Definition
1 Proteinuria (>3.5 g per 24 hours) (*Note:* the other features can all be explained by loss of protein.)
2 Hypoalbuminaemia (serum albumin <30 g/L, due to proteinuria)
3 Oedema (due to hypoalbuminaemia)
4 Hyperlipidaemia (due to increased LDL and cholesterol, possibly from loss of plasma factors that regulate lipoprotein synthesis)
Causes
Primary renal pathology
1 Membranous glomerulonephritis
2 Minimal change glomerulonephritis
3 Focal and segmental glomerulosclerosis
Secondary renal pathology
1 Drugs: e.g. penicillamine, lithium, heroin, non-steroidal anti-inflammatory drugs
2 Systemic disease: e.g. SLE, diabetes mellitus, amyloidosis
3 Malignancy: e.g. carcinoma, lymphoma, multiple myeloma
4 Infections: e.g. hepatitis B, hepatitis C, infective endocarditis, malaria, HIV

LDL = low density lipoprotein.

SLE = systemic lupus erythematosus.

HIV = human immunodeficiency virus.

If proteinuria is detected on dipstick testing, this should be quantified and careful urine (phase-contrast) microscopy should be carried out to look for evidence of active renal disease.

Glucose and ketones

A semi-quantitative measurement of glucose and ketones is available. Glycosuria usually indicates diabetes mellitus, but can occur with other diseases (Table 7.13). False-positive or false-negative results can occur with vitamin C (large doses), bacteria, oxidising detergents and hydrochloric acid, tetracyclines or levodopa ingestion.

Table 7.13 Causes of glycosuria and ketonuria

Glycosuria
Diabetes mellitus
Other reducing substances (false-positives): metabolites of salicylates, ascorbic acid, galactose, fructose
Impaired renal tubular ability to absorb glucose (renal glycosuria)
• e.g. Fanconi* syndrome (proximal renal tubular disease)
Ketonuria
Diabetic ketoacidosis
Starvation

* Guido Fanconi (1892–1972), Zürich paediatrician. Considered a founder of modern paediatrics, he described this in 1936. It had previously been described by Guido De-Toni in 1933 and is sometimes called the De-Toni-Fanconi syndrome.

Ketones in the urine of patients with diabetes mellitus are an important indication of the presence of diabetic ketoacidosis (Table 7.13). The three

indication of the presence of diabetic ketoacidosis (Table 7.13). The three ketone bodies are acetone, beta-hydroxybutyric acid and acetoacetic acid. Lack of glucose (starvation) or lack of glucose availability for the cells (diabetes mellitus) causes activation of carnitine acetyltransferase, which accelerates fatty-acid oxidation in the liver. However, the pathway for the conversion of fatty acids becomes saturated, leading to ketone body formation. The strip colour tests react only to acetoacetic acid. Ketonuria may also be seen associated with fasting, vomiting and strenuous exercise.

Blood

Blood in the urine (haematuria) is abnormal and can be seen with the naked eye if 0.5 mL is present per litre of urine (Table 7.14). Blood may be a contaminant of the urine when women are menstruating. A positive dipstick test is abnormal and suggests haematuria, haemoglobinuria (uncommon) or myoglobinuria (also uncommon). The presence of more than a trace of protein in the urine in addition suggests that the blood is of renal origin. False-positives may occur when there is a high concentration of certain bacteria and false-negative results can occur if vitamin C is being taken.

Table 7.14 Causes of positive dipstick test for blood in the urine

Haematuria
Renal

Glomerulonephritis
Polycystic kidney disease
Pyelonephritis
Renal cell carcinoma
Analgesic nephropathy
Malignant hypertension
Renal infarction, e.g. infective endocarditis, vasculitis
Bleeding disorders
Renal tract
Cystitis
Calculi
Bladder or ureteric tumour
Prostatic disease, e.g. cancer, benign prostatic hypertrophy
Urethritis
Haemoglobinuria
Intravascular haemolysis, e.g. microangiopathic haemolytic anaemia, march haemoglobulinuria, prosthetic heart valve, paroxysmal nocturnal haemoglobinuria, chronic cold agglutinin disease
Myoglobinuria
This is due to rhabdomyolysis (muscle destruction): • Muscle infarction, e.g. trauma • Excessive muscle contraction, e.g. convulsions, hyperthermia, marathon running • Viral myositis, e.g. influenza, Legionnaires' disease • Drugs or toxins, e.g. alcohol, snake venom, statins • Idiopathic

Nitrite

If positive, this usually indicates infection with bacteria that produce nitrite. More-specific dipstick tests for white cells are now available; a positive test has an LR of 4.2 for a urinary infection and a negative test has an LR of 0.3.[9]

The urine sediment

Every patient with suspected renal disease should have a midstream urine sample examined. Centrifuge 10 mL of the urine at 2000 rpm for 4 minutes. Remove the supernatant, leaving 0.5 mL; shake well to re-suspend, then place one drop on a slide with a coverslip. Look at the slide using a low-power microscope, and at specific formed elements under the high-power field (hpf) for identification. There is a significant false-negative rate when there are low numbers of formed elements in the urine.

Look for red blood cells, white blood cells and casts.

Red blood cells (RBCs)

These appear as small circular objects without a nucleus. Usually none are seen, although up to 5 RBCs/low-power field (lpf) may be normal in very concentrated urine. If their numbers are increased, try to determine whether the RBCs originate from the glomeruli (more than 80% of the RBCs are dysmorphic—irregular in size and shape) or the renal tract (the RBCs are typically uniform).

White blood cells (WBCs)

These cells have lobulated nuclei. Usually fewer than 6 WBCs/hpf are present, although up to 10 may be normal in very concentrated urine. Tubular epithelial cells have a compact nucleus and are larger. Pyuria indicates urinary tract inflammation. Bacteria may also be seen if there is infection, but bacterial contamination is more likely if squamous epithelial cells (which are larger and have single nuclei) are prominent. Sterile pyuria is characteristic of renal tuberculosis but may also occur in acute or chronic tubulo-interstitial disease. Multistix test strips will often test for the presence of WBCs.

of WBCs.

Casts

Casts are cylindrical moulds formed in the lumen of the renal tubules or collecting ducts. They are signs of a damaged glomerular basement membrane or damaged tubules. The size of a cast is determined by the dimension of the lumen of the nephron in which it forms. The presence of casts is a very important abnormality and means renal disease.

Hyaline casts are long cylindrical structures. One or two RBCs or WBCs may be present in the cast. Normally there are fewer than 1 per lpf. They consist largely of Tamm-Horsfall mucoprotein secreted by the renal tubules.

Granular casts are abnormal cylindrical granular structures that arise from the tubules, usually in patients with proteinuria. They consist of hyaline material containing fragments of serum proteins.

