look carefully at the sclerae, which in exophthalmos are not covered by the lower eyelid. Next look from behind over the patient's forehead for exophthalmos, where the eye will be visible anterior to the superior orbital margin. Now examine for the complications of proptosis, which include: (i) chemosis (oedema of the conjunctiva and injection of the sclera, particularly over the insertion of the lateral rectus); (ii) conjunctivitis; (iii) corneal ulceration (due to inability to close the eyelids); (iv) optic atrophy (rare and possibly due to optic nerve stretching); and (v) ophthalmoplegia (the inferior rectus muscle power tends to be lost first, and later convergence is weakened).

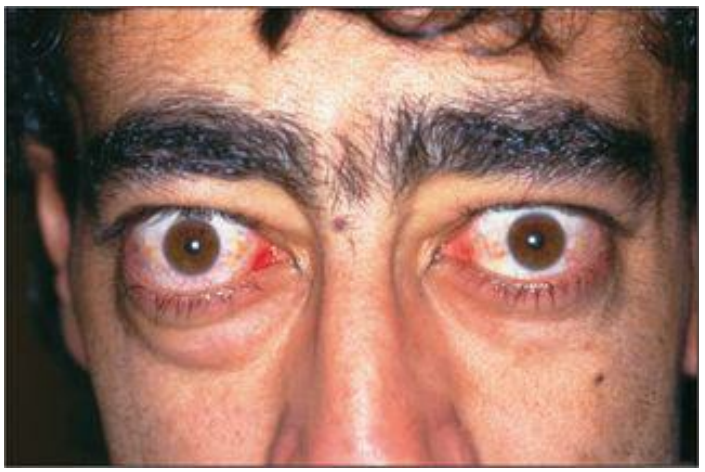


Figure 10.7 Thyrotoxicosis: thyroid stare and exophthalmos

TABLE 10.5 Causes of exophthalmos

Bilateral Graves' disease
Unilateral Tumours of the orbit: e.g. dermoid, optic nerve glioma, neurofibroma, granuloma Cavernous sinus thrombosis Graves' disease

Pseudotumours of the orbit

The mechanism of exophthalmos is uncertain. It occurs only in Graves' disease. It may precede the onset of thyrotoxicosis, or may persist after the patient has become euthyroid. It is characterised by an inflammatory infiltrate of the orbital contents, but not of the globe itself. The orbital muscles are particularly affected, and an increase in their size accounts for most of the increased volume of the orbital contents and therefore for protrusion of the globe. It is probably due to an autoimmune abnormality.

Next examine for the components of thyroid ophthalmopathy, which are related to sympathetic overactivity and are not specific for Graves' disease. Look for the thyroid stare (a frightened expression) and lid retraction (Dalrymple's sign[f]), where there is sclera visible above the iris. Test for lid lag (von Graefe's sign[g]) by asking the patient to follow your finger as it descends at a moderate rate from the upper to the lower part of the visual field. Descent of the upper lid lags behind descent of the eyeball.

If ptosis is present, one should rule out myasthenia gravis, which can be associated with autoimmune disease.

The neck

Examine for thyroid enlargement, which is usually detectable (60%–90% of patients). In Graves' disease the gland is classically diffusely enlarged and is smooth and firm. An associated thrill is usually present but this finding is not specific for thyrotoxicosis caused by Graves' disease. Absence of thyroid enlargement makes Graves' disease unlikely, but does not exclude it. Possible thyroid abnormalities in patients who are thyrotoxic but do not have Graves' disease include a toxic multinodular goitre, a solitary nodule (toxic adenoma), and painless, postpartum or subacute (de Quervain's[h]) thyroiditis. In de Quervain's thyroiditis there is typically a moderately enlarged firm and tender gland. Thyrotoxicosis may occur without any goitre, particularly in elderly patients. Alternatively, in hyperthyroidism due to a rare abnormality of trophoblastic tissue (a hydatidiform mole or choriocarcinoma of the testis or uterus), or excessive thyroid hormone replacement, the thyroid gland will not usually be palpable.

If a thyroidectomy scar is present, assess for hypoparathyroidism (Chvostek's[i] or Trousseau's[j] signs; page 311). These signs are most often present in the first few days after operation.

The arms

Ask the patient to raise the arms above the head and so test for proximal myopathy.

The chest

Gynaecomastia (page 315) occurs occasionally. Examine the heart for systolic flow murmurs (due to increased cardiac output) and signs of congestive cardiac failure, which may be precipitated by thyrotoxicosis in older people.

The legs

Look first for pretibial myxoedema. This takes the form of bilateral firm, elevated dermal nodules and plaques, which can be pink, brown or skin-coloured. They are caused by mucopolysaccharide accumulation. Despite the name, this occurs only in Graves' disease and not in hypothyroidism. Test now for proximal myopathy and hyperreflexia in the legs which is present in only about a quarter of cases.

Hypothyroidism (myxoedema)

Hypothyroidism (deficiency of thyroid hormone) is due to primary disease of the thyroid or, less commonly, is secondary to pituitary or hypothalamic failure (Table 10.6). Myxoedema implies a more severe form of hypothyroidism. In myxoedema, for unknown reasons, hydrophilic mucopolysaccharides accumulate in the ground substance of tissues including the skin. This results in excessive interstitial fluid, which is relatively immobile, causing skin thickening and a doughy induration.

TABLE 10.6 Thyrotoxicosis and hypothyroidism

Causes of thyrotoxicosis
Primary
Graves' disease
Toxic multinodular goitre

Toxic multinodular goitre
Toxic uninodular goitre: usually a toxic adenoma
Hashimoto's thyroiditis (early in its course; later it produces hypothyroidism)
Subacute thyroiditis (transient)
Postpartum thyroiditis (non-tender)
Iodine-induced ('Jod-Basedow phenomenon'*—iodine given after a previously deficient diet)

Secondary
Pituitary (very rare): TSH hypersecretion
Hydatidiform moles or choriocarcinomas: HCG secretion (rare)
Struma ovarii (rare)
Drugs, e.g. excess thyroid hormone ingestion, amiodarone

Causes of hypothyroidism

Primary
Without a goitre (decreased or absent thyroid tissue):
- Idiopathic atrophy
- Treatment of thyrotoxicosis—e.g. ^{131}I, surgery
- Agenesis or a lingual thyroid
- Unresponsiveness to TSH

With a goitre (decreased thyroid hormone synthesis):
- Chronic autoimmune diseases—e.g. Hashimoto's thyroiditis
- Drugs, e.g. lithium, amiodarone
- Inborn errors (enzyme deficiency)
- Endemic iodine deficiency or iodine-induced hypothyroidism

Secondary
Pituitary lesions (Table 10.8)
Tertiary
Hypothalamic lesions
Transient

Thyroid hormone treatment withdrawn
Subacute thyroiditis
Postpartum thyroiditis

TSH = thyroid stimulating hormone. HCG = human chorionic gonadotrophin.

* Carl von Basedow (1799–1854), German general practitioner, described this in 1840 (Jod = iodine in German).

The symptoms of hypothyroidism are insidious but patients or their relatives may have noticed cold intolerance, muscle pains, oedema, constipation, a hoarse voice, dry skin, memory loss, depression or weight gain (*Questions box 10.2*).

Questions box 10.2

Questions to ask the patient with suspected hypothyroidism

1. Have you found cold weather more difficult to cope with recently?
2. Have you had problems with constipation?
3. Have you gained weight?
4. Have you noticed that your skin has become dry?
5. Do you think your memory is not as good as it was? Have you felt depressed?
6. Do you think your voice has become hoarse?—Hypothyroid speech (characteristically slow and nasal) occurs in one-third of patients
7. Have you noticed swelling of your legs?

Examine the patient with suspected hypothyroidism as follows (see *Good signs guide 10.3*).

GOOD SIGNS GUIDE 10.3 Hypothyroidism

Sign	Positive LR	Negative LR
Skin		
Coarse	5.6	0.7
Cool and dry	4.7	0.9
Cold palms	NS	NS
Dry palms	NS	NS
Periorbital puffiness	2.8	0.6
Puffiness of wrists	2.9	0.7

Loss of eyebrow hair	1.9	NS
Speech		
Hypothyroid speech	5.4	0.7
Thyroid gland		
Goitre	2.8	0.6
Pulse		
<70/min	4.1	0.8

NS = not significant.

From McGee S, Evidence-based physical diagnosis, 2nd edn. St Louis: Saunders, 2007.

General inspection

Look for signs of obvious mental and physical sluggishness, or evidence of the very rare 'myxoedema madness'. Hypothyroid speech is a feature in about a third of patients. This is characteristically slow, nasal and deep in pitch. Obesity is no more common than in euthyroid people.

The hands

Note peripheral cyanosis (due to reduced cardiac output) and swelling of the skin, which may appear cool and dry. The yellow discoloration of hypercarotenaemia (there is slowing down of hepatic metabolism of carotene) may be seen on the palms. Look for palmar crease pallor—anaemia may be due to: (i) chronic disease; (ii) folate deficiency secondary to bacterial overgrowth, or vitamin B_{12} deficiency due to associated pernicious anaemia; or (iii) iron deficiency due to menorrhagia.

Take the pulse, which may be of small volume and slow. Test for sensory loss, as the carpal tunnel is thickened in myxoedema.

The arms

Test for proximal myopathy (rare) and a 'hung-up' biceps or Achilles tendon reflex (see below).

The face

Inspect the face (Figure 10.8). The skin, but not the sclerae, may appear yellow due to hypercarotenaemia. The skin may be generally thickened, and alopecia may be present, as may vitiligo (an associated autoimmune disease).

