family history of the disorder) [7,50,53]. It resembles T2DM because glucocorticoid excess causes hyperglycemia primarily by inducing insulin resistance, reflected by hyperinsulinemia [53]. Insulin-stimulated glucose uptake and utilization by peripheral tissues are both reduced, while hepatic glucose production is greatly increased through stimulation of gluconeogenesis [50,54]. This results from the direct activation of hepatic gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK), and an increasing supply of glucogenic substrates (amino acids and glycerol) generated by muscle proteolysis and peripheral adipose tissue lipolysis (Figure 17.8) [55]. Glucocorticoids also have permissive effects on the gluconeogenesis induced by epinephrine (adrena-
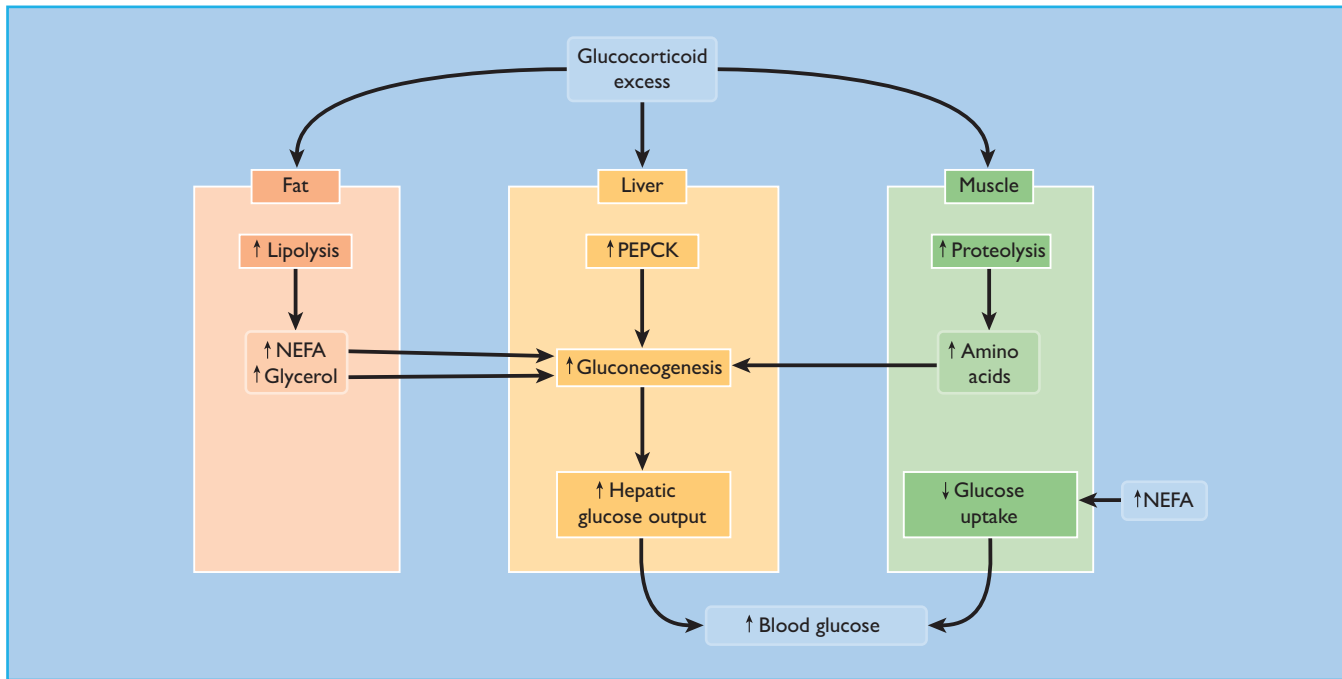
Figure 17.8 Mechanisms of hyperglycemia and diabetes in Cushing syndrome. NEFA, non-esterified fatty acids; PEPCK, phosphoenolpyruvate carboxykinase.

line) and glucagon. Besides enhancing hepatic gluconeogenesis, glucocorticoids also increase hepatic glycogen storage [55].

With endogenous causes of Cushing syndrome, the hyperglycemia can sometimes be effectively treated with sulfonylureas, but many cases require insulin therapy [56]. For Cushing syndrome caused by exogenous drugs, treatment can be tailored from knowledge of the timing and half-life of the glucocorticoid drug as a predictable period of hyperglycemia follows. For instance, prednisolone administered for reversible airways disease at breakfast will generate elevated glucocorticoid levels throughout the remainder of the day with levels falling in the evening. This profile makes the choice of an intermediate acting insulin administered at breakfast appropriate (see Chapter 27).

Diagnosis and treatment of Cushing syndrome

For exogenously administered glucocorticoids, the diagnosis and treatment of Cushing syndrome are straightforward: wherever possible remove or reduce the offending medication. The major challenge in diagnosing Cushing syndrome resulting from endogenous causes is frequently one of simply considering the condition as the underlying cause of otherwise very common symptoms such as tiredness and weight gain. Avoiding this pitfall is aided by thorough clinical examination when more specific signs may be detected, for instance violaceous stretch marks (called "striae"; Figure 17.7c) or proximal myopathy [50–52]. This issue may be particularly pertinent to the T2DM clinic, with some evidence that occult Cushing syndrome may affect 2% of patients [57].