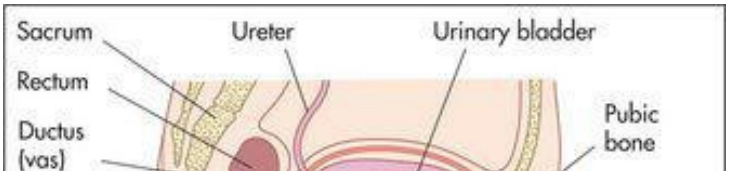
Red cell casts are always abnormal and indicate primary glomerular disease (haematuria of glomerular origin or vasculitis). They contain 10 to 50 red cells, which are well defined.

With **white cell casts** many WBCs adhere to or inside the cast. These are abnormal, indicating bacterial pyelonephritis or, less commonly, glomerulonephritis, kidney infarction or vasculitis.

Fatty casts (i.e. the presence of fat in casts) are suggestive of the nephrotic syndrome.

Male genitalia

Inspect the genitals (Figures 7.9 and 7.10) for evidence of mucosal ulceration. This can occur in a number of systemic diseases, including Reiter's syndrome and the rare Behçet's syndrome. For aesthetic and protective reasons, it is essential to wear gloves for this examination. Retract the foreskin to expose the glans penis. This mucosal surface is prone to inflammation or ulceration in both infective and connective tissue diseases (Table 7.15). Look also for urethral discharge. If there is a history of discharge, attempt to express fluid by compressing or 'milking' the shaft. Any fluid obtained must be sent for microscopic examination and culture.



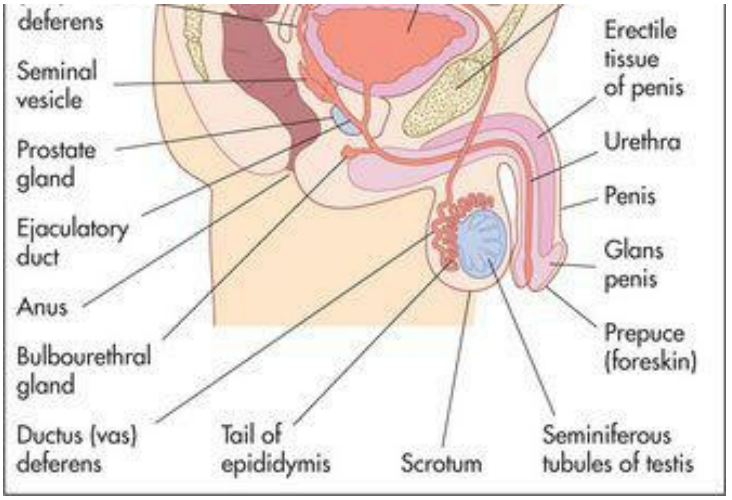
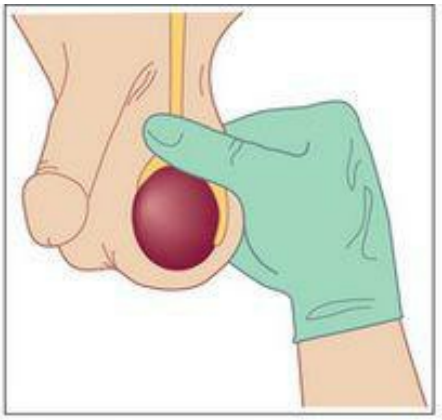
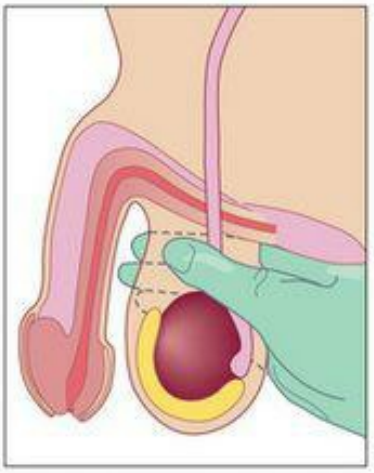


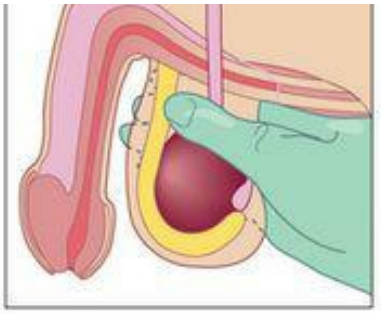
Figure 7.9 Basic male reproductive anatomy



(a) To palpate the epididymis, feel along the posterior pole of the testis



(b) Scrotal swelling—fingers can 'get above' mass



(c) Inguinal hernia with descent into the scrotum—fingers cannot 'get above' mass

Figure 7.10 Examination of scrotum

From Douglas G, Nicol F and Robertson C, Macleod's Clinical Examination, 12th edn. Edinburgh: Churchill Livingstone, 2009, with permission

Table 7.15 Causes of genital lesions

Ulcerative
Herpes simplex (vesicles followed by ulcers: tender)
Syphilis (non-tender)
Malignancy (squamous cell carcinoma: non-tender)
Chancroid (*Haemophilus ducreyi* infection: tender)
Behçet's syndrome
Non-ulcerative
Balanitis, due to Reiter's syndrome or poor hygiene
Venereal warts
Primary skin disease, e.g. psoriasis
Note: Always consider HIV infection.

Inspect the scrotum with the patient standing. Usually the left testis hangs lower than the right. This is the only part of the body that consistently does not appear bilaterally symmetrical on inspection. Torsion of the testis may cause the involved testis to appear higher and to lie more transversely than normal. Inspect for oedema of the skin, sebaceous cysts, tinea cruris (an erythematous rash caused by a fungal infection of the moist skin of the groin) or scabies. Scrotal oedema is common in severe cardiac failure and may occur with the nephrotic syndrome and ascites.

Palpate each testis gently using the fingers and thumb of the right hand or cradle the testis between the middle and index fingers of the right hand and palpate it with the ipsilateral thumb.[13] The testes are normally equal in size, smooth and relatively firm. Absence of one or both testes may be due to previous excision, failure of the testis to descend, or a retractile testis. In children the testes may retract as examination of the scrotum begins because of a marked cremasteric reflex. A maldescended testis (one that lies permanently in the inguinal canal or higher) has a high chance of developing malignancy. An exquisitely tender, indurated testis suggests orchitis.[14] This is often due to mumps in postpubertal patients and occurs about 5 days after the parotitis. An undescended testis may be palpable in the inguinal canal, usually at or above the external inguinal ring. The presence of small firm testes suggests an endocrine disease (hypogonadism) or testicular atrophy due to alcohol or drug ingestion.

Feel posteriorly for the epididymis and then upwards for the vas deferens and the spermatic cord. It should be possible to differentiate the vas from the testis.

A varicocele feels like a bag of worms in the scrotum. The testis on the side of the varicocele often lies horizontally. It is unclear whether this is a cause or effect of the varicocele. A left varicocele is sometimes found when there is underlying left renal tumour or left renal vein thrombosis. The significance of the rarer right varicocele is disputed.[15]

Differential diagnosis of a scrotal mass (Figure 7.11)

If a mass is palpable in the scrotum, decide first whether it is possible to get above it. Have the patient stand up. If no upper border is palpable, it must be descending down the inguinal canal from the abdomen and is therefore an inguino-scrotal hernia (page 178).