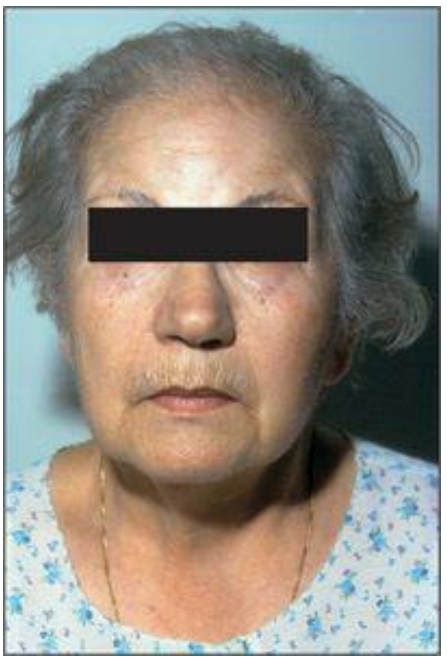


Figure 10.8 Myxoedema

Inspect the eyes for periorbital oedema. Loss or thinning of the outer third of the eyebrows can occur in myxoedema but is also common in healthy persons. Look for xanthelasma (due to associated hypercholesterolaemia). Palpate for coolness and dryness of the skin and hair. There may be thinning of the scalp hair.

Look at the tongue for swelling. Ask the patient to speak, and listen for coarse, croaking, slow speech. Bilateral nerve deafness may occur with endemic or congenital hypothyroidism.

The thyroid gland

A primary decrease in thyroid hormone results in a compensatory oversecretion of TSH. A goitre will result if there is viable thyroid tissue.

Many cases of hypothyroidism are not associated with an enlarged gland as there is little thyroid tissue. The exceptions include severe iodine deficiency, enzyme deficiency (inborn errors of metabolism), late Hashimoto's disease or treated (with radioactive iodine) thyrotoxicosis (Table

Hashimoto's disease or treated (with radioactive iodine) thyrotoxicosis (Table 10.6).

The chest

Examine the heart for a pericardial effusion and the lungs for pleural effusions.

The legs

There may be non-pitting oedema. Ask the patient to kneel on a chair with the ankles exposed. Tap the Achilles tendon with a reflex hammer. There is apparently normal (in fact slightly slowed) contraction followed by delayed relaxation of the foot in hypothyroidism (the 'hung-up' reflex). Examine for signs of peripheral neuropathy and for other uncommon neurological abnormalities associated with hypothyroidism (Table 10.7).

TABLE 10.7 Neurological associations of hypothyroidism

Common
Entrapment: carpal tunnel, tarsal tunnel
Delayed ankle jerks
Muscle cramps
Uncommon
Peripheral neuropathy
Proximal myopathy
Hypokalaemic periodic paralysis
Cerebellar syndrome
Psychosis

Psychosis
Coma
Unmasking of myasthenia gravis
Cerebrovascular disease
High cerebrovascular fluid protein
Nerve deafness

The pituitary

Pituitary tumours can present in two ways: as a result of (i) local effects such as headaches, visual field loss and loss of acuity; and (ii) changes in pituitary hormone secretion. These changes include: (i) excess growth hormone, causing acromegaly; (ii) excess adrenocorticotrophic hormone (ACTH), causing Cushing's syndrome; (iii) excess prolactin, causing galactorrhoea, secondary amenorrhoea or male infertility or deficiency (hypopituitarism), and (iv) excess thyroid stimulating hormone (TSH), causing hyperthyroidism.

Panhypopituitarism (all pituitary hormones are deficient)

This is a deficiency of most or all of the pituitary hormones and is usually due to a space-occupying lesion or destruction of the pituitary gland (Table 10.8). Hormone production is often lost in the following order: (i) growth hormone (dwarfism in children, insulin sensitivity in adults); (ii) prolactin (failure of lactation after delivery); (iii) gonadotrophins (loss of secondary sexual characteristics, secondary amenorrhoea in women, loss of libido and infertility in men); (iv) TSH (hypothyroidism); and (v) ACTH (hypoadrenalism, with loss of secondary sexual hair due to decreased adrenal androgen production).

TABLE 10.8 Causes of hypopituitarism

Space-occupying lesion • Pituitary tumour (non-secretory or secretory) • Other tumours: craniopharyngioma, metastatic carcinoma, sarcoma • Granulomata: e.g. sarcoid, tuberculosis
latrogenic: e.g. surgery or irradiation
Head injury
Sheehan's syndrome* (postpartum pituitary haemorrhage resulting in necrosis of the gland)
Empty sella syndrome (often an incidental MRI scan finding and not always associated with pituitary insufficiency)
Infarction or pituitary apoplexy
Idiopathic

* Harold Sheehan (b. 1900), professor of pathology, Liverpool, England, described the syndrome in 1937.

However, isolated single hormonal deficiencies or multiple deficiencies may occur in any combination.

Questions box 10.3

Questions to ask the patient with suspected pan-hypopituitarism

1. Have you had problems with lethargy, weakness and fatigue, or weight loss or poor appetite?—Adrenocorticoid deficiency

2. Have you gained weight, found cold weather more intolerable or had constipation?—Thyroid stimulating hormone deficiency

3. (Men) Have you noticed reduced sexual interest (libido), reduced muscle strength, erectile dysfunction or had problems with infertility?—Follicle stimulating hormone (FSH)

deficiency

4. (Women) Have you had less bleeding during menstruation?—Oligomenorrhoea due to FSH deficiency

5. Have you noticed reduced exercise ability and energy?—Growth hormone deficiency in adults

6. Have you had headaches or visual disturbance?—Pituitary enlargement

General inspection

The patient may be of short stature (failure of growth hormone secretion before growth is complete). Look for pallor of the skin (due to anaemia or occasionally ACTH deficiency because of the loss of its melanocyte-stimulating activity), fine-wrinkled skin and lack of body hair (due to gonadotrophin deficiency). There may be complete absence of the secondary sexual characteristics (Table 10.9) if gonadotrophin failure occurred before puberty.

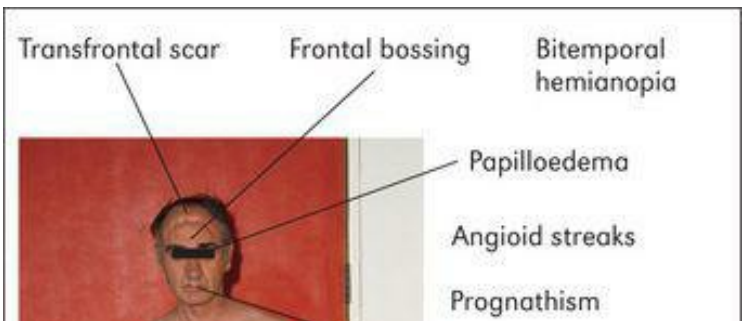
TABLE 10.9 Secondary sexual development (Tanner stages)

This occurs at puberty in response to pituitary gonadotrophins
Males
1. Preadolescent 2. Enlargement of testes and scrotum 3. Lengthening of penis 4. Increase in penis breadth, glans development and scrotal darkening

5. Adult: above, plus public hair spread to medial surface of the thighs	
Females	
Breasts 1. Preadolescent 2. Breast bud (elevation of breasts and papilla) 3. Enlargement of breast and areola (no separation of contours) 4. Areola and papilla project above breast level (secondary mound) 5. Adult: areola is recessed and papilla projects	**Pubic hair** 1. No pubic hair 2. Sparse growth, mainly over the labia 3. Darker, coarser, more curled hairs but sparse over the junction of the pubes 4. Adult type but no hair spread to medial surface of thighs 5. Adult: horizontal pattern and hair spread to medial thighs

The face

Look at the face more closely. Multiple skin wrinkles around the eyes are characteristic of gonadotrophin deficiency. Inspect the forehead carefully for hypophysectomy scars—transfrontal scars will be apparent (Figure 10.9) but not transsphenoidal ones, as this operation is performed through the base of the nose, via an incision under the upper lip.



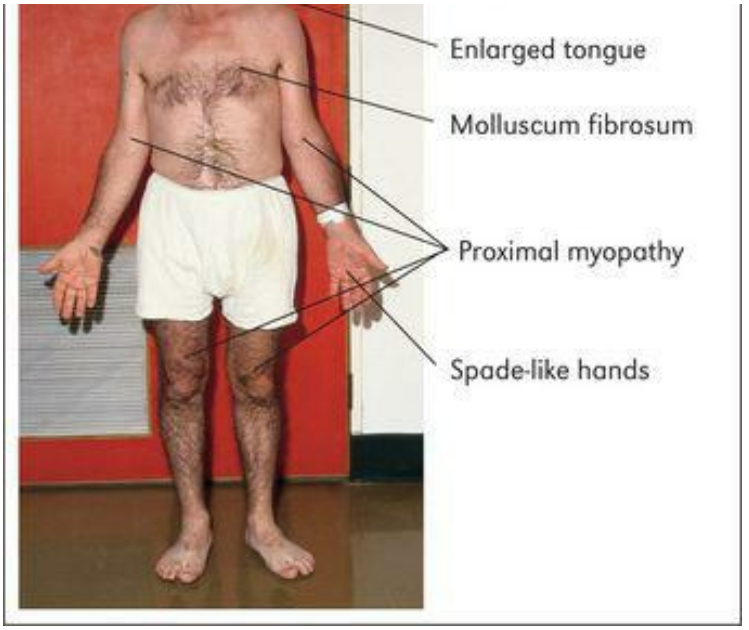


Figure 10.9 Acromegaly

Examine the eyes (Chapter 13). The visual fields must be assessed for any defects, especially bitemporal hemianopia (an enlarging pituitary tumour may compress the optic chiasm), and the fundi examined for optic atrophy (optic nerve compression from a pituitary tumour). Assess the third, fourth, sixth and first divisions of the fifth cranial nerves, as these may be affected by extrapituitary tumour expansion into the cavernous sinus (Figure 10.10).