The first goal is to establish the presence of either autonomous secretion or excessive levels of cortisol [50–52]. Several screening

tests with high sensitivity have been designed (Table 17.4). Circulating cortisol is relatively high during the day and low at bedtime. Maintained daytime levels at night indicate excess. This can be tested by measuring midnight serum cortisol, although this requires prior acclimatization of inpatients for at least 24 hours and quiet surroundings as cortisol levels rise with minimal stress. Where assays have been validated, bedtime salivary cortisol measurement can be very useful as patients can post samples to the laboratory from home. Levels are approximately 10% of those in serum so care must be taken to avoid contamination with blood (e.g. from brushing teeth). The "low dose" dexamethasone suppression tests interrogate the potential loss of physiologic negative feedback at the corticotroph leading to autonomous ACTH secretion. The formal 48-hour test is marginally more specific [51]; however, it is also more inconvenient to perform in the outpatient setting compared with the overnight 1 mg suppression test. Caution needs to be exercised in patients where dexamethasone metabolism is enhanced (e.g. by antiepileptic medication) as this can lead to false-positive results. An alternative screening test examines total excretion of cortisol in a 24-hour urine collection, commonly on several occasions, as an integrated assessment of one day's adrenocortical function. It is usual for endocrinologists to apply more than one of these various screening tests, which, if failed, provides proof of excess glucocorticoids and a diagnosis of Cushing syndrome.

Several endocrine tests have been developed to differentiate the various etiologies of endogenous Cushing syndrome (Table 17.4) [50–52]. Undetectable serum ACTH indicates an adrenocortical

Table 17.4 Diagnosis of Cushing syndrome from endogenous causes.

Test	Interpretation
Screening tests to diagnose Cushing syndrome	
Midnight serum cortisol measurement or bedtime salivary cortisol assay	Maintained daytime levels at night-time indicates autonomous cortisol production of Cushing syndrome
1 mg overnight DST. Oral dexamethasone taken at midnight	Serum cortisol >50 nmol/L at following 9 AM consistent with Cushing syndrome
Formal low-dose DST (0.5 mg × 8 doses 6-hourly ending at 3AM)	Serum cortisol >50 nmol/L at following 9 AM consistent with Cushing syndrome
24-hour urinary free cortisol measurement	Elevated values support diagnosis of Cushing syndrome
Tests to localize cause of cortisol excess	
Serum ACTH measurement	If suppressed, indicates autonomous adrenocortical overproduction of cortisol (e.g. an adrenocortical adenoma)
If serum ACTH detectable:	
High dose dexamethasone suppression test (2 mg × 8 doses 6-hourly ending at 3 AM)	>50% suppression of 9 AM serum cortisol from pre- to post-test indicates anterior pituitary source; <50% suppression indicates extrapituitary "ectopic" source of ACTH
Bilateral IPS sampling	Gradient from IPS to periphery of >2:1 supports anterior pituitary source (test can also incorporate CRH administration; see text)
MRI (can include gadolinium enhancement)	Should only be considered once biochemical evidence of pituitary source obtained. Helpful for surgeon in planning trans-sphenoidal surgery

ACTH, adenocorticotropic hormone; CRH, corticotropin releasing hormone; DST, dexamethasone suppression test; IPS, inferior petrosal sinus; MRI, magnetic resonance imaging.

source of excessive cortisol causing suppression of ACTH secretion by the anterior pituitary. It can be particularly challenging to distinguish between anterior pituitary and ectopic sources of ACTH causing Cushing syndrome. Corticotroph adenomas, especially intrasellar ones, usually retain a partial capacity for negative feedback; the "high dose" dexamethasone suppression test, administered as eight 2-mg doses every 6 hours, can be expected to reduce cortisol levels by at least 50%. As this cause underlies the original description of the disorder by Harvey Cushing in 1912, pituitary-driven glucocorticoid excess is called Cushing disease. Extrapituitary tumors secreting ectopic ACTH less commonly display this degree of negative feedback such that ACTH levels and consequently cortisol levels are likely to be higher. Although these tumors may be relatively indolent carcinoids, more commonly they are aggressive carcinomas of the

bronchus characterized by a rapid onset of symptoms within a few months, marked hypokalemia and weight loss. The high level of *POMC* gene expression and dysregulated post-translational processing also leads to significant melanocyte stimulating hormone (MSH) secretion resulting in skin pigmentation. Venous sampling of the bilateral inferior petrosal sinuses can distinguish between ectopic or anterior pituitary sources of excessive ACTH. For pituitary sources, a gradient in ACTH levels of at least 2:1 (or 3:1 after the injection of 100 μg corticotropin releasing hormone [CRH] intravenously) should be found between central and peripheral samples. Although it can be very useful, bilateral inferior petrosal sinus sampling (BIPSS) also carries the risk of thrombosis in approximately 1% of cases, meaning that its use by endocrinologists is not always considered warranted. This is especially true where preceding biochemical tests have been conclusive and MRI shows clear radiologic evidence for a tumor. Where biochemistry is supportive of a pituitary source of ACTH excess, but the MRI is equivocal, even after gadolinium enhancement, BIPSS can help to lateralize a corticotroph adenoma by detecting a clear gradient between the right and left sinuses or vice versa. Sources of ectopic ACTH, most commonly in the chest, can be imaged with fine cut computerized tomography (CT), MRI or by using isotope-labeled scintigraphy to detect somatostatin receptors present on approximately two-thirds of ectopic ACTH-secreting carcinoid tumors. Autonomous cortisol-secreting tumors of the adrenal cortex can be imaged satisfactorily by CT or MRI when it can be possible to make assessment of functionality according to lipid content; features of high lipid content implying a tumor with active steroidogenesis.

Wherever possible, curative approaches are undertaken to normalize cortisol secretion as Cushing syndrome carries a high morbidity and markedly increases mortality from cardiovascular causes [50–52,58]. For adrenocortical sources, unilateral adrenalectomy is performed. For ectopic ACTH-secreting tumors, excision of carcinoids is potentially curative, whereas the natural history of carcinoma of the bronchus with ectopic hormone secretion usually makes palliative care more appropriate. Medical therapy to treat corticotroph adenomas remains disappointing. Some excitement was gained for high dose peroxisome proliferator-activated receptor γ (PPAR-γ) agonists but larger trials have been disappointing. Pituitary tumors are treated by either trans-sphenoidal surgery or radiotherapy when the indications and complications are largely the same as for those described in the section on acromegaly. The fact that ACTH-secreting adenomas are commonly microadenomas can increase the chances of curative surgery, although this remains heavily operator-dependent. If surgery is delayed, suppressants of adrenocortical steroidogenesis such as ketoconazole or metyrapone can be used temporarily where patients are highly symptomatic [50–52]. In extremis, bilateral adrenalectomy provides a rapid resolution of excessive cortisol secretion, although the total loss of negative feedback to a corticotroph adenoma can result in dangerous pituitary tumor growth that becomes refractory to further treatment, a scenario called Nelson syndrome. In patients where ACTH levels continue

to rise, concomitant radiotherapy to the anterior pituitary can help reduce the risk of this problem arising.