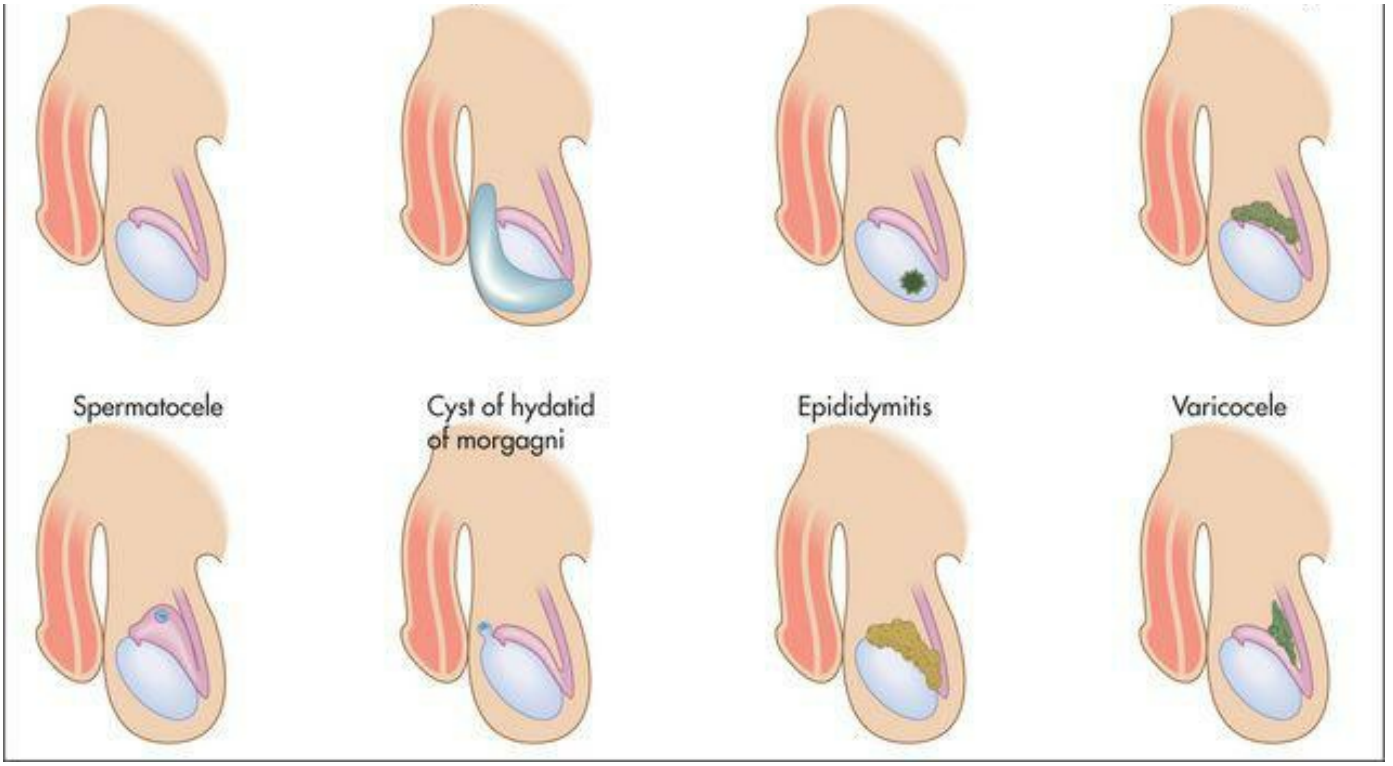


Figure 7.11 Differential diagnosis of a scrotal mass

Adapted from Dunphy JE, Botsford TW. Physical examination of the surgical patient. An introduction to clinical surgery, 4th edn. Philadelphia: WB Saunders, 1975.

If it is possible to get above the mass, it is necessary to decide whether it is separate from or part of the testis, and to test for translucency. This is performed using a transilluminoscope (a torch) (Figure 7.12). With the patient in a darkened room, a small torch is applied to the side of the swelling by invaginating the scrotal wall. A cystic mass will light up while a solid mass remains dark.

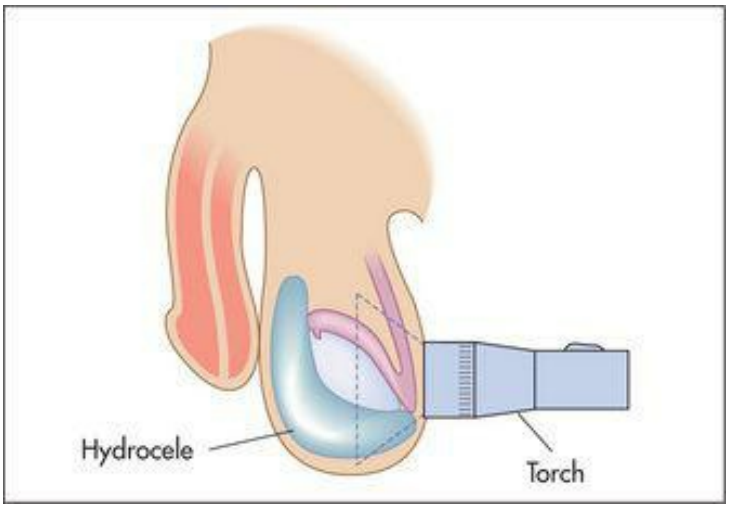
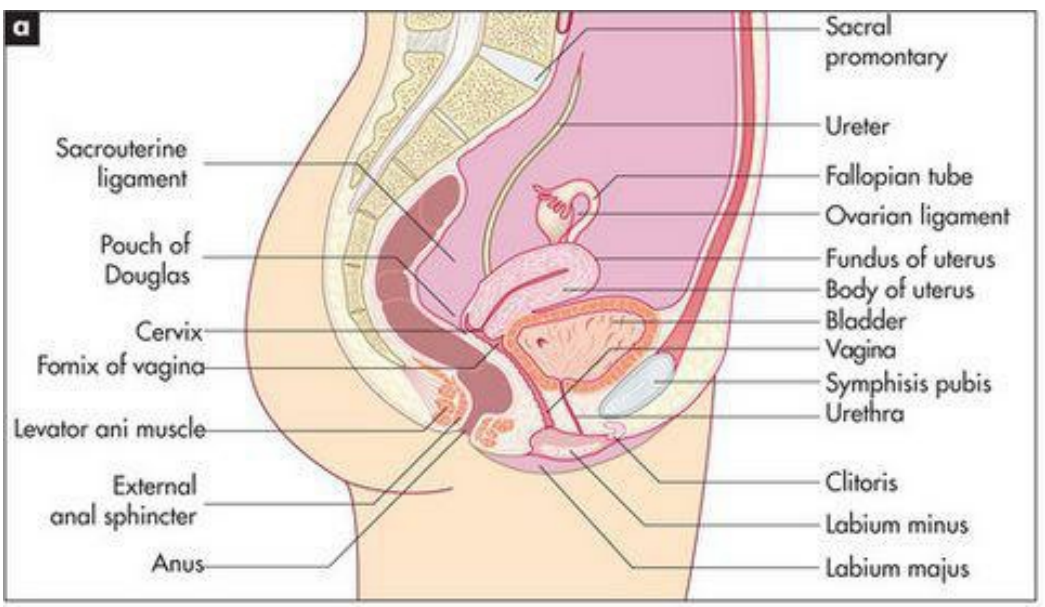