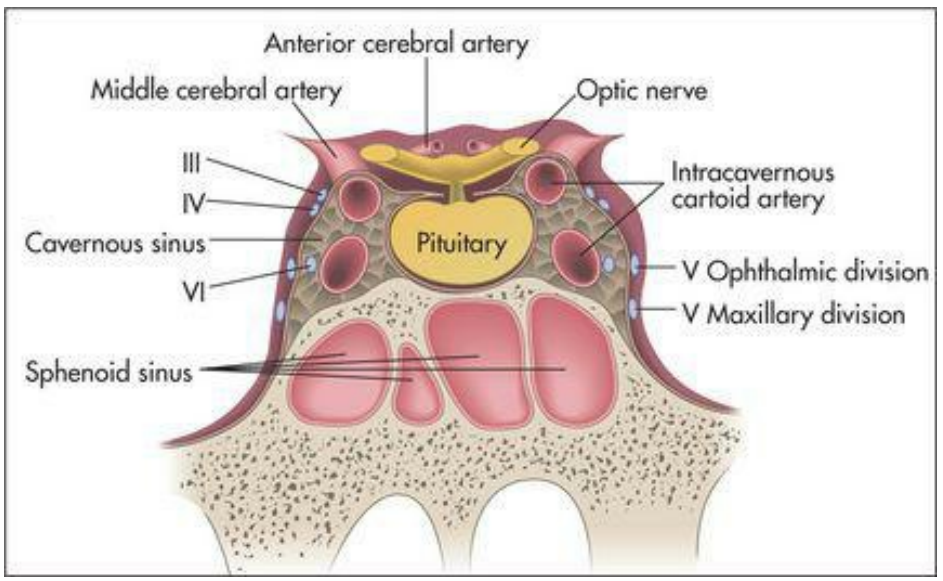


Figure 10.10 The cavernous sinus and its relationship with the cranial nerves and pituitary gland

Feel the facial hair over the bearded area in men for normal beard growth (which is lost with gonadotrophin deficiency).

The chest

Go on to the chest. Look for skin pallor and for a decrease in nipple pigmentation. In men, decreased body hair (axillary and chest) may be present. In women, secondary breast atrophy may be found.

The genital region

Loss of pubic hair occurs in both sexes. In men, testicular atrophy may be present. Atrophied testes are characteristically small and firm. The normal-sized testis is about 15–25 mL in volume.

The ankle reflexes

Test for 'hung-up' jerks (Figure 10.11). These are an important sign of pituitary hypothyroidism. Occasionally, pituitary hypothyroid patients may be slightly overweight, but the classical myxoedematous appearance is usually absent.

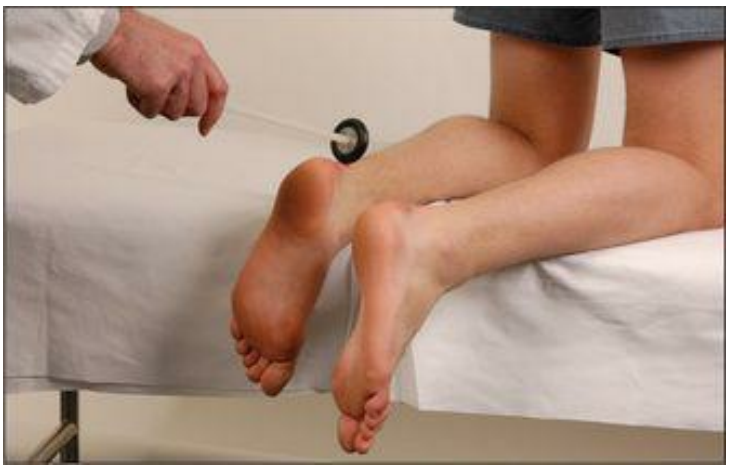


Figure 10.11 Testing ankle jerks (second method— see also page 372)
This method best demonstrates the 'hung-up' reflexes of hypothyroidism. Look for rapid dorsiflexion followed by slow plantar flexion after the tendon is tapped.

Acromegaly[k]

This is excessive secretion of growth hormone, typically due to an

eosinophilic pituitary adenoma.[l] Growth hormone stimulates the liver and other tissues to produce somatomedins which in turn promote growth. Growth hormone is also a protein anabolic hormone exerting its effects at the ribosomal level, and it is diabetogenic as it exerts an anti-insulin effect in muscle and increases hepatic glucose release. The disease has a very gradual onset and patients may not have noticed symptoms. Most patients, however, have headache caused by stretching of the dura by the enlarging pituitary tumour.

Gigantism is the result of growth hormone hypersecretion occurring before puberty and fusion of the epiphyses. It results in massive skeletal as well as soft-tissue growth. Acromegaly occurs when the growth plates have fused, so that only soft-tissue and flat-bone enlargement are possible.

General inspection

The face and body habitus[m] may be characteristic (Figure 10.9).

The hands

Sit the patient on the side of the bed or in a chair and look at the hands. Notice a wide spade-like shape (due to soft tissue and bony enlargement). Increased sweating and warmth of the palms may be noted. This is due to an increased metabolic rate. The skin may appear thickened. Changes of osteoarthritis in the hands are common and are due to skeletal overgrowth. Examine for median nerve entrapment, which can occur because of soft-tissue overgrowth in the carpal tunnel area.

The arms

Proximal myopathy may be present (page 391). Palpate behind the medial epicondyle (the ‘funny bone’) for ulnar nerve thickening.

The axillae

Carefully inspect the axillae for skin tags (called molluscum fibrosum, which are non-tender skin-coloured protrusions). Summon up courage and feel for greasy skin. Look for acanthosis nigricans.

The face

Look for a large supraorbital ridge, which causes frontal bossing (this may also occur occasionally in Paget's disease, rickets, achondroplasia or hydrocephalus). The lips may be thickened.

Examine the eyes for visual field defects; classically there may be bitemporal hemianopia if the pituitary tumour is large. Look in the fundi for optic atrophy (due to nerve compression) and papilloedema (due to raised intracranial pressure with an extensive tumour). The presence of angioid streaks (red, brown or grey streaks that are three to five times the diameter of a retinal vein and appear to emanate from the optic disc) should also be sought: these are due to degeneration and fibrosis of Bruch's membrane. One should also note hypertensive changes or diabetic changes in the fundus. Ocular palsies may occur with an extensive pituitary tumour.

Look in the mouth for an enlarged tongue that may not fit neatly between the teeth. The teeth themselves may be splayed and separated, with malocclusion as the jaw enlarges. The lower jaw may look square and firm (as it does on some American actors). When the jaw protrudes it is called prognathism (Greek *pro* 'forwards', *gnathos* 'jaw').

The neck

The thyroid may be diffusely enlarged or multinodular (all the internal organs may enlarge under the influence of growth hormone). Listen to the voice for hoarseness.

The chest

Look for coarse body hair and gynaecomastia. Examine the heart for signs of arrhythmias, cardiomegaly and congestive cardiac failure, which may be due to ischaemic heart disease, hypertension or cardiomyopathy (all more common in acromegaly).

The back

Inspect for kyphosis.

The abdomen

Examine for hepatic, splenic and renal enlargement, and go on to look for testicular atrophy (the latter indicating gonadotrophin deficiency secondary to an enlarging pituitary tumour). Acromegaly can be associated with a mixed pituitary tumour and resultant hyperprolactinaemia can also cause testicular atrophy.

The lower limbs

Look for signs of osteoarthritis in the hips especially, and knees (page 269), and for pseudogout. Foot drop may be present because of common peroneal nerve entrapment (page 376).

The urine and blood pressure

Test the urine for glucose, as excess growth hormone is diabetogenic in 25% of cases. Take the blood pressure to test for hypertension.

Finally, decide if the disease is active or not. Signs of active disease include: (i) large numbers of skin tags (skin tags can occur commonly in normal people); (ii) excessive sweating; (iii) presence of glycosuria; (iv) increasing visual field loss; (v) enlarging goitre; and (vi) hypertension. *Note:* Headache also suggests disease activity.

Other pituitary syndromes

Cushing's syndrome can occur as a result of excess pituitary ACTH secretion. Hyperthyroidism can occur as a result of excess pituitary TSH production. Prolactinomas of the pituitary can cause galactorrhoea (production of milk) in both women and men.

The adrenals

Cushing's syndrome

This is due to a chronic excess of glucocorticoids. Steroids have multiple effects on the body, due to stimulation of the DNA-dependent synthesis of select messenger ribonucleic acids (RNAs). This leads to the formation of enzymes, which alter cell function and result in increased protein catabolism and gluconeogenesis. Remember that Cushing's disease is specifically

pituitary ACTH overproduction, while Cushing's syndrome is due to excessive steroid hormone production from any cause (Table 10.10; see *Good signs guide 10.4*, *Questions box 10.4*).