Outcome of Cushing syndrome and disturbance to glucose tolerance

After successful surgery, the patient is reliant on external glucocorticoid administered as oral hydrocortisone, but a return of cortisol secretion from the adrenal gland(s) can be anticipated over ensuing weeks. Commonly, a physiologic return of diurnal rhythm is never achieved postoperatively [59]. For some, the extensiveness of anterior pituitary surgery, or the long-term suppression either of normal corticotrophs (pituitary or ectopic ACTH secreting tumors) or normal adrenocortical cells (cortisol-secreting tumors) causes a permanent state of hypocortisolism because of underactivity of remaining tissue. This can require continued hydrocortisone administration as for patients with Addison disease, except that mineralocorticoid replacement should not be required.

With successful treatment of Cushing syndrome (Figure 17.7), glucose intolerance may resolve. In such instances, when the patient might be entirely dependent on replacement doses of hydrocortisone, care needs to be taken not to cause hypoglycemia by continued antidiabetes medication. By contrast, persisting abnormalities are relatively common, most likely associated with persistent visceral obesity and metabolic syndrome [59]. On close analysis in one case series, there was a marked persistence of visceral obesity and glucose intolerance in approximately 60% of patients who fulfilled criteria for remission of Cushing syndrome [60].

Effects of diabetes on hypothalamic–anterior pituitary–adrenal cortex axis

Evidence of overactivity of the hypothalamic–pituitary–adrenal (HPA) axis has been reported in children, adolescents and adults with diabetes, including moderate increases in urinary free cortisol excretion, plasma cortisol and ACTH concentrations [61–64]. These abnormalities have been related to the duration of diabetes [62,63] and to the presence of diabetic neuropathy [64]. Serum cortisol levels fall as metabolic control improves [65].

Pheochromocytoma

Etiology, incidence and clinical features of pheochromocytoma

Pheochromocytomas are catecholamine-secreting tumors arising from the chromaffin cells of the adrenal medulla (Figure 17.9) [66,67]. Approximately 10% lie in extra-adrenal sites (paragangliomas) along the sympathetic chain in para-aortic or chest regions and approximately 10% are bilateral. Although most pheochromocytomas are sporadic, advances in molecular genetics have demonstrated that a hereditary basis underlies approximately one-fifth to one-quarter of diagnoses, not just in well-known syndromes, such as MEN2, von Recklinghausen

neurofibromatosis and von Hippel–Lindau disease [66]. Such advances have also associated particular genetic defects to tumor type. For instance, succinate dehydrogenase subunit B (*SDHB*) and succinate dehydrogenase subunit D (*SDHD*) mutations are more frequent in extra-adrenal tumors [66]. Mutations in *SDHB* are more commonly associated with a malignant phenotype [68]. The risk of malignancy also increases with tumor size [68].

The clinical manifestations of pheochromocytoma are largely caused by hypersecretion of catecholamines, classically as a triad of symptoms: headaches, sweating and tachycardia [69]. Hypertension is the most common clinical finding and occurs in 80–90% of cases. It can be paroxysmal or sustained, the latter occurring especially in children and in noradrenaline-secreting tumors [66]. Other symptoms may be secondary to the co-secretion of various other peptide hormones such as vasoactive intestinal peptide (VIP), substance P, atrial natriuretic factor, endothelin-1, CRH and GHRH [70]. The normal adrenal medulla predominantly secretes epinephrine, converted from norepinephrine by methylation. This reaction is governed by the enzyme phenylethanolamine-*N*-methyltransferase (PNMT), the expression of which is dependent on high concentrations of cortisol draining centripetally from the outer adrenal cortex towards the adrenal vein [69]. For this reason, larger tumors with more marked disturbance of the normal anatomy or extra-adrenal pheochromocytomas are notable for predominantly secreting norepinephrine as conversion to epinephrine is compromised.

Features of disturbance to glucose tolerance in pheochromocytoma

Hyperglycemia occurs in up to approximately 50% of patients with pheochromocytoma. The prevalence of diabetes is approximately 35% [71]. Its presence in a young hypertensive person of normal body weight should raise suspicion of pheochromocytoma. The predominant mechanism is catecholamine-mediated reduction in insulin sensitivity and insulin secretion, predominantly caused by epinephrine rather than norepinephrine (Figure 17.10) [72,73]. Epinephrine inhibits β-cell insulin secretion via stimulation of α_2-adrenergic receptors [74]. In the liver, epinephrine activates β_2-adrenoceptors to enhance glycogenolysis transiently and gluconeogenesis in a more sustained fashion [75–77]. This hepatic gluconeogenesis is fueled by the precursors, lactate, alanine and glycerol, generated by β_2-adrenergic stimulation of muscle glycolysis and adipose tissue lipolysis. Lipolysis in adipose tissue is also stimulated via the β_1- and β_3-adrenoceptors. In addition, epinephrine can impair glucose utilization in muscle through direct β_2-adrenergic effects. The predominance of these β_2-adrenergic effects probably explains why epinephrine, with its higher affinity for β_2-receptors, is more potent than norepinephrine in producing hyperglycemia [75,77]. All these effects are potent mechanisms that raise blood glucose, explaining why epinephrine release is an important component in correcting hypoglycemia after inhibition of insulin and increased glucagon secretion in the hierarchy of counter-regulatory responses (see Chapter 33).