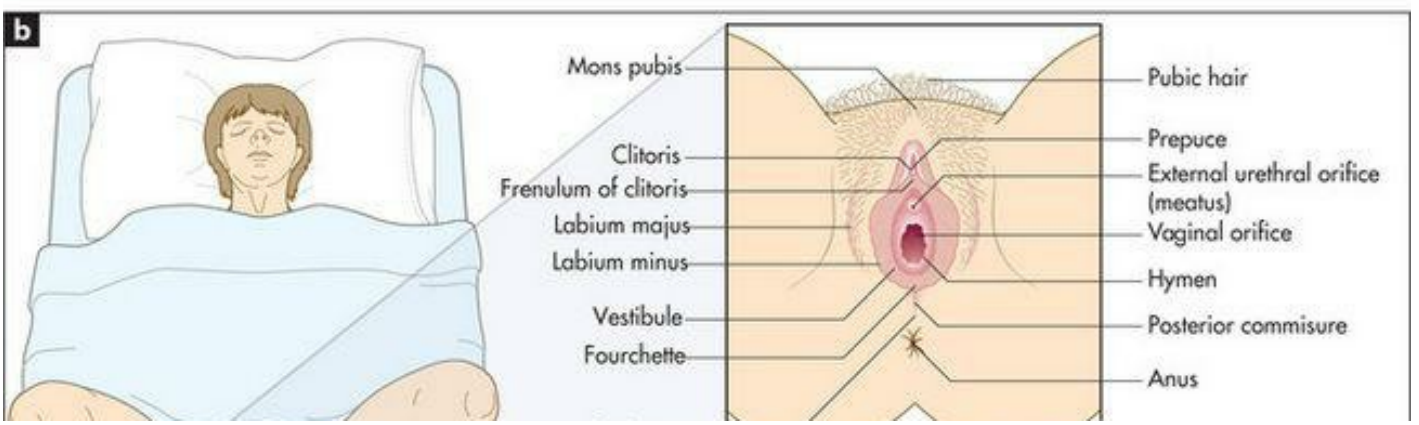
Figure 7.12 Transillumination of the scrotum

A mass that is part of the testis and that is solid (non-translucent) is likely to be a tumour, or rarely a syphilitic gumma. The testes may be enlarged and hard in men with leukaemia. A mass that is cystic (translucent) with the testis within it is a hydrocele (a collection of fluid in the tunica vaginalis of the testis). A mass that appears separate from the testis and transilluminates is probably a cyst of the epididymis, while a similar mass that fails to transilluminate is probably the result of chronic epididymitis. By feeling along the testicular–epididymal groove it is usually possible to separate an epididymal mass from the testis itself.

Pelvic examination

The pelvic examination should be performed as the final part of any complete physical examination.[16] It is essential to obtain informed consent and for male students and doctors to have a chaperone. The patient's privacy must be promised and ensured. Gloves must be worn (Figure 7.13).





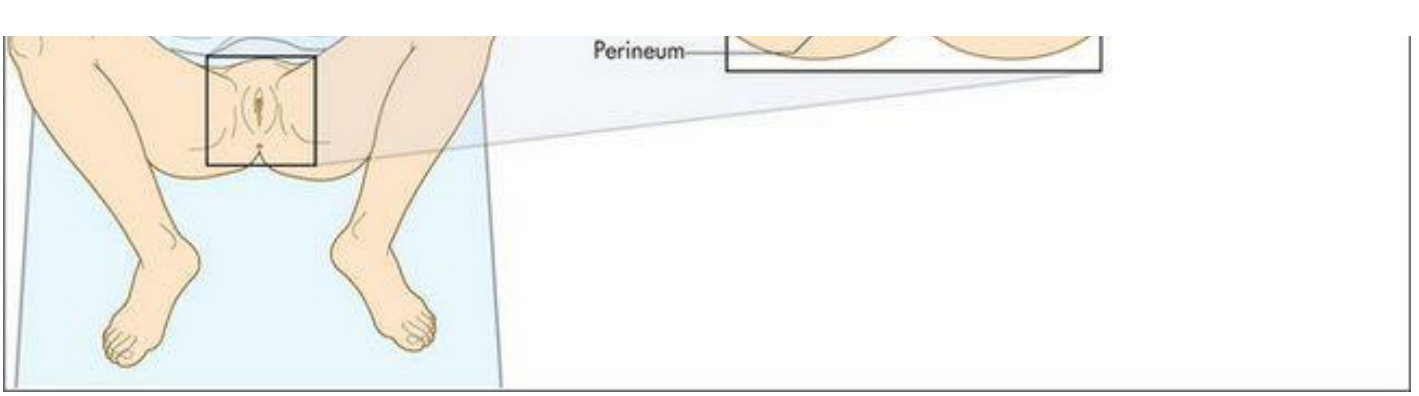


Figure 7.13 Basic female reproductive anatomy
(a) Lateral view, showing the relationship of the genitals to the rectum and bladder. (b) Position for examination.

From Douglas G, Nicol F and Robertson C, Macleod's Clinical Examination, 12th edn. Edinburgh: Churchill Livingstone, 2009, with permission

The patient should have first emptied her bladder. She should be on her back with her legs apart, ankles together and her knees bent (the frog-legged position). The left lateral position is used when the woman cannot assume the lithotomy position or when a view of the anterior vaginal wall is required: for example, when a urinary fistula is suspected.

The perineum should be brightly illuminated by a lamp. Put a glove on each hand. Inspect first the external genitalia. Note any rash (e.g. sclerotic white areas of leucoplakia, or redness, swelling and excoriation from thrush or trichomoniasis), ulceration, warts, scars, sinus openings or other lesions. Separate the labia with the thumb and forefinger of the right hand. A Bartholin[h] cyst or abscess is palpated between the thumb and index finger in the posterior part of the labia major; the normal gland is impalpable. Note the size and shape of the clitoris, and the presence or absence of a discharge from the urethral orifice and vaginal outlet. A bloody vaginal discharge suggests menstruation, a miscarriage, cancer or a cervical polyp or erosion. A purulent discharge suggests vaginitis, cervicitis or endometritis (e.g. gonorrhoea) or a retained tampon. *Trichomonas vaginalis* causes a frothy, watery, pale, yellow-white discharge, while thrush (*Candida albicans*) causes a thick cheesy discharge associated with excoriations and pruritus. Physiological discharge may be present, this is almost colourless.