TABLE 10.10 Causes of Cushing's syndrome

Exogenous administration of excess steroids or ACTH (most common)
Adrenal hyperplasia • Secondary to pituitary ACTH production (Cushing's disease) Microadenoma Macroadenoma Pituitary-hypothalamic dysfunction • Secondary to ACTH-producing tumours— e.g. small cell lung carcinoma
Adrenal neoplasia • Adenoma • Carcinoma (rare)

ACTH = adrenocorticotrophic hormone.

GOOD SIGNS GUIDE 10.4 Cushing's syndrome

Sign	Positive LR	Negative LR
Vital signs		
Hypertension	2.3	0.8
Body habitus		
Moon face	1.6	0.1
Central obesity	3.0	0.2
General obesity	0.1	2.5

Skin findings		
Thin skinfold (women)	115.6	0.2
Plethora	2.7	0.3
Hirsutism (women)	1.7	0.7
Ecchymoses	4.5	0.5
Red or purple striae	1.9	0.7
Acne	2.2	0.6
Extremities		
Proximal muscle weakness	NS	0.4
Oedema	1.8	0.7

NS = not significant.

From McGee S, Evidence-based physical diagnosis, 2nd edn. St Louis: Saunders, 2007

Questions box 10.4

Questions to ask the patient with suspected Cushing's syndrome

! denotes symptoms for the possible diagnosis of an urgent or dangerous problem.

1. Have you gained a lot of weight recently? How much?

2. Do you bruise easily?

3. Has your skin become thin?

4. Have you had problems with acne?

5. Have you felt agitated and been unable to sleep?

6. Have you had problems with weakness of your muscles or difficulty getting up out of chairs?—Proximal myopathy

7. Have you had problems maintaining erections (men) or had amenorrhoea (women)?

The hands

Skinfold thickness is best assessed on the backs of the hands and may be reliable only as a sign of Cushing's in young women. The skinfold should be thicker than 1.8 mm.

Standing

Have the patient undress to the underpants and, if possible, stand up (Figure 10.12). Look from the front, back and sides. Note *moon-like facies* and *central obesity*. The limbs appear thin despite sometimes very gross truncal (mostly intra-abdominal rather than subcutaneous fat) obesity.[n] This is the characteristic fat distribution that occurs with steroid excess. *Bruising* may be present (due to loss of perivascular supporting tissue–protein catabolism). Look for excessive *pigmentation* on the extensor surfaces (because of melanocyte-stimulating-hormone [MSH]-like activity in the ACTH molecule). Ask the patient to squat at this point to test for *proximal myopathy*, due to mobilisation of muscle tissue or excessive urinary potassium loss. Look at the back for the '*buffalo hump*', which is due to fat deposition over the interscapular area. Palpate for bony *tenderness* of the vertebral bodies due to crush fractures from osteoporosis (a steroid anti-vitamin-D effect and increased urinary calcium excretion may be responsible in part for disruption of the bone matrix).

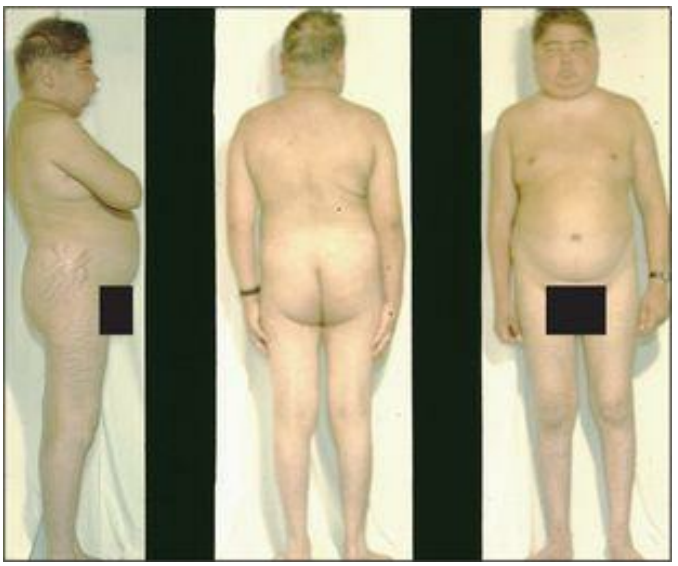


Figure 10.12 Buffalo hump and central obesity in Cushing's syndrome

From McDonald FS, ed., Mayo Clinic images in internal medicine, with permission. © Mayo Clinic Scientific Press and CRC Press.

Sitting

Ask the patient to sit on the side of the bed, but remember that he or she may be suffering from steroid psychosis and refuse to do anything you ask.

The face and neck

Look for plethora (this occurs in the absence of polycythaemia which, however, may also be present). The face may have a typical moon shape due to fat deposition in the upper part. Inspect for acne and hirsutism (if adrenal androgen secretion is also increased). Telangiectasiae may also be present.

Examine the visual fields for signs of a pituitary tumour, and the fundi for optic atrophy, papilloedema and hypertensive or diabetic changes. Look for supraclavicular fat pads.

The abdomen

Lay the patient in bed on one pillow. Examine the abdomen for purple striae, which are due to weakening and disruption of collagen fibres in the dermis, leading to exposure of vascular subcutaneous tissues. In patients with Cushing's syndrome these are wider (1 cm) than those seen in people who have gained weight rapidly for other reasons. They may also be present near the axillae on the upper arms or on the inside of the thighs. Palpate for adrenal masses (rarely a large adrenal carcinoma will be palpable over the renal area). Palpate for hepatomegaly due to fat deposition or rarely to adrenal carcinoma deposits.

The legs

Palpate for oedema (due to salt and water retention). Look for bruising and poor wound healing.

The urinalysis and blood pressure

Test the urine for sugar (as steroids are diabetogenic; this is due to an increase in hepatic gluconeogenesis and an anti-insulin effect on peripheral tissues). Hypertension is common due to salt and water retention (an aldosterone effect) and possibly to increased angiotensin secretion or a direct effect on blood vessels.

Synthesis of signs

Certain signs are of some aetiological value in Cushing's syndrome.

• **Signs which suggest that adrenal carcinoma may be the underlying cause:** (i) a palpable abdominal mass; (ii) signs of virilisation in the female; (iii) gynaecomastia in the male.

• **Signs which suggest that ectopic ACTH production may be the cause:** (i) absence of the Cushingoid body habitus unless the responsible tumour has been slow growing and allowed time for Cushingoid features to develop; (ii) more prominent oedema and hypertension; (iii) marked muscle weakness. *Note:* When Cushing's is due to ectopic ACTH production from a small cell carcinoma, the patient is much more likely to be male (positive LR 13)[4] and the history to be of more rapid onset of the symptoms and signs (18 months: positive LR 15).[4]

• **Significance of hyperpigmentation:** this suggests an extra-adrenal tumour, or enlargement of an ACTH-secreting pituitary adenoma following adrenalectomy (Nelson's[o] syndrome).

Addison's disease[p]

This is adrenocortical hypofunction with reduction in the secretion of glucocorticoids and mineralocorticoids. It is most often due to autoimmune disease of the adrenal glands. Other causes are listed in Table 10.11.

TABLE 10.11 Causes of Addison's disease

Chronic

Primary Autoimmune adrenal disease Infection (tuberculosis, HIV) Granuloma Following heparin therapy Malignant infiltration Haemochromatosis Adrenoleucodystrophy *Secondary* Pituitary or hypothalamic disease
Acute Septicaemia: meningococcal Adrenalectomy Any stress in a patient with chronic hypoadrenalism or abrupt cessation of prolonged high-dose steroid therapy

If this disease is suspected, look for cachexia. Then, with the patient undressed, look for pigmentation in the palmar creases (Figure 10.13), elbows, gums and buccal mucosa, genital areas and in scars. This occurs because of compensatory ACTH hypersecretion in primary hypoadrenalism (when there is adrenal disease), as ACTH has melanocyte-stimulating activity. Also inspect for vitiligo (localised hypomelanosis), an autoimmune disease that is commonly associated with autoimmune adrenal failure.

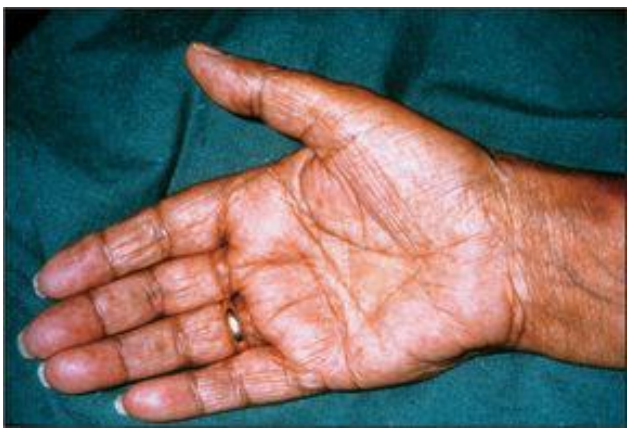


Figure 10.13 Palmar crease pigmentation in Addison's disease

Take the blood pressure and test for postural hypotension. Remember that the rest of the autoimmune disease cluster may be associated with autoimmune adrenal failure (Table 10.12).