(a)

(b)

(c)
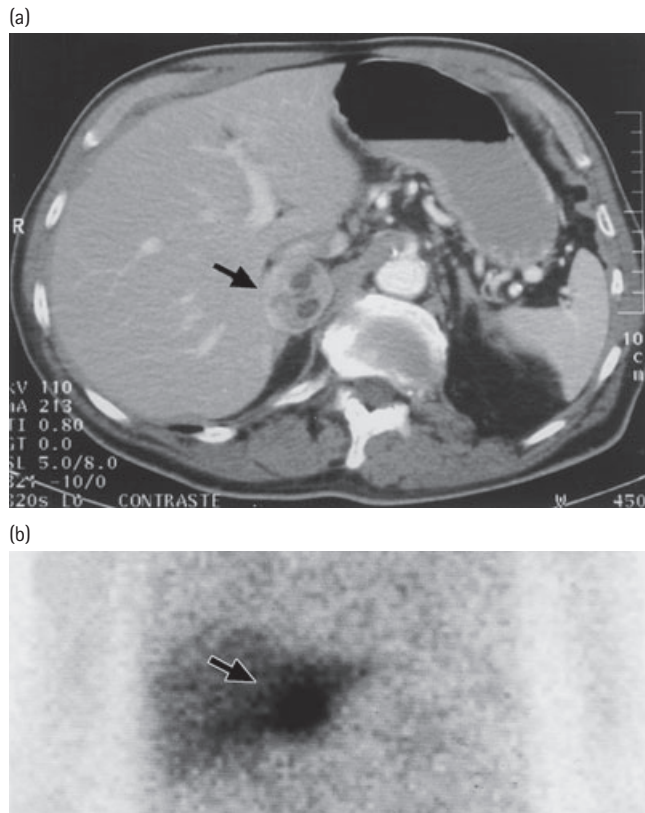
Figure 17.9 Pheochromocytoma in a 75-year-old man with recent-onset type 2 diabetes treated with a sulfonylurea, who was admitted on an emergency basis with severe chest pain and hypertension (blood pressure 240/130 mmHg). Blood glucose on admission was 27 mmol/L. Urinary catecholamine excretion was greatly increased, and a pheochromocytoma of the right adrenal was demon-

strated by: (a) computed tomography; (b) scanning with ^{131}I-metaiodobenzylguanidine, which is taken up by catecholamine-synthesizing tissues; and (c) positron emission tomography with ^{18}F-fluorodeoxyglucose. After laparoscopic removal of the tumor, diabetes and hypertension both resolved.

Diagnosis and treatment of pheochromocytoma

Pheochromocytomas are diagnosed by demonstrating an excess of circulating catecholamines [66–68]. As a proxy marker, this can be achieved by several 24-hour urine collections measuring catecholamines, such as epinephrine, norepinephrine and their metabolites. Assessment of the metabolite vanylmandelic acid is inadequate as it has a high false-negative rate [66]. Where specific circumstances dictate, for instance in screening those with a genetic predisposition to pheochromocytoma, or where urinary results are equivocal, serum measurement of normetanephrine and metanephrine are very sensitive and specific markers of pheochromocytoma (normetanephrine is the more sensitive) [67]. Imaging the tumor can be performed by either MRI or CT. Treatment is surgical removal of the tumor as an adrenalectomy, increasingly performed laparoscopically unless malignancy is suspected [66–68]. Preoperative preparation must

be meticulous to prevent both a hypertensive crisis during manipulation of the tumor and cardiovascular collapse after its removal. This is achieved by initial α-receptor blockade followed by beta-blocker. The order of implementation is important to prevent a hypertensive crisis from unopposed α-adrenoceptor stimulation. The preoperative α-adrenergic blockade often controls hypertension, but has less effect on glucose intolerance [75,78]. In malignant pheochromocytoma where surgery is not possible, adrenolytic drugs, such as mitotane, can be used palliatively.