Ask the patient to bear down; a cystocele (descent of the bladder through the anterior vaginal wall) or rectocele (descent of the rectum through the posterior vaginal wall) or uterine prolapse may become apparent. Then ask the patient to cough; this may demonstrate stress incontinence. Note the presence of vaginal atrophy in older women.

Next insert the lubricated index and middle finger into the vagina. Locate the cervix first: it normally points towards the posterior vaginal wall. Note the position, size, shape, consistency, tenderness and mobility. Next palpate the

anterior, posterior and lateral fornices. Usually the ovaries are not palpable. If a mass is palpable, its characteristics and location should be noted.

Bimanual palpation of the uterus is now performed; the fingers in the vagina are kept high up and rotated to face upwards while the left hand presses downwards and backwards above the pubic symphysis. Note whether the uterus is anterior (anteverted) or posterior (retroverted). Also note its size, shape and consistency and feel for tenderness and mobility. A large nodular mobile uterus suggests fibroids, while smooth enlargement of the uterus suggests pregnancy, adenomyosis or submucous fibroids.

A speculum examination of the vagina and cervix is made by introducing a well-lubricated warm bivalve speculum in an upwards direction and with the blades (bills) parallel to the labia and closed, while the other hand separates the labia. Lubricant may interfere with some cytology examinations and warm water can be used instead. The blades are opened under direct inspection once the speculum is fully introduced and rotated. The vagina and cervix are inspected. A smear for cervical cytology (Papanicolaou or 'Pap' smear) can be taken to detect cervical dysplasia or cancer. This is done using a spatula that is placed firmly against the cervical os and rotated through 360 degrees. The test is more accurate if some endocervical cells are also obtained. This can be done with a separate brush designed to fit into the os. A smear of vaginal wall cells for hormonal assessment can be taken with the other end of the spatula. The samples are smeared thinly on microscopic slides and placed immediately in fixative. Wet slides can also be prepared for *Trichomonas* or thrush, and cultures obtained for chlamydia and gonorrhoea if indicated.

Summary

Examination of a patient with chronic kidney disease: a suggested method (Figure 7.14)

Lay the patient flat in bed while performing the usual **general inspection**. Note particularly the patient's mental state and the presence of a sallow complexion, whether the patient appears properly hydrated and whether there is any hyperventilation or hiccupping.

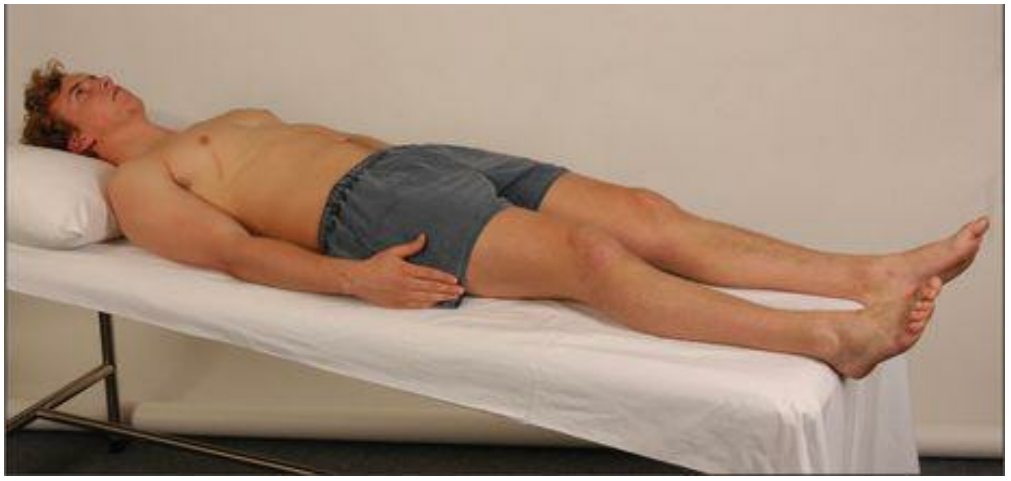


Figure 7.14 Chronic kidney disease examination

1. **General inspection**
   Mental state
   Hyperventilation (acidosis), hiccups
   Sallow complexion ('uraemic tinge')
   Hydration
   Subcutaneous nodules (calcium phosphate deposits)

2. **Hands**
   Nails—leuconychia; white lines; distal brown arc
   Arterio-venous fistulae
   Asterixis
   Neuropathy

3. **Arms**
   Bruising
   Pigmentation
   Scratch marks/excoriations
   Myopathy

4. **Face**
   Eyes—anaemia, jaundice, band keratopathy
   Mouth—dryness, ulcers, fetor, gingival hypertrophy
   Rash (lupus, vasculitis etc)

5. **Neck**
   Jugular venous pressure
   Carotid bruits
   Scars from previous vascath insertion
   Parathyroidectomy scars

6. **Abdomen**

Tenckhoff catheter
Scars—dialysis, operations
Kidneys—transplant kidney
Bladder
Liver
Lymph nodes
Ascites
Bruits
Rectal examination (prostatomegaly, frozen pelvis, bleeding)

7. **Back**
   Nephrectomy scar
   Tenderness
   Oedema

8. **Chest**
   Heart—heaving apex, pericarditis, failure
   Lungs—infection, pulmonary oedema

9. **Legs**
   Oedema—nephrotic syndrome, cardiac failure
   Bruising
   Pigmentation
   Scratch marks/excoriation
   Neuropathy
   Vascular access

10. **Urine analysis**
    Specific gravity, pH
    Glucose—diabetes mellitus
    Blood—'nephritis', infection, stone
    Protein—'nephritis' etc

11. **Other**
    Blood pressure—lying and standing
    Fundoscopy—hypertensive and diabetic changes etc
    Rash, livedo reticularis

The detailed examination begins with the **hands** and the examination of the nails, which may reveal leuconychia, white transverse lines (Muehrcke's nails), a single white band (Mees' lines), or a distal brown arc (half-and-half nails). Examine the wrists and arms for a vascular access fistula. Get the

patient to hold out the hands and look for asterixis. Then inspect the **arms** for bruising, subcutaneous nodules (calcium phosphate deposits), pigmentation, scratch marks and gouty tophi.

Go on now to the **face** and begin by examining the eyes for anaemia, jaundice or band keratopathy. Examine the mouth for dryness, ulcers or fetor, and note the presence of any vasculitic rash on the face.

Check the **neck** for surgical scars, and listen for carotid bruts. Look at the jugular venous pressure with the patient at 45 degrees.