TABLE 10.12 A classification of conditions found in various combinations in autoimmune polyglandular syndromes

Type I (rare autosomal recessive)	Type II (more common, HLA DRB1, DQA1, DQB1)
1. Chronic mucocutaneous candidiasis 2. Hypoparathyroidism 3. Addison's disease	1. Insulin-requiring diabetes (type 1) 2. Autoimmune thyroid disease 3. Addison's disease 4. Myasthenia gravis 5. Pernicious anaemia 6. Primary gonadal failure

Calcium metabolism

Primary hyperparathyroidism

This is due to excess parathyroid hormone (Table 10.13), which results in an increased serum calcium level, increased renal phosphate excretion and increased formation of 1,25-dihydroxycholecalciferol by activation of adenyl cyclase in the bone and kidneys. Primary hyperparathyroidism causes

problems with ‘stones’ (renal stones), ‘bones’ (osteopenia and pseudogout), ‘abdominal groans’ (constipation, peptic ulcer and pancreatitis) and ‘psychological moans’ (confusion) (*Questions box 10.5*).

TABLE 10.13 Types of hyperparathyroidism

Primary Adenoma (80%) Hyperplasia Carcinoma (rare)
Secondary Hyperplasia following chronic renal failure
Tertiary (autonomous) The appearance of autonomous hyperparathyroidism is a complication of secondary hyperparathyroidism

---

Questions box 10.5

Questions to ask the patient with suspected hyperparathyroidism

! denotes symptoms for the possible diagnosis of an urgent or dangerous problem.

1. Have you had kidney stones?
2. Have you had any fractures?
3. Have you been troubled by abdominal pain? Have you had constipation?

4. Have you been depressed or had hallucinations?—Psychiatric disorders

5. Have you had episodes of confusion, irritability, extreme tiredness or even unconsciousness?—Neurological symptoms

Other causes of hypercalcaemia are listed in Table 10.14.

TABLE 10.14 Important causes of hypercalcaemia

Primary hyperparathyroidism
Carcinoma (from bone metastases or humoral mediators)
Thiazide diuretics
Vitamin D excess
Excessive production of vitamin D metabolites: e.g. sarcoidosis, certain T cell lymphomas
Thyrotoxicosis
Associated with renal failure (e.g. severe secondary hyperparathyroidism)
Multiple myeloma
Familial hypocalciuric hypercalcaemia
Prolonged immobilisation or space flight

General inspection

Note the mental state of the patient. Severe hypercalcaemia may cause coma or convulsions. Assess hydration (polyuria from hypercalcaemia may cause

of convulsions. Assess hydration (polyuria from hypercalcaemia may cause dehydration).

The face

Look in the eyes for band keratopathy, which is rare (page 209).

The body and lower limbs

Palpate the shoulders, sternum, ribs, spine and hips for bony tenderness, deformity or evidence of previous fractures. Test for proximal muscle weakness. Look for pseudogout. Take the blood pressure, as hypertension may occur.

Urinalysis

Test for blood in the urine (renal stones).

The MEN syndromes

The multiple endocrine neoplasias (MENs), types I and II, are autosomal dominant conditions. Hyperparathyroidism can be associated with both. MEN type I (due to a mutation on chromosome 11) is associated with tumours of the parathyroid, pituitary and pancreatic islet cells. MEN type IIA (due to a mutation on chromosome 10 involving the c-*ret* proto-oncogene) is associated with medullary carcinoma of the thyroid, hyperparathyroidism and phaeochromocytoma. MEN type IIB is characterised by mucosal neuromas (often on the lips and tongue) and medullary carcinoma of the thyroid plus phaeochromocytoma.

Hypoparathyroidism

This results in hypocalcaemia with neuromuscular consequences (tetany) (*Questions Box 10.6*).

Questions box 10.6

Questions to ask the patient with suspected hypocalcaemia

Questions to ask the patient with suspected hypocalcaemia

! denotes symptoms for the possible diagnosis of an urgent or dangerous problem.

1. Have you recently had surgery to remove the parathyroid glands?
2. Have you had tingling around the mouth or in the fingers?
3. Have you had muscle cramps?
4. Have you had fits or seizures?

It is usually a postoperative complication after thyroidectomy, but can be idiopathic. Hypocalcaemia can also result from end-organ resistance to parathyroid hormone (pseudohypoparathyroidism) (Table 10.15).

TABLE 10.15 Causes of hypocalcaemia

Hypoparathyroidism: after thyroidectomy, idiopathic
Malabsorption
Deficiency of vitamin D
Chronic renal failure
Acute pancreatitis
Pseudohypoparathyroidism
Magnesium deficiency
Hypocalcaemia of malignant disease

Look first for Trousseau's and Chvostek's signs. *Trousseau's sign* is elicited with a blood pressure cuff placed on the arm with the pressure raised above the patient's systolic pressure. Typical contraction of the hand occurs within 2 minutes when hypocalcaemia has caused neuromuscular irritability.

The thumb becomes strongly adducted, and the fingers are extended, except at the metacarpophalangeal joints. The appearance is that of an obstetrician about to remove the placenta manually and is called the *main d'accoucheur*.

Chvostek's sign is performed by tapping gently over the facial (seventh) cranial nerve under the ear. The nerve is hyperexcitable in hypocalcaemia and a brisk muscular twitch occurs on the same side of the face.

Next test for hyperreflexia, again due to neuromuscular irritability.

Look at the nails for fragility and monilial infection. Note any dryness of the skin. Go to the face and look for deformity of the teeth. Examine the eyes for cataracts or papilloedema. These signs may all occur in idiopathic hypoparathyroidism, an autoimmune disease. Cataracts may also follow surgically induced hypoparathyroidism.

Pseudohypoparathyroidism

In this disease the patients have tetany (due to hypocalcaemia) as well as typical skeletal abnormalities. These include short stature, a round face, a short neck, thin stocky build and very characteristically short fourth or fifth fingers or toes (due to metacarpal or metatarsal shortening; this can be unilateral or bilateral) (Figure 10.14). Ask the patient to make a fist to demonstrate the characteristic clinical signs.

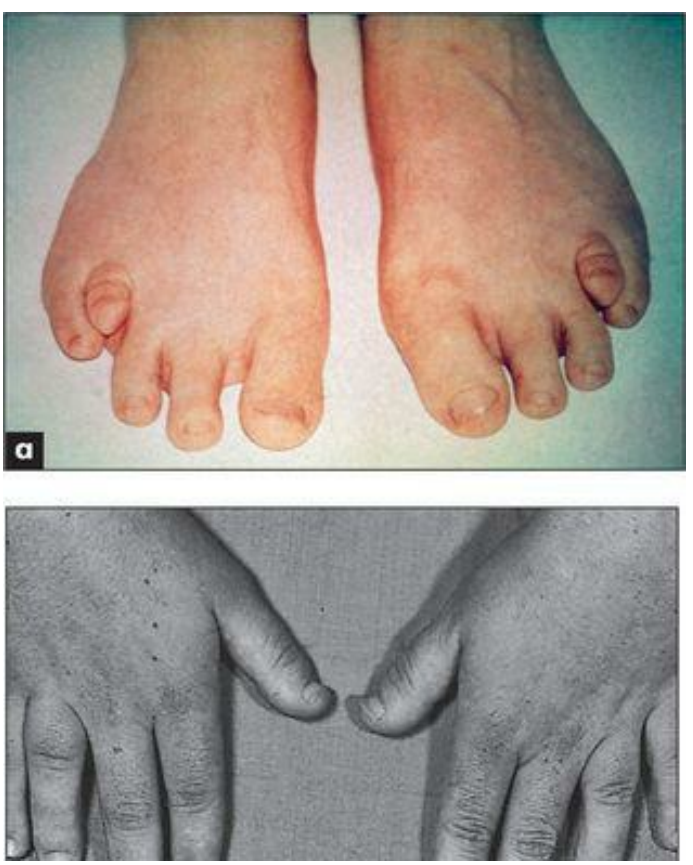


Figure 10.14 Pseudohypoparathyroidism: (a) feet; (b) hands

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Pseudopseudohypoparathyroidism

This amusing name is given to a disease where there is no tetany (calcium concentration in the blood is normal), but the characteristic skeletal deformities are present.

Syndromes associated with short stature

These conditions begin in childhood.

General inspection

First measure the height of the patient; in children this should be compared with percentile charts for age and sex. Look for the classical appearance of Turner's syndrome, Down syndrome, achondroplasia or rickets (Figure 10.15), which may explain the short stature. The height of parents and siblings should be checked as well.

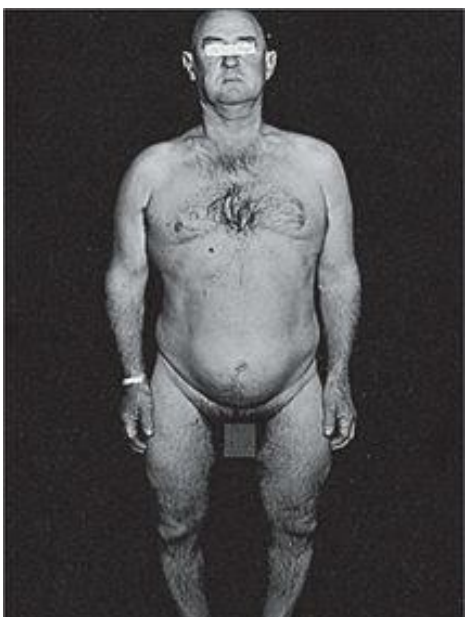

Figure 10.15 Rickets (postrachitic patient)
Look for frontal bossing, proximal myopathy of arms and thighs, and bowing of the ulna, femur and tibia.

Note any evidence of weight loss, including loose skinfolds, which may suggest a nutritional cause (starvation, malabsorption or protein loss). Look for signs of hypopituitarism or hypothyroidism, or steroid excess. Sexual precocity (early onset of secondary sexual characteristics) causes relative tallness at first but short stature later.