Outcome of pheochromocytoma and disturbance to glucose tolerance

Removal of the tumor corrects the metabolic abnormalities. If presentation, diagnosis and treatment have occurred without undue delay, it also resolves the hypertension [56,75,78,79].
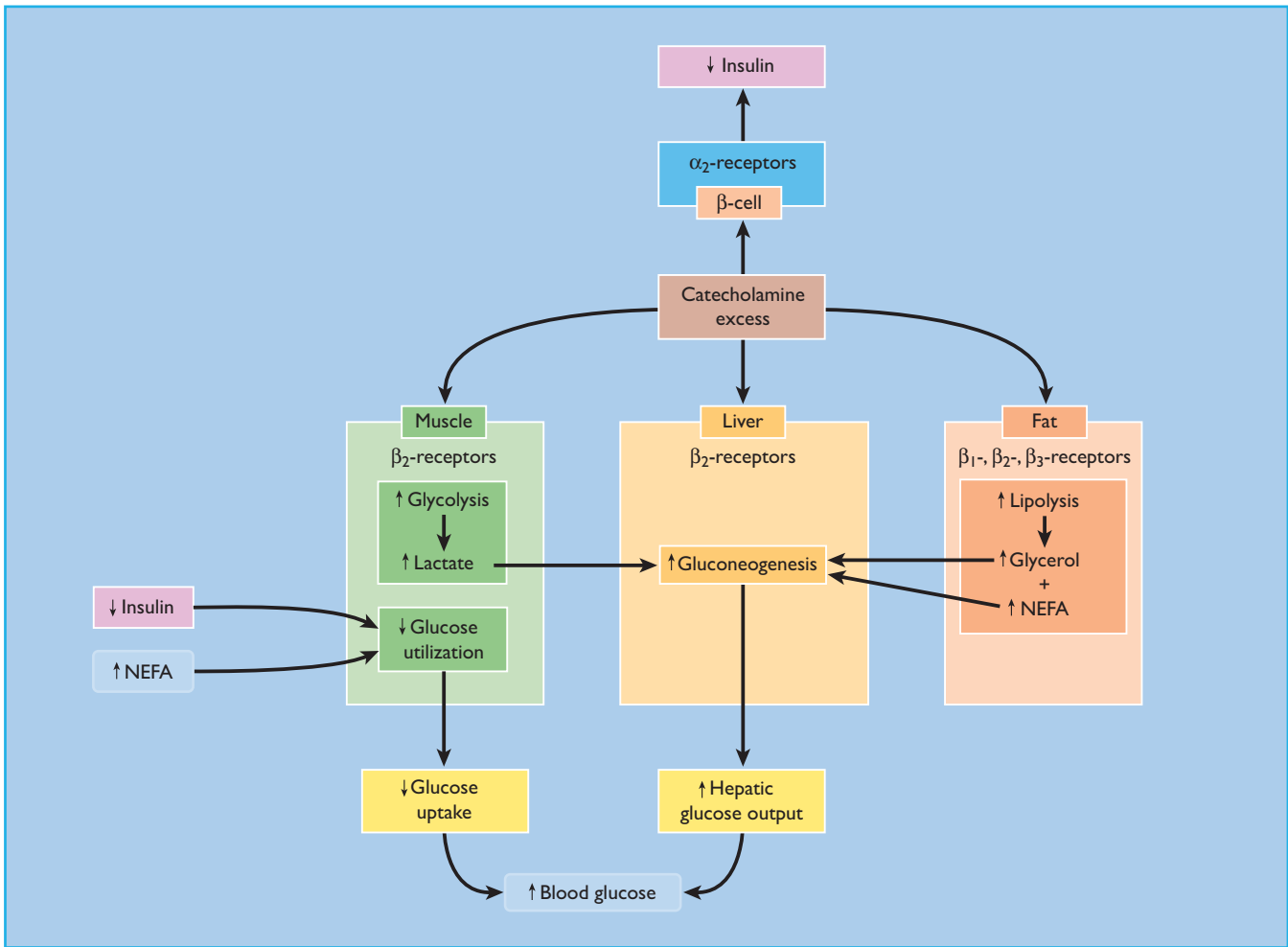
Figure 17.10 Mechanisms of hyperglycemia in pheochromocytoma. NEFA, non-esterified fatty acid.

Although practice varies, greater understanding of the molecular genetics of pheochromocytoma makes clinical genetics input advisable; some laboratories now undertake germline mutation analyses in seemingly isolated tumors [66]. It is also straightforward to exclude hyperparathyroidism by measuring serum calcium as this simple test, if normal, goes a long way to excluding MEN1. Some clinics offer annual follow-up screening for pheochromocytoma by 24-hour urine collection. Patients with pheochromocytomas caused by identified genetic disorders should be followed up at least annually in dedicated clinical genetics endocrinology clinics.

Effects of diabetes on adrenal medulla function

Function of the adrenal medulla may be selectively impaired in patients with long-standing diabetes and hypoglycemia unawareness; attenuation of the epinephrine response to hypoglycemia can delay the restoration of normal serum glucose levels. Epinephrine responses can remain normal to other stimuli, indicating failure of sympathetic activation at a specific, possibly hypothalamic, level (see Chapter 33).

Other endocrine conditions causing disturbance of glucose tolerance

Glucagonoma

Glucagonoma is a rare tumor of the α-cell of the pancreatic islet. The first clear-cut case was reported in 1942, but the "glucagonoma syndrome" (in a series of nine patients with similar symptoms) was not described until 1974 [80,81]. It may form part of MEN1 caused by mutations in the tumor suppressor gene, *MENIN* [82]. In a series of 21 patients [83], the syndrome's most striking clinical features were weight loss (71%), necrolytic migratory erythema (67%) (Figure 17.11a), diabetes (38%), cheilosis or stomatitis (29%) and diarrhea (29%). In this report, patients with the combination of necrolytic migratory erythema and diabetes mellitus were diagnosed more rapidly (after a mean of 7 months), but some cases remain undetected for years. Glucagonoma should always be considered in patients with diabetes and unexplained weight loss or a chronic skin rash.

(a)