The patient should next be lying flat while the **abdomen** is examined for scars indicating peritoneal dialysis or operations, including renal transplants. Palpate for the kidneys, including transplanted kidneys, then examine the liver and spleen. Feel for an abdominal aortic aneurysm. Percuss over the bladder, determine if there is ascites, and listen for renal bruits. Rectal examination is indicated to detect prostatomegaly or bleeding.

Sit the patient up and palpate the **back** for tenderness and sacral oedema.

Examine the **heart** for signs of pericarditis or cardiac failure and the **lungs** for pulmonary oedema.

Lay the patient down again. Look at the **legs** for oedema (due to the nephrotic syndrome or cardiac failure), bruising, pigmentation, scratch marks or the presence of gout. Examine for peripheral neuropathy (decreased sensation, loss of the more distal reflexes).

Urinalysis is performed, testing for specific gravity, pH, glucose, blood, protein or leucocytes. Examination ends with measurement of the **blood pressure**, lying and standing (for orthostatic hypotension), and **fundoscopy** to look for hypertensive and diabetic changes.

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[a] In secondary hyperparathyroidism, serum calcium is low and phosphate is high. In tertiary hyperparathyroidism, where parathyroid function has become autonomous, serum calcium and phosphate levels are both high.

[b] Georgios N Papanicolaou (1884–1962). After studying at the University of Athens he worked in the pathology department at New York Hospital.

[c] Cecil Alport, 1880–1959, South African physician who worked in London and Egypt, described this syndrome in 1927 while working at St Mary's Hospital, London.

[d] RC Meuhrcke reported this sign in the *British Medical Journal* in 1956.

[e] RA Mees, Dutch physician, reported this sign in 1919. It had previously been reported (1901) in the *Lancet* by E Reynolds among drinkers of beer contaminated by arsenic in the north of England.

[f] Joseph Honoré Simon Beau (1806–1865), Paris physician.

[g] Henry Bence-Jones (1818–73), physician at St George's Hospital, London, described this in 1848.

[h] Caspar Bartholin Secundus (1655–1738), professor of philosophy at Copenhagen at the age of 19, then professor of medicine, anatomy and physics. He described the glands in 1677.

Chapter 8

The haematological system

> [T]he blood is the generative part, the fountain of life, the first to live, the last to die and the primary seat to the soul.
> *William Harvey (1578–1657)*

The haematological history

Presenting symptoms (Table 8.1)

Patients with anaemia may present with weakness, tiredness, dyspnoea

Patients with anaemia may present with weakness, tiredness, dyspnoea, fatigue or postural dizziness. Anaemia due to iron deficiency is often the result of gastrointestinal blood loss, or sometimes recurrent heavy menstrual blood loss, and so these symptoms should be sought. Disorders of platelet function or blood clotting may present with easy-bruising or bleeding problems. Recurrent infection may be the first symptom of a disorder of the immune system, including leukaemia or HIV infection. The patient may have noticed lymph node enlargement, which can occur with lymphoma or leukaemia. Not all lumps are lymph nodes; consider the differential diagnosis (Table 8.2). Ask about fever, its duration and pattern. Lymphomas can be a cause of chronic fever, and viral infections such as cytomegalovirus and infectious mononucleosis are associated with haematological abnormalities and fever.

TABLE 8.1 Haematological history

Major symptoms
Symptoms of anaemia: weakness, tiredness, dyspnoea, fatigue, postural dizziness
Bleeding (menstrual, gastrointestinal, after dental extractions)
Easy bruising, purpura, thrombotic tendency
Lymph gland enlargement
Bone pain
Infection, fever or jaundice
Enlargement of the tongue from amyloidosis
Paraesthesiae (e.g. B_{12} deficiency)
Skin rash
Weight loss

Weight loss

TABLE 8.2 Differential diagnosis of lymphadenopathy

1 Lipoma—usually large and soft; may not be in lymph node area
2 Abscess—tender and erythematous, may be fluctuant
3 Sebaceous cyst—intradermal location
4 Thyroid nodule—forms part of thyroid gland
5 Secondary to recent immunisation

Treatment

Anaemia may have been treated with iron supplements or B_{12} injections. Anti-inflammatory drugs or anticoagulants may be the cause of bleeding. Treatment for leukaemia or lymphoma may have involved chemotherapy, radiotherapy, or both; or bone marrow transplant. There may have been blood transfusions in the past.

Past history

A history of gastric surgery or malabsorption may give a clue regarding the underlying cause of an anaemia. Anaemia in patients with systemic disease such as rheumatoid arthritis or uraemia can be multifactorial. Previous blood transfusions may have been required to treat the anaemia. On the other hand, patients with polycythaemia may have had many venesections (page 236).

Social history

A patient's racial origin is relevant. Thalassaemia is common in people of Mediterranean or southern Asian origin. Rarely, very strict vegetarian diets can result in vitamin B_{12} deficiency. Find out the patient's occupation and

whether there has been work exposure to toxins such as benzene (risk of leukaemia). Has the patient had previous chemotherapy for a malignancy (drug-related development of leukaemia)? Does the patient drink alcohol?

Family history

There may be a history of thalassaemia or sickle cell anaemia in the family. Haemophilia is a sex-linked recessive disease while von Willebrand's disease[a] is autosomal dominant with incomplete penetrance (Table 8.3).

TABLE 8.3 Causes of ecchymoses

Trauma
Thrombocytopenia or platelet dysfunction (Table 8.4)
Coagulation disorders *Acquired* Vitamin K deficiency (leading to factor II, VII, IX and X deficiency) Liver disease (impaired synthesis of clotting factors) Anticoagulants, e.g. heparin, warfarin, proteins with anticoagulant activity Disseminated intravascular coagulation *Congenital* (rarely cause ecchymoses and usually present with haemorrhage) Haemophilia A (factor VIII deficiency) Haemophilia B (factor IX deficiency, Christmas disease)

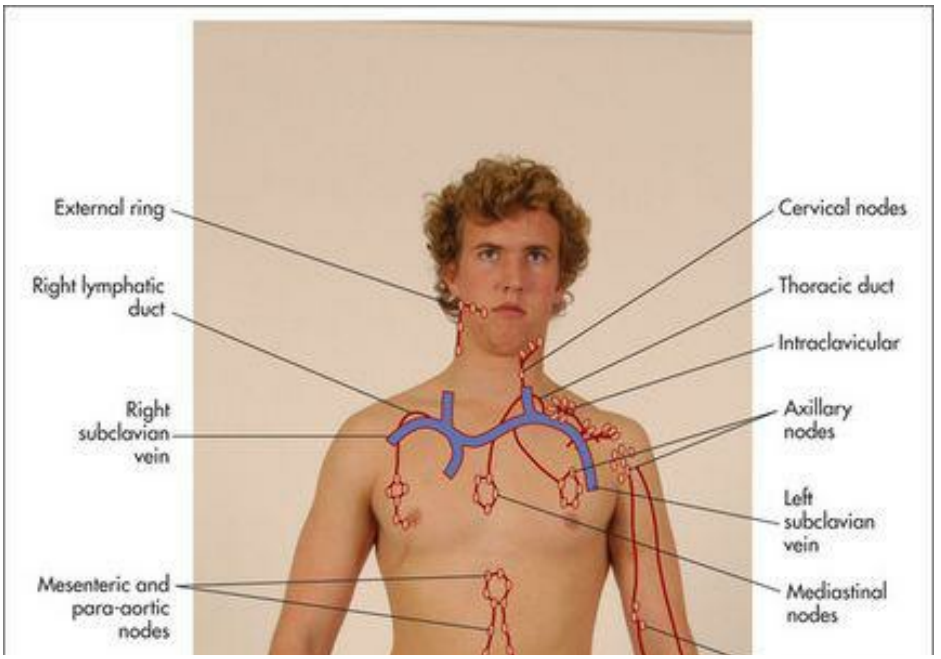
Haemophilia B (factor IX deficiency, Christmas disease) Von Willebrand's disease (an inherited abnormality of the von Willebrand protein, which is part of the factor VIII complex and causes a defect in platelet adhesion)
Senile ecchymoses (due to loss of skin elasticity)