The chest

Examine for evidence of cyanotic congenital heart disease and pulmonary disease, such as cystic fibrosis.

The abdomen

Look for evidence of hepatic failure or renal failure (a cause of growth retardation when it occurs in children).

Turner's syndrome (45XO)

Sexual infantilism (failure of development of secondary sexual characteristics) —female genitalia.

Upper limbs

Lymphoedema of the hands; short fourth metacarpal bones; hyperplastic nails; increased carrying angle; hypertension.

Facies

Micrognathia (small chin); epicanthic folds ptosis; fish-like mouth; deformed or low-set ears; hearing loss.

Neck

Webbing of the neck; low hairline; redundant skinfolds on the back of the neck.

Chest

Widely spaced nipples (a shield-like chest); coarctation of the aorta.

Other

Pigmented naevi; keloid formation; lymphoedema of the legs.

Down syndrome (Trisomy 21)

Facies

Oblique orbital fissures; conjunctivitis; Brushfield spots on the iris; small simple ears; flat nasal bridge; mouth hanging open; protruding tongue; narrow high-arched palate.

Hands

Short broad hands; incurving fifth finger; single palmar crease; hyperflexible joints.

Chest

Congenital heart disease; especially endocardial cushion defects.

Other

Straight pubic hair; gaps between the first and second toes; mental deficiency usually present.

Rickets (Figure 10.15)

Defective mineralisation of the *growing* skeleton, due to lack of vitamin D (e.g. nutritional or chronic renal failure) or hypophosphataemia (e.g. renal tubular disorders).

Upper limbs

Tetany; hypotonia, proximal myopathy; bowing of the radius and ulna.

Facies

Frontal bossing; parietal flattening.

Chest

'Rickety rosary'—thickening of costochondral junctions; Harrison's groove—indentation of lower ribs at the diaphragmatic attachment.

Lower limbs

Bowing of femur and tibia; hypotonia, proximal myopathy; fractures.

Achondroplasia (dwarfism)

This is an autosomal-dominant disease of cartilage caused by mutation of the fibroblast growth factor receptor gene.

Short stature, short limbs, normal trunk, relatively large head, saddle-shaped nose, exaggerated lumbar lordosis and occasionally spinal cord compression are features.

Hirsutism

This is excessive hairiness in a woman beyond what is considered normal for her race (Table 10.16). It is caused by androgen (including testosterone) excess. In the examination of such a patient, it is important to decide whether virilisation is also present. Virilisation is the appearance of male secondary sexual characteristics (clitoromegaly, frontal hair recession, male body habitus and deepening of the voice) and indicates that excessive androgen is present.

TABLE 10.16 Causes of hirsutism

Polycystic ovary syndrome (commonest cause)
Idiopathic
Adrenal: androgen-secreting tumours e.g. Cushing's syndrome, congenital adrenal hyperplasia, virilising tumour (more often a carcinoma than an adenoma)
Ovarian: androgen-secreting tumour
Drugs: phenytoin, diazoxide, streptomycin, minoxidil, anabolic steroids e.g. testosterone
Other: acromegaly, porphyria cutanea tarda

General inspection

Ask the patient to undress to her underwear. Note the hair distribution over the face and in the midline, front and back. In general, an obvious male balding pattern (a receding hairline), hair over the beard area or on the back and chest, and hair in the escutcheon (umbilicus to groin in the midline) is usually abnormal. Look for obvious acromegaly or Cushing's syndrome and for the skin changes of porphyria cutanea tarda.

Ask the patient to remove her underclothing and lie flat. Look for signs of virilism. These include breast atrophy and increased muscle bulk of the arms and legs, male pattern of pubic hair, and enlargement of the clitoris. Look in the axillae; the patient with polycystic ovarian syndrome may have acanthosis nigricans (and associated insulin resistance).

The abdomen

Palpate for adrenal masses, polycystic ovaries or an ovarian tumour (these are rarely palpable).

The blood pressure

Hypertension occurs in the rare C11-hydroxylase deficiency, which is a virilising condition.

Gynaecomastia (Figure 10.16)

This is 'true' enlargement of the male breasts.[5] Careful examination will detect up to 4 cm of palpable breast tissue in 30% of normal young men; this percentage increases with age. These men are unaware of any breast abnormality. Gynaecomastia occurs in up to 50% of adolescent boys, and also in elderly men in whom it is due to falling testosterone levels. Fat deposition ('false' enlargement) in obese men can be confused with gynaecomastia.

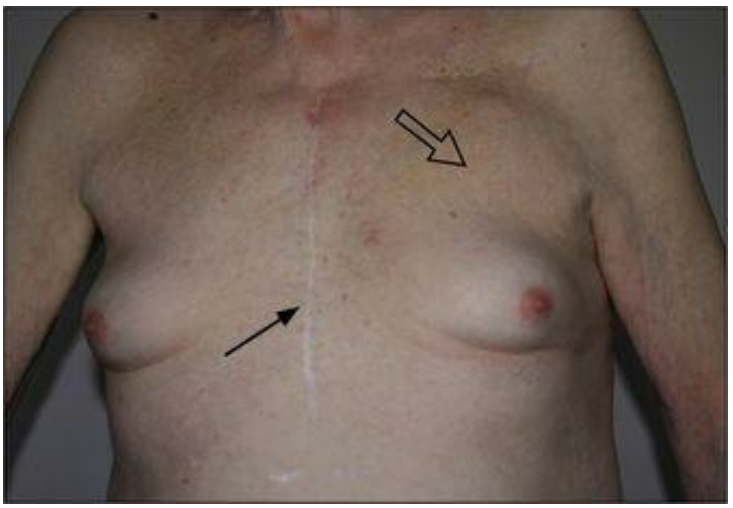

Figure 10.16 Gynaecomastia
This patient takes spironolactone for heart failure. Note median sternotomy scar (arrow) and defibrillator box (open arrow).

Examine the breasts (page 435) for evidence of localised disease (e.g. malignancy, which is rare), tenderness, which indicates rapid growth, and any discharge from the nipple. Detection of breast tissue in men is best performed with the patient sitting up. Squeeze the breast behind the patient's nipple between the thumb and forefinger. Try to detect an edge between subcutaneous fat and true breast tissue.

Examine the genitalia now for sexual ambiguity and the testes for absence or a reduced size. Note any loss of secondary sexual characteristics.

Look especially for signs of *Klinefelter's syndrome* (47,XXY). These patients are tall, have decreased body hair and characteristically small, firm

testes.

Look also for signs of panhypopituitarism or chronic liver disease. Thyrotoxicosis can occasionally be a cause.

Finally, examine the visual fields and fundi for evidence of a pituitary tumour.

Causes of pathological gynaecomastia are summarised in Table 10.17.

TABLE 10.17 Differential diagnosis (causes) of pathological gynaecomastia

Increased oestrogen production
Leydig cell tumour (oestrogen)
Adrenal carcinoma (oestrogen)
Bronchial carcinoma (human chorionic gonadotrophin)
Liver disease (increased conversion of oestrogen from androgens)
Thyrotoxicosis (increased conversion of oestrogen from androgens)
Starvation
Decreased androgen production (hypogonadal states)
Klinefelter's syndrome
Secondary testicular failure: orchitis, castration, trauma
Testicular feminisation syndrome
Drugs
Oestrogen receptor binders: oestrogen, digoxin, marijuana
Anti-androgens: spironolactone, cimetidine

Diabetes mellitus[q]

Diabetes mellitus is characterised by hyperglycaemia due to an absolute or relative deficiency of insulin. The causes of diabetes are listed in Table 10.18. The disease can present with asymptomatic glycosuria detected on routine physical examination or with symptoms of diabetes (Table 10.1), ranging from polyuria to coma as a result of diabetic ketoacidosis (*Questions box 10.7*).

TABLE 10.18 Causes of diabetes mellitus

Criteria for diagnosis of diabetes mellitus: fasting plasma venous blood sugar level of 7.0 mmol/L or more (≥126 mg/dL), or a 2-hour postprandial blood sugar level of 11.1 mmol/L or more (≥200 mg/dL), on more than one occasion.
I. Type 1 • Type 1A (autoimmune destruction of beta cells in the pancreas) • Adult-onset type 1 (islet cell antibodies)
II. Type 2 (insulin deficiency and resistance)
III. Other types of diabetes A. Mutations leading to abnormalities of β cell function B. Inherited defects of insulin action: e.g. lipoatrophic diabetes (characterised by generalised lipoatrophy, hepatomegaly, hirsutism, acanthosis nigricans, hyperpigmentation and hyperlipidaemia) C. Diseases of the exocrine pancreas: e.g. chronic pancreatitis,

carcinoma, haemochromatosis D. Endocrine abnormalities: e.g. acromegaly, Cushing's syndrome, phaeochromocytoma, glucagonoma, somatostatinoma E. Drug-induced: e.g. steroids, the contraceptive pill, streptozotocin, diazoxide, phenytoin, thiazide diuretics F. Infections: e.g. cytomegalovirus, coxsackie, congenital rubella G. Rare forms of immune-mediated diabetes: e.g. anti-insulin receptor antibodies H. Genetic abnormalities associates with diabetes: e.g. Down's syndrome, Klinefelter's syndrome, Turner's syndrome J. Stiff person syndrome (progressive muscle stiffness of axial muscles)
IV. Gestational diabetes mellitus

Questions box 10.7

Questions to ask the diabetic patient

! denotes symptoms for the possible diagnosis of an urgent or dangerous problem.