(b)
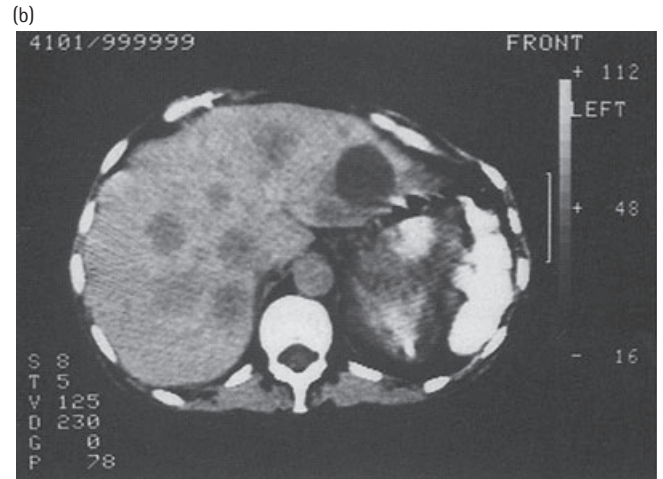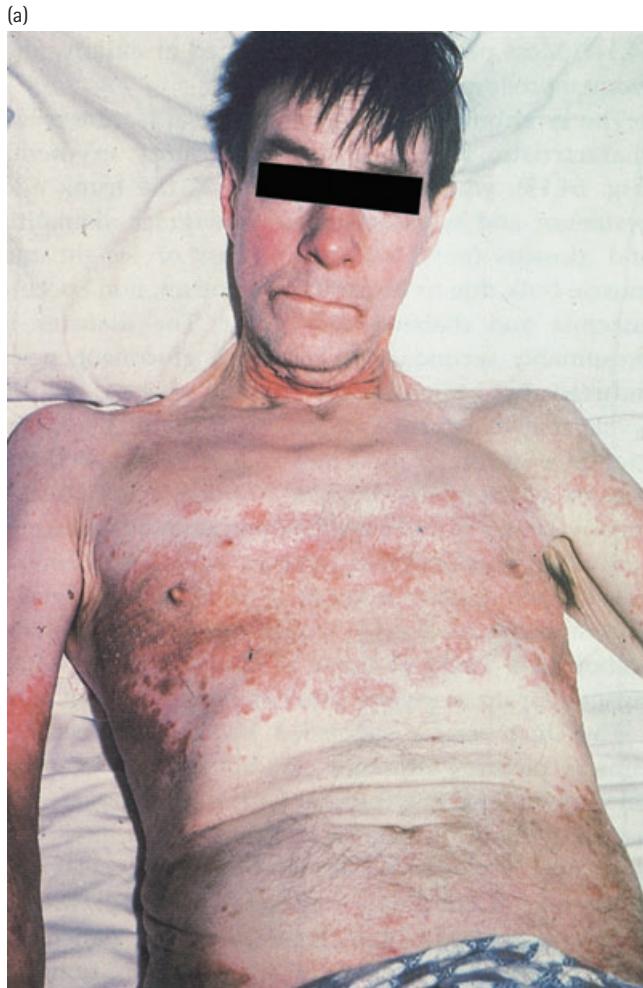
Figure 17.11 Glucagonoma showing characteristic necrolytic migratory erythema (a) and multiple hepatic metastases (b). This patient had non-ketotic diabetes, controlled with low dosages of insulin; the rash recurred many times despite treatment with somatostatin analog. He died from pulmonary embolus. Courtesy of Professor Stephen Bloom, Imperial College School of Medicine, London.

Necrolytic migratory erythema (Figure 17.11a) is described in full in Chapter 47. It usually involves the buttocks, groin, thighs and distal extremities, and characteristically remits and relapses [80,81]. Hyperglucagonemia may contribute to the rash, as may hypoaminoacidemia through glucagon's enhancement of amino acid uptake by the liver and zinc deficiency [81]. The glucagonoma syndrome is also characterized by a normochromic normocytic anemia, a tendency to thrombosis (pulmonary embolism is a common cause of death) and neuropsychiatric disturbances [80]. Reporting of the prevalence of diabetes in glucagonoma has been variable but it probably affects approximately three-quarters of individuals [80]. In cohorts with this detection rate, the hyperglycemia has most commonly been mild and may respond to oral hypoglycemic agents. In studies with lower rates of diagnosis, 75% of patients required insulin [80]. The hyperglycemia is largely brought about by the effects of glucagon on stimulating hepatic gluconeogenesis and, in adequately fed individuals, glycogenolysis [81].

The diagnosis is suggested by finding a pancreatic mass and high fasting plasma glucagon concentration in the absence of other causes of hyperglucagonemia (e.g. severe stress, hepatic and renal failure, poorly controlled diabetes, small-bowel malabsorption and synthetic androgenic drugs) [80,81]. Surgical removal of the tumor is the treatment of choice, but 50% of tumors have metastasized to the liver by the time of diagnosis (Figure 17.11b) [83]. Treatment can then be completed by hepatic artery embolization and/or chemotherapy; somatostatin analogs can also suppress glucagon secretion. The rash may respond to normalization of glucagon levels following removal of the tumor or the use of somatostatin analogs; the administration of zinc, a high-protein diet and control of the diabetes with insulin may also help [80,81,83].

Somatostatinoma

Somatostatinomas are extremely rare tumors arising in 1 in 40 million individuals from δ-cells of the pancreatic islet or enteroendocrine cells of the duodenum and ampulla of Vater [84]. They may be sporadic or as part of genetic syndromes, such as MEN1 [84]. The first two somatostatinomas were found incidentally during cholecystectomy [85,86], but a subsequent case was

diagnosed preoperatively and extensively investigated [87]. The diagnosis was suggested by the triad of diabetes, steatorrhea and gallstones, associated with a tumor of the duodenum [87]. These features, together with hypochlorhydria, are attributable to the widespread inhibitory effects of somatostatin on endocrine and exocrine secretions [84]. Consistent with inhibition of both insulin and glucagon by somatostatin, hyperglycemia is mild, non-ketotic and satisfactorily controlled without insulin [87].

Diagnosis is made by clinical presentation, measuring elevated fasting levels of circulating somatostatin and imaging by CT or MRI. Octreotide scintigraphy can also be used to localize the tumor. Surgical resection is the treatment of choice and can be curative. Where tumors are large and malignant with metastases at the time of diagnosis, debulking, embolization and chemotherapy (including radiolabeled somatostatin analogs) are appropriate [84].

VIPoma

The first VIP-secreting tumor was recognized by Verner and Morrison in 1958 [88]. Classic features are caused by elevated circulating VIP levels and include watery diarrhea (pancreatic cholera), hypokalemia and achlorhydria [89]. Hypercalcemia and glucose intolerance occur in half of the patients, but overt diabetes is unusual; hyperglycemia is probably secondary to the glycogenolytic effect of VIP and/or to hypokalemia, which can impair both insulin secretion and insulin sensitivity. Diagnosis is aided by serum assay for fasting VIP levels. The tumors are usually large and have metastasized from the pancreatic tail by the time of diagnosis. Debulking surgery forms the mainstay of treatment and 10-year survival is approximately 40% [89].