The haematological examination

Haematological assessment does not depend only on the microscopic examination of the blood constituents. Physical signs, followed by examination of the blood film, can give vital clues about underlying disease. Haematological disease can affect the red blood cells, the white cells, the platelets and other haemostatic mechanisms as well as the mononuclear-phagocyte (reticuloendothelial) system.

Examination anatomy

An important part of the examination involves assessment of all the palpable groups of lymph nodes. As each group is examined its usual drainage area must be kept in mind (Figure 8.1). It follows that whenever an abnormality is discovered anywhere that might be due to infection or malignancy its draining lymph nodes must be examined.



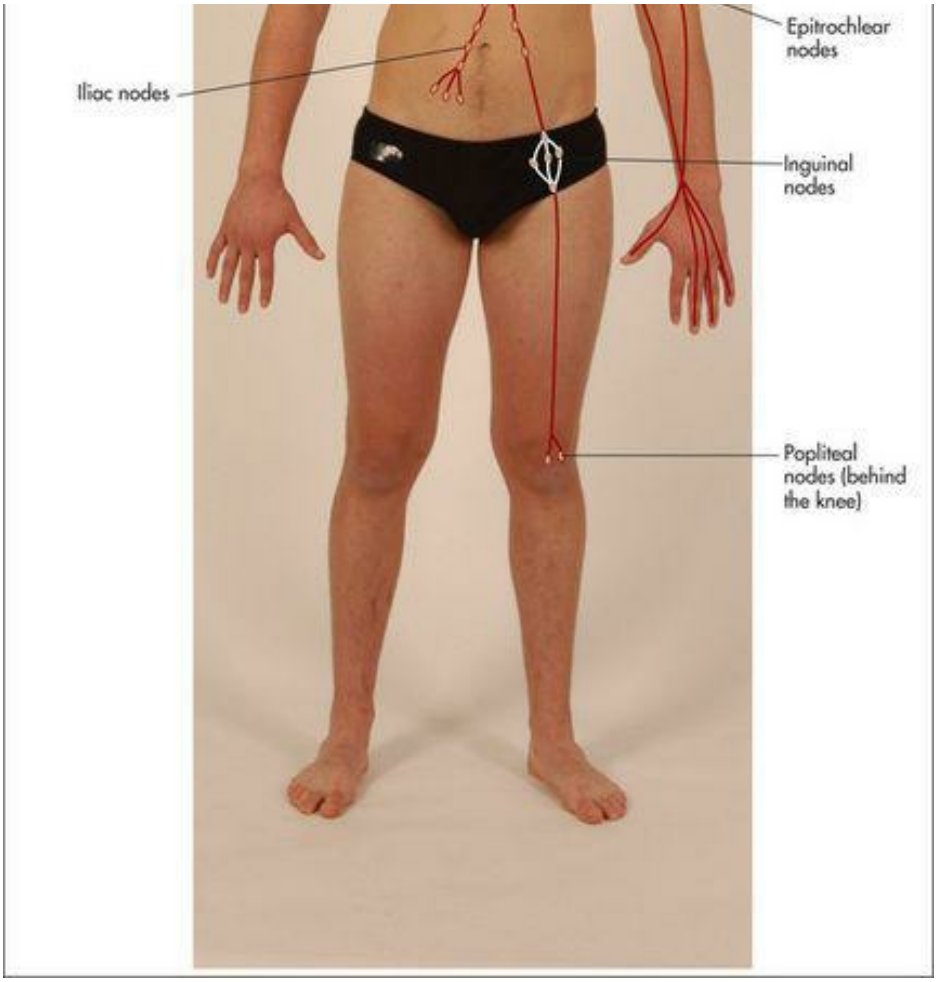


Figure 8.1 Usual drainage areas of lymph nodes

Adapted from Epstein O et al, Clinical Examination, 4th edn, Edinburgh: Mosby, 2008.

General appearance

Position the patient as for the gastrointestinal examination—lying on the bed with one pillow. Look for signs of wasting and for *pallor* (which may be an indication of anaemia—*Good signs guide 3.1*, page 26) .[1-3] Note the patient's *racial* origin (e.g. thalassaemia). If there is any *bruising*, look at its distribution and extent. *Jaundice* may be present and can indicate haemolytic anaemia. *Scratch marks* (following pruritus, which sometimes occurs with lymphoma and myeloproliferative disease) should be noted.

The hands

The detailed examination begins in the usual way with assessment of the hands. Look at the nails for *koilonychia*—these are dry, brittle, ridged,

spoon-shaped nails, which are rarely seen today. They can be due to severe iron deficiency anaemia, although the mechanism is unknown. Occasionally koilonychia may be due to fungal infection. They may also be seen in Raynaud's phenomenon. Digital infarction (Figure 8.2) may be a sign of abnormal globulins (e.g. cryoglobulinaemia). Pallor of the nail beds may occur in anaemia but is an unreliable sign. Pallor of the *palmar creases* suggests that the haemoglobin level is less than 70 g/L, but this is also a rather unreliable sign.[1]

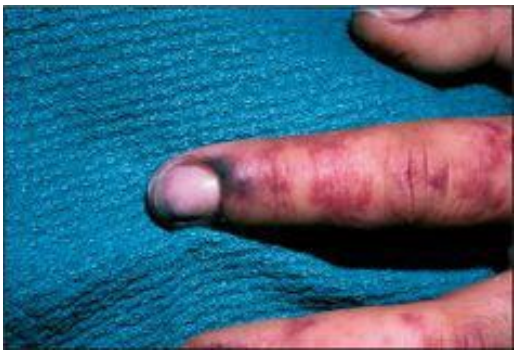


Figure 8.2 Digital infarction

Note any changes of rheumatoid or gouty *arthritis*, or connective tissue disease (Chapter 9). Rheumatoid arthritis, when associated with splenomegaly and neutropenia, is called Felty's syndrome[b]: the mechanism of the neutropenia is unknown, but it can result in severe infection. Felty's syndrome can also be associated with thrombocytopenia (Figure 8.3), haemolytic anaemia, skin pigmentation and leg ulceration. Gouty tophi and arthropathy may be present in the hands. Gout may be a manifestation of a myeloproliferative disease. Connective tissue diseases can cause anaemia because of the associated chronic inflammation.