1. What was your age at the time the diabetes was diagnosed?

2. Did you require insulin from the start?

3. What was the problem that led to the diagnosis?—Polyuria, thirst, weight loss, recurrent skin infections, screening assessment !

4. What previous and current drug treatment are you taking for diabetes?

5. What diet has been prescribed? What do you understand about your diabetic diet?

6. What blood sugar testing do you do? What are the usual results?

7. Have you had any problems with hypoglycaemia (treatment-induced low blood sugar)? Have you had episodes of sweating, confusion, malaise or unconsciousness? !

8. Do you know what action should be taken if these acute symptoms (of hypo- or hyperglycaemia) occur?—Check sugar level, take glucose tablet, go to hospital

9. Have you had keto-acidosis (very high blood sugars associated with acidosis) and needed admission to hospital?—Polyuria, dehydration, confusion, unconsciousness

10. Have you had complications of diabetes—eyes, nerves, blood vessels, kidneys?

11. What regular testing has been performed for these problems?

12. How do you and your family cope with this chronic condition?

13. Have you been able to work?

General inspection (Figure 10.17)

Assess for evidence of dehydration because the osmotic diuresis caused by a glucose load in the urine can cause massive fluid loss. Note obesity (non-insulin-dependent diabetics are usually obese) or signs of recent weight loss (this can be evidence of uncontrolled glycosuria).

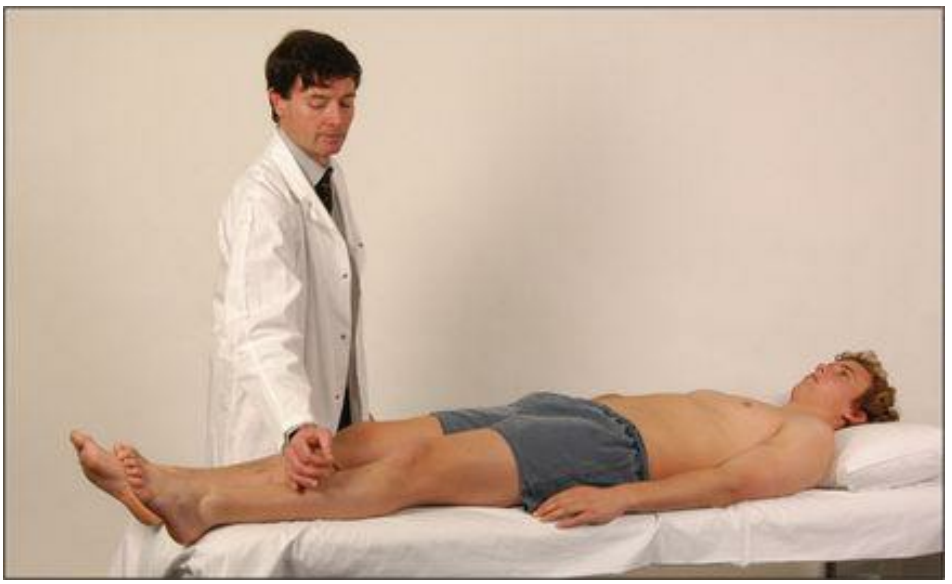

Figure 10.17 Diabetes mellitus
Lying

1. **General inspection**

Weight—obesity
Hydration
Endocrine facies
Pigmentation—haemochromatosis, etc

2. **Legs**
   Inspect
   - Skin—necrobiosis, hair loss, infection, pigmented scars, atrophy, ulceration, injection sites
   - Muscle wasting

   Palpate
   - Temperature of feet (cold, blue due to 'small' or 'large' vessel disease)
   - Peripheral pulses

   Femoral (auscultate)
   Popliteal
   Posterior tibial
   Dorsalis pedis

3. **Arms**
   Inspect
   - Injection sites
   - Skin lesions

   Pulse

4. **Eyes**
   Fundi—cataracts, rubeosis, retinal disease
   III nerve palsy, etc

5. **Mouth**
   Monilia
   Infection

6. **Neck**
   Carotid arteries—palpate, auscultate

7. **Chest**
   Signs of infection

8. **Abdomen**
   Liver—fat infiltration; rarely haemochromatosis
   Neurological assessment
   - Femoral nerve mononeuritis
   - Peripheral neuropathy

- Peripheral neuropathy

9. **Other**
   Urine analysis—glycosuria, ketones, proteinuria
   Blood pressure—lying and standing
   Oedema

Look for one of the abnormal endocrine facies (e.g. Cushing's syndrome or acromegaly) and for pigmentation (e.g. haemochromatosis—bronze diabetes) as these may cause secondary diabetes.

The patient may be comatose due to dehydration, acidosis or plasma hyperosmolality. Kussmaul's breathing ('air hunger') is present in diabetic ketoacidosis due to the acidosis (this occurs because fat metabolism is increased to compensate for the lack of availability of glucose; excess acetyl-coenzyme A is produced, which is converted in the liver to ketone bodies, and two of these are organic acids).

The lower limbs

Unlike most other systematic examinations, assessment of the diabetic can profitably begin with the legs, as many of the major physical signs are found to be here. In particular, vascular and neurological abnormalities in the feet must not be missed.[6]

Inspection

Look at the skin. The *skin* of the feet and lower legs may be hairless and atrophied due to small-vessel vascular disease and resultant ischaemia (the mechanism is uncertain, but may be related to lipoprotein alterations in the vessel walls).

Note any leg *ulcers*, particularly on the toes or any area of the feet exposed to pressure (Figure 10.18). These ulcers are due to a combination of ischaemia and peripheral neuropathy (the cause of the neuropathy is unknown, but may be related to small vessel ischaemia and glycosylation of neural proteins).

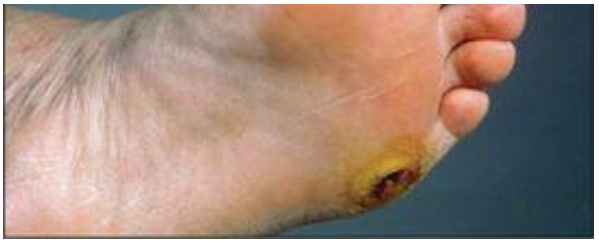

Figure 10.18 Diabetic (neuropathic) ulcer

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Look for superficial skin *infection*, such as boils, cellulitis and fungal infections. These are more common in diabetics because of a combination of high tissue glucose levels and ischaemia, which provides a favourable environment for the growth of organisms.

Note any *pigmented scars* (late diabetic dermopathy). There may be small rounded plaques with raised borders lying in a linear fashion over the shins (diabetic dermopathy).

Necrobiosis lipoidica diabeticorum is a reasonably specific skin manifestation of diabetes mellitus, but is rare (fewer than 1% of diabetics) (Figure 10.19). It is found over the shins, where a central yellow scarred area is surrounded by a red margin when the condition is active. These plaques may ulcerate.

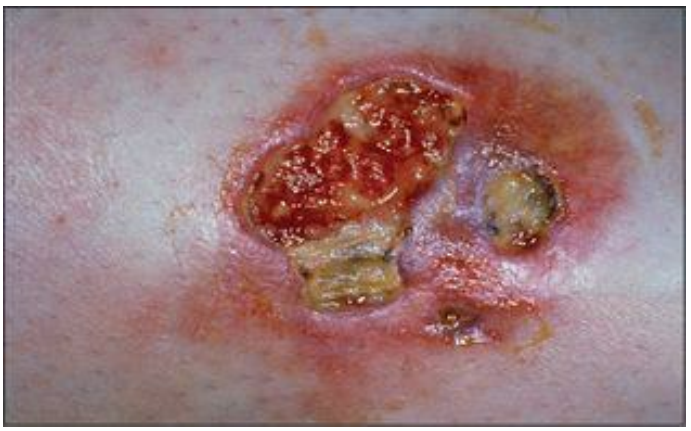

Figure 10.19 Necrobiosis lipoidica diabeticorum

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Look now at the thighs for insulin injection sites. These may be associated with localised *fat atrophy* and *fat hypertrophy*, and may be related to impure insulin use which causes a localised immune reaction (modern genetically engineered insulins have made these rare). Note any *quadriceps muscle wasting* due to femoral nerve mononeuropathy, which is called

muscle wasting due to femoral nerve mononeuropathy, which is called (inaccurately) diabetic amyotrophy.

Inspect the knees for the very rare Charcot's joints (grossly deformed disorganised joints, due to loss of proprioception or pain, or both; this leads to recurrent and unnoticed injury to the joint) (Figure 10.20).

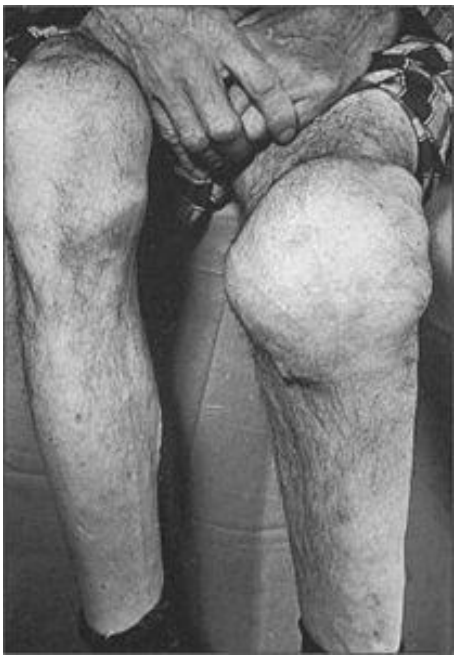

Figure 10.20 Charcot's joint of left knee

Palpation

Palpate any injection sites for fat atrophy or hypertrophy. Feel all the peripheral pulses and the temperature of the feet, and test the capillary return. Absent peripheral pulses, cold extremities and reduced capillary return are all evidence of peripheral vascular disease.