Hyperthyroidism

Hyperthyroidism is defined by overproduction of thyroid hormones. Hyperthyroidism leads to thyrotoxicosis; the manifestations of increased circulating thyroid hormones (Table 17.5) [90]. Ignoring the association of autoimmune hyperthyroidism (Graves disease) with T1DM, thyrotoxicosis per se can disturb glucose tolerance in approximately one-third of individuals, with diabetes occurring in a further 8% of patients [91]. There is evidence for insulin resistance as the primary defect [90,91], especially in those who are overweight [92], although insulin secretion may also be impaired [91,93]. Glucose production and expression of the hepatocyte glucose transporter 2 (GLUT-2) protein are enhanced by thyroid hormone excess [94,95]. The insulin resistance is improved with restoration of euthyroidism even if body mass index (BMI) rises [91]. When hyperthyroidism develops in insulin-treated patients with diabetes, glucose control deteriorates and insulin requirements increase in approximately half the patients; these changes are reversed following treatment of hyperthyroidism [96]. In addition to these alterations in insulin secretion and action, the response to oral glucose tolerance testing is also altered in hyperthyroidism because of faster intestinal absorption [97].

Table 17.5 Clinical features of thyrotoxicosis plus features associated with Graves disease.

Clinical features of thyrotoxicosis
Weight loss despite full, possibly increased, appetite
Tremor
Heat intolerance and sweating
Agitation and nervousness
Palpitations, shortness of breath/tachycardia ± atrial fibrillation
Glucose intolerance
Amenorrhea/oligomenorrhea and consequent subfertility
Diarrhea
Hair loss
Easy fatigability, muscle weakness and loss of muscle mass
Rapid growth rate and accelerated bone maturation (children)

Specific features associated with Graves disease
Bruit in a diffuse, firm goiter
Thyroid eye disease, also called Graves orbitopathy
Pretibial myxoedema – thickened skin over the lower tibia
Thyroid acropachy (clubbing of the fingers)
Other autoimmune features (e.g. vitiligo)

Primary hyperaldosteronism

Primary hyperaldosteronism was originally described by Conn in 1955 in a patient with hypertension, hypokalemia and neuromuscular symptoms associated with an adrenocortical adenoma secreting aldosterone [69]. A benign adenoma is the most common primary cause (65%) with bilateral hyperplasia accounting for 30% of cases. A handful of cases are brought about by a genetic recombination event between the genes encoding two closely related steroidogenic enzymes. This causes aldosterone secretion under the regulation of ACTH, which is suppressible by glucocorticoids [69]. Although debate is active over whether more subtle normokalemic aldosterone excess is a wider cause of hypertension, the relevance of primary hyperaldosteronism to glucose tolerance relies largely on the hypokalemia, which is part of the classic Conn syndrome as low serum potassium impairs insulin secretion [56,69]. Others have questioned whether aldosterone might exert other diabetogenic effects on glucose metabolism, although this remains unclear [98]. Glucose intolerance has been reported in approximately 50% of patients [99]. This is generally mild and overt diabetes is unusual. Defective insulin release has been implicated with delayed or reduced insulin responses following oral glucose challenge. Removal of the aldosteronoma or potassium loading can correct these defects [99].

Primary hyperparathyroidism

Primary hyperparathyroidism is secondary to hypersecretion of parathyroid hormone (PTH), usually by a parathyroid adenoma and less commonly by parathyroid hyperplasia [100]. The prevalence of diabetes in primary hyperparathyroidism is approximately threefold higher than in the general population [101–103], with some cases requiring insulin therapy. Insulin resistance with

hyperinsulinemia is generally held responsible, with raised intracellular calcium limiting cellular glucose uptake [103]. It has been debated whether parathyroidectomy for primary hyperparathyroidism improves glucose homeostasis: some reports argue that it is beneficial for both diabetes and impaired glucose tolerance [104,105] while others find less effect [106,107]. Possibly this relates to duration and severity of the calcium disturbance. With the widespread availability of serum biochemistry, hyperparathyroidism is shifting from a symptomatic disorder to an asymptomatic one where serum calcium tends to be only marginally elevated. In the latter scenario, glucose tolerance appears less affected [108].

Hypopituitarism with growth hormone deficiency

In children, lack of GH increases insulin sensitivity such that young GH-deficient children tend to develop fasting and readily provoked hypoglycemia [109,110]. Using insulin tolerance tests, GH-deficient children were more insulin-sensitive than short children with normal GH secretion [109]. This exaggerated insulin sensitivity attenuates with age and puberty, possibly following increased gonadal steroid production [109] such that adults with GH deficiency demonstrate insulin resistance [12]. Given that GH excess is diabetogenic and acute GH administration raises fasting glucose and fasting insulin levels, and reduces insulin sensitivity [14,17], the value of GH replacement to improve glucose tolerance is likely to be related to whether it can be administered physiologically.

Given this challenge, it is not surprising that the long-term results of GH replacement are somewhat conflicting [12]: a 30-month study showed a deterioration in glucose tolerance and insulin sensitivity despite an increase in lean body tissue and a reduction of fat mass [111]; another study of 6 months' duration found rises in fasting glucose and HbA$_{1c}$ without effects on peripheral or hepatic sensitivity [112]; however, a 5-year trial concluded that GH replacement decreased HbA$_{1c}$ levels [113]. Another study, evaluating the impact of GH therapy in GH-deficient patients during transition from childhood to adulthood, showed that the beneficial effects of chronic treatment on body composition did not overcome the direct antagonistic effects on insulin action [114]. Insulin secretion may also deteriorate during GH administration [111]. Thus, the replacement of GH in hypopituitary patients with diabetes is contentious: long-term treatment with GH may improve insulin sensitivity via improvements in body composition; however, such patients need to be monitored regularly and overtreatment that might lead to the development of diabetes should be avoided [12,115].