Neurological examination

Assess formally for peripheral neuropathy, including dorsal column loss (diabetic pseudotabes), and tap the reflexes. Test proximal muscle power (diabetic amyotrophy).

The upper limbs

Look at the nails for signs of *Candida* infection. Take the blood pressure

lying and standing, as diabetic autonomic neuropathy can cause postural hypotension.

The face

The eyes

Test visual acuity. This may be permanently impaired because of retinal disease or temporarily disturbed because of changes in the shape of the lens associated with hyperglycaemia and water retention. Look for Argyll Robertson pupils[r], which are a rare complication of diabetes.

Using the ophthalmoscope, begin by examining for rubeosis (new blood vessel formation over the iris, which can cause glaucoma) (Figure 10.21). Then note any cataracts, which are related to sorbitol deposition in the lens (when glucose is present in high concentrations in the tissues it is converted to sorbitol by aldose reductase).

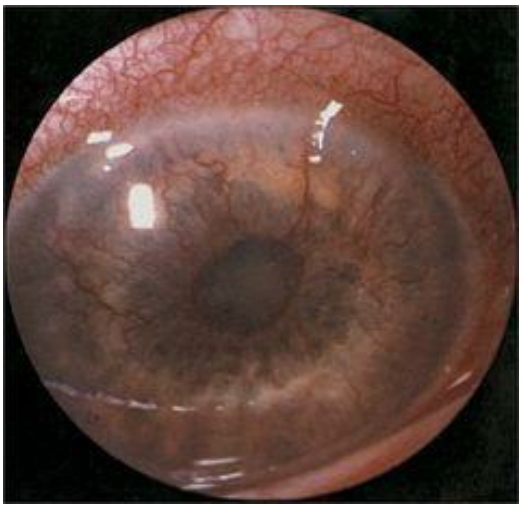

Figure 10.21 Rubeosis iridis
Shows new vessels on the anterior surface of the iris. These are secondary to ischaemia (often due to diabetes).

Now examine the retina, where many exciting changes may await the fundoscopist. There are two main types of retinal change in diabetes: non-proliferative and proliferative.

Non-proliferative changes (Figure 10.22) are directly related to ischaemia of blood vessels and include: (i) two types of haemorrhages—*dot haemorrhages,* which occur in the inner retinal layers, and *blot haemorrhages*, which are larger and which occur more superficially in the

nerve fibre layer; (ii) *microaneurysms,* which are due to vessel wall damage; and (iii) two types of exudates—*hard exudates,* which have straight edges, and *soft exudates* (cottonwool spots), which have a fluffy appearance.

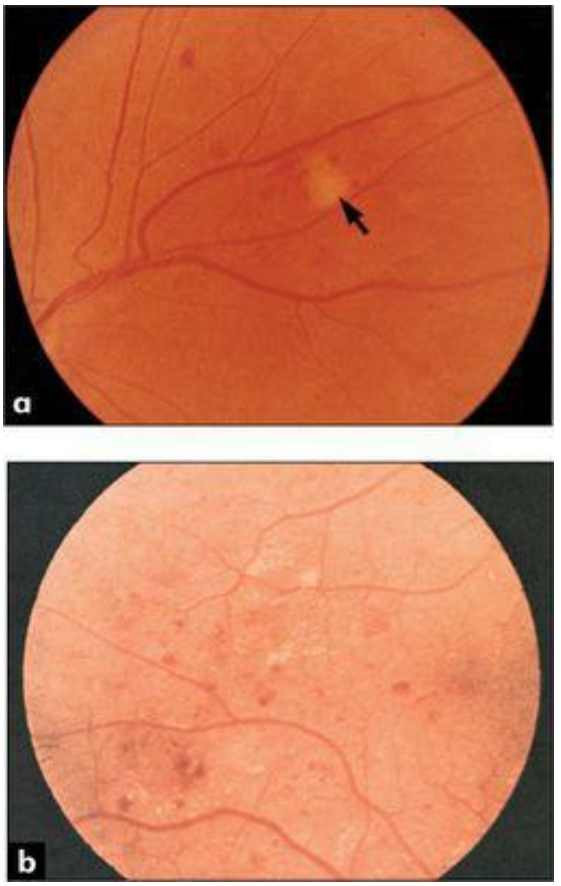

Figure 10.22 Diabetic retinopathy

(a) Soft exudate (arrow) and small haemorrhages.

(b) Microaneurysms (dots), retinal haemorrhages (blots) and hard yellow exudates.

Proliferative changes (Figure 10.23) are changes in blood vessels in response to ischaemia of the retina. They are characterised by new vessel formation, which can lead to vitreal haemorrhage, scar formation and eventually retinal detachment. The *detached retina* appears as an opalescent sheet that balloons forward into the vitreous. The underlying choroid is visible through the detached retina as a bright red-coloured sheet. Look also for *laser scars* (small brown or yellow spots), which are secondary to photocoagulation of new vessels by laser therapy.

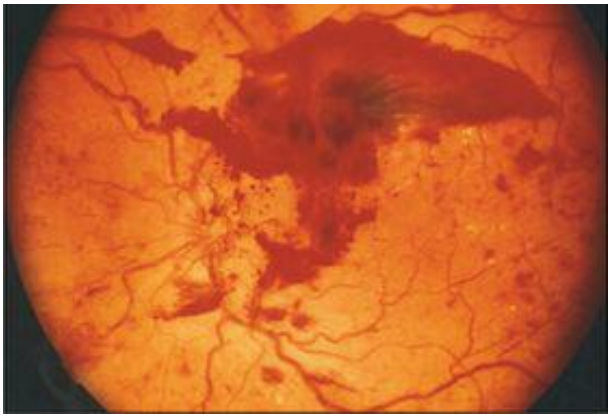

Figure 10.23 Proliferative diabetic retinopathy

Assess the third, fourth and sixth cranial nerves. In particular examine for a diabetic third nerve palsy from ischaemia, which usually spares the pupil (as infarction of the third nerve affects the inner pupillary fibres more than the outer fibres; in this way it differs from compressive lesions, which have the opposite effect).

Other cranial nerves may be affected sometimes because of cerebrovascular accidents (large vessel atheroma). *Rhinocerebral mucormycosis* may rarely develop in very poorly controlled diabetic patients, causing periorbital and perinasal swelling and cranial nerve palsies.

The ears

Look in the ears for evidence of infection. The rare *malignant otitis externa*, usually due to *Pseudomonas aeruginosa*, causes a mound of granulation tissue in the external canal, and facial nerve palsy in 50% of cases.

The mouth

Look for evidence of *Candida* infection.

The neck and shoulders

Examine the carotid arteries for evidence of vascular disease.

Rarely there may be thickening of the skin of the upper back and shoulders (scleroedema diabeticorum—this diffuse cutaneous infiltration has a very different distribution from scleroderma, with which it is sometimes confused). Look for acanthosis nigricans—associated with insulin resistance.

The abdomen

Palpate for hepatomegaly (fatty infiltration, or due to haemochromatosis).

Urinalysis

Test for glucose and protein. Diabetic nephropathy (from glomerulonephritis, renal arterial disease or pyelonephritis) can cause proteinuria. The presence of nitrite and/or blood is of value as asymptomatic urinary tract infections can occur. In advanced disease there may be signs of renal failure.

Paget's disease (osteitis deformans)

This disease is characterised by excessive reabsorption of bone by osteoclasts and compensatory disorganised deposition of new bone. It is possibly a disease of viral origin.

General inspection

Note short stature (due to bending of the long bones of the limbs) and any obvious deformity of the head and lower limbs.

Head and face

Inspect the scalp for enlargement in the frontal and parietal areas and measure the head circumference (greater than 55 cm is usually abnormal). There may be prominent skull veins. Palpate for increased bony warmth and auscultate over the skull for systolic bruits. Both of these are due to increased vascularity of the skull vault. Oddly enough, bronchial breath sounds may be audible over the pagetic skull through the stethoscope. These are due to increased bone conduction of air. An area of very localised bony swelling and warmth may indicate development of a bony sarcoma (1% of cases of Paget's disease may develop this complication).

Examine the eyes. Assess visual acuity and visual fields, and look in the fundi for angioid streaks and optic atrophy. Retinitis pigmentosa occurs rather more rarely. Test for hearing loss (due to bony ossicle involvement or eighth nerve compression by bony enlargement).

Examine the remaining cranial nerves; all may be involved because of bony overgrowth of the foramina or be caused by basilar invagination (platybasia: where the posterior fossa becomes flat and the basal angle

(platybasia, where the posterior fossa becomes flat and the basal angle increased).

The neck

Patients with basilar invagination have a short neck and low hairline. The head is held in extension and neck movements are decreased. Assess the jugular venous pressure, as a high output cardiac failure may be present, particularly if there is coexistent ischaemic heart disease.

The heart

Examine for signs of cardiac failure.

The back

Inspect for kyphosis (due to vertebral involvement causing collapse of the vertebral bodies). Tap for localised tenderness, feel for warmth and auscultate for systolic bruits over the vertebral bodies.

The legs

Inspect for anterior bowing of the tibia and lateral bowing of the femur (Figure 10.24). Feel for bony warmth and tenderness. Note any changes of osteoarthritis in the hips and knees, which often coexist with Paget's disease. Note any localised warm swelling, which may indicate sarcoma.