Endocrine disorders that associate with diabetes

Several endocrine disorders that are associated with T1DM because of a common etiology and similar pathology (e.g. autoimmune adrenalitis [Addison disease] or autoimmune thyroid disease). Attention in these disorders is warranted for the onset of new autoimmune pathologies. In patients with T1DM, screening can be justified to exclude hyperthyroidism or hypothyroidism by measuring serum thyroid stimulating hormone (TSH) annually. The development of Addison disease in patients with T1DM markedly increases sensitivity to insulin such that unanticipated hypoglycemic reactions occur as dose requirements fall. Even in the absence of diabetes and insulin therapy, Addison disease can cause hypoglycemia, especially in children. Rare conditions resembling T1DM with associated endocrinopathies, such as the autoimmune polyglandular syndromes or POEMS syndrome may occur. Monogenic causes of diabetes that affect other endocrine organs are covered in Chapter 15. Examples (and their respective endocrine disorder) include the various types of hemochromatosis (primary hypogonadism), Wolfram syndrome (diabetes insipidus) and Kearns–Sayre syndrome (hypoparathyroidism, hypogonadism and hypopituitarism). Here, polycystic ovarian syndrome (PCOS) is addressed as a complex endocrine disorder that includes insulin resistance. The hormonal alterations in PCOS share relevance with some of the mechanisms underlying glucose homeostasis in pregnancy and obesity, covered in Chapters 53 and 14, respectively.

Polycystic ovarian syndrome

PCOS is defined as clinical or biochemical hyperandrogenism with oligo- or anovulation where other definable causes have been excluded [116–120]. Some definitions incorporate the detection of multiple ovarian cysts into the diagnosis [119,120], although these occur in approximately half of patients with Cushing syndrome and are non-discriminatory (Figure 17.12) [121,122]. PCOS occurs in 5–10% of women of reproductive age and is characterized primarily by insulin resistance although there is also evidence of β-cell dysfunction [123,124]. Impaired glucose tolerance and T2DM are present in nearly 40% and 7.5–10%, respectively, of women with PCOS, with the former having a tendency to progress to T2DM and being associated with an approximate threefold higher risk of gestational diabetes [123,124]. These data are confounded to some degree by the effect of obesity, but the incidence of PCOS remains increased across ethnicities whereas obesity rates vary [124]. Indeed, it can be argued that PCOS in women with normal BMI represents the most severe form of the disorder where genetic screening programs are most likely to identify PCOS susceptibility genes.

The source of the androgens is both the adrenal cortex and the ovary [124]. The raised insulin levels can stimulate androgen production by the ovary and interfere with other aspects of ovarian function. Within the adrenal cortex, where insulin receptors are expressed in the zona fasciculata of the adrenal cortex [125], there is some evidence that insulin can influence glucocorticoid versus sex steroid precursor production [124].

The diagnosis of PCOS is one of exclusion, meaning that clinical and biochemical findings are only supportive of the condition

(a)

(b)
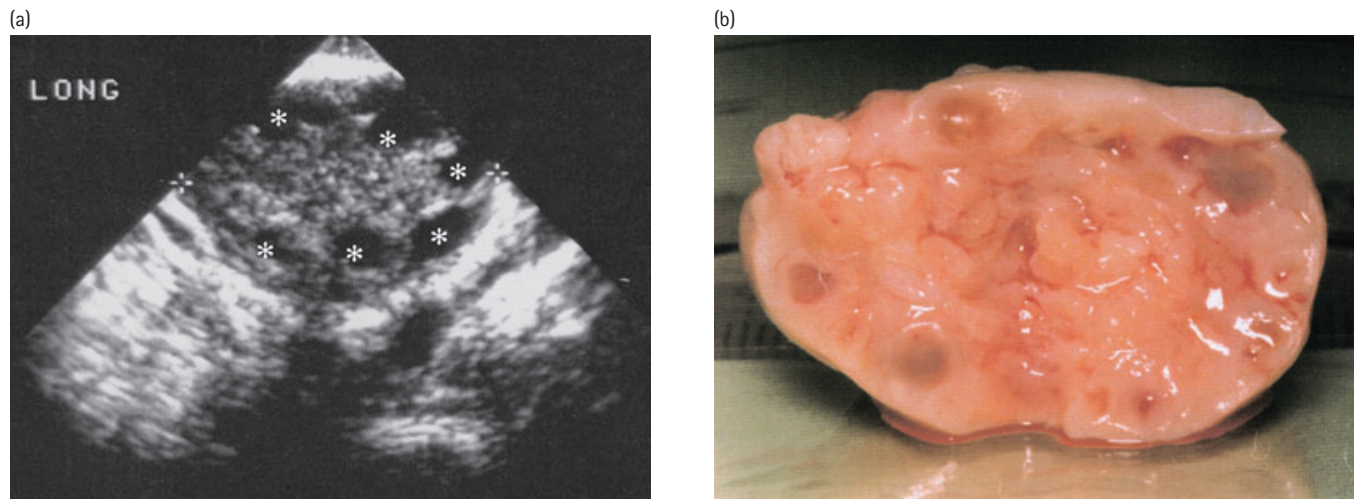
Figure 17.12 Polycystic ovary syndrome, showing (a) characteristic ultrasonographic appearance of large, mainly peripheral cysts (asterisks) and (b) the cut surface of a polycystic ovary. From Franks [129], with permission from *New England Journal of Medicine*. Courtesy of (a) Dr D. Kiddy and (b) Professor Steve Franks, Imperial College School of Medicine, London, UK.

[116,121]. Serum estradiol is detectable and usually >200 pmol/L. Endocrine abnormalities include increases in serum luteinizing hormone (LH) leading to a raised LH : FSH (follicle stimulating hormone) ratio, androstenedione and testosterone concentrations. Serum sex hormone-binding globulin (SHBG) levels are commonly low. Ovarian ultrasound is useful to help exclude the presence of a tumor underlying the androgen excess [121].

Further evidence that the condition is caused by insulin resistance comes from its amelioration with exercise and agents that improve insulin sensitivity such as metformin or thiazolidinediones [126]. As well as lowering blood glucose, these agents improve menstrual regularity and increase the chance of ovulatory cycles [126].

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