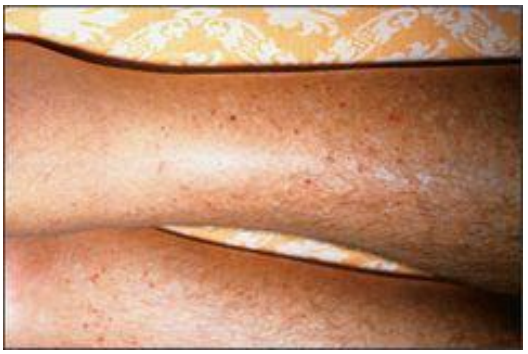


Figure 8.3 Thrombocytopenic purpura

Now take the *pulse*. A tachycardia may be present. Anaemic patients

have an increased cardiac output and compensating tachycardia because of the reduced oxygen-carrying capacity of their blood.

Look for *purpura* (Figure 8.3), which is really any sort of bruising, due to haemorrhage into the skin. The lesions can vary in size from pinheads called *petechiae* (from Latin *petechia* 'a spot') (Table 8.4) to large bruises called *ecchymoses* (Table 8.3).

TABLE 8.4 Causes of petechiae

Thrombocytopenia

Platelet count <100 x 10^9/L

Increased destruction

Immunological:
- immune thrombocytopenic purpura (ITP)
- systemic lupus erythematosus
- drugs, e.g. quinine, sulfonamides, methyldopa

- Non-immunological:
  - damage, e.g. prosthetic heart valve
  - consumption, e.g. disseminated intravascular coagulation (DIC)
  - loss, e.g. haemorrhage

Reduced production

Marrow aplasia, e.g. drugs, chemicals, radiation

Marrow invasion, e.g. carcinoma, myeloma, leukaemia, fibrosis

Sequestration

Hypersplenism

Platelet dysfunction

Congenital or familial

Acquired:

- myeloproliferative disease
- dysproteinaemia
- chronic renal failure, chronic liver disease
- drugs, e.g. aspirin

Bleeding due to small vessel disease

Infection:

- infective endocarditis
- septicaemia (e.g. meningococcal)
- viral exanthemata (e.g. measles)

Drugs, e.g. steroids

Scurvy (vitamin C deficiency)—classically perifollicular purpura on the lower limbs, which is almost diagnostic of this condition

Cushing's syndrome

Vasculitis:

- polyarteritis nodosa
- Henoch-Schönlein purpura*

Fat embolism

Dysproteinaemia

* Eduard Henoch (1820–1910), professor of paediatrics, Berlin, described this in 1865, and Johannes Schönlein (1793–1864), Berlin physician, described it in 1868.

If the petechiae are raised (*palpable purpura*), this suggests an underlying systemic vasculitis, where the lesions are painful, or bacteraemia.

The forearms

If thrombocytopenia or capillary fragility is suspected, the Hess test[c] can be performed.[d]

Epitrochlear nodes

These must always be palpated. The best method is to flex the patient's elbow to 90 degrees, abduct the upper arm a little and then place the palm of the right hand under the patient's right elbow (Figure 8.4). The examiner's thumb can then be placed over the appropriate area, which is proximal and slightly anterior to the medial epicondyle. This is repeated with the left hand for the other side. An enlarged epitrochlear node is usually pathological. It occurs with local infection, non-Hodgkin's lymphoma[e] or rarely syphilis. Note the features and different causes as listed in tables 8.5 and 8.6. Certain symptoms and signs suggest that lymphadenopathy may be the result of a significant disease (*Good signs guide 8.1*).

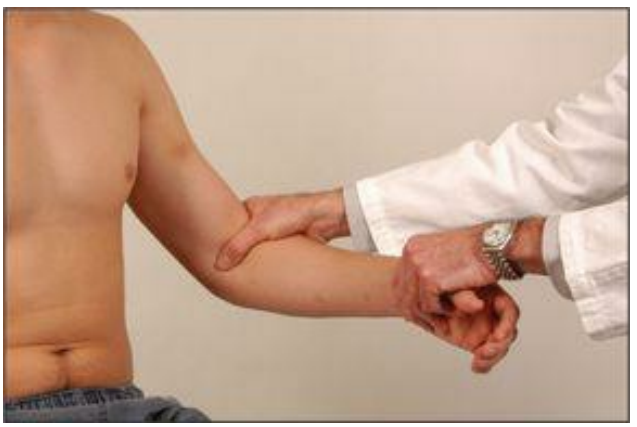


Figure 8.4 Feeling for the epitrochlear lymph node

TABLE 8.5 Characteristics of lymph nodes

During the palpation of lymph nodes the following features must be considered:

Site

Palpable nodes may be localised to one region (e.g. local infection, early lymphoma) or generalised (e.g. late lymphoma).

The palpable lymph node areas are:

- epitrochlear
- axillary
- cervical and occipital
- supraclavicular
- para-aortic (rarely palpable)
- inguinal
- popliteal

Size

Large nodes are usually abnormal (greater than 1 cm)

Consistency

Hard nodes suggest carcinoma deposits, soft nodes may be normal, and rubbery nodes may be due to lymphoma

Tenderness

This implies infection or acute inflammation

Fixation

Nodes that are fixed to underlying structures are more likely to be infiltrated by carcinoma than mobile nodes

Overlying skin

Inflammation of the overlying skin suggests infection, and tethering to the overlying skin suggests carcinoma

TABLE 8.6 Causes of localised lymphadenopathy

1 Inguinal nodes; infection of lower limb, sexually transmitted disease, abdominal or pelvic malignancy; immunisations
2 Axillary nodes; infections of the upper limb, carcinoma of the breast, disseminated malignancy; immunisations
3 Epitrochlear nodes; infection of the arm, lymphoma, sarcoidosis
4 Left supraclavicular nodes; metastatic malignancy from the chest, abdomen (especially stomach—Troiser's sign) or pelvis
5 Right supraclavicular nodes; malignancy from the chest or oesophagus

GOOD SIGNS GUIDE 8.1 Factors suggesting lymphadenopathy is associated with significant disease

	LR if present	LR if absent
Age > 40	2.4	0.4
Weight loss	3.4	0.8
Fever	NS	NS

Head and neck but not supraclavicular	NS	NS
Supraclavicular	3.2	0.8
Axillary	0.8	NS
Inguinal	0.6	NS
Size:		
< 4 cm^2	0.4	—
4–9 cm^2	NS	—
> 9 cm^2	8.4	—
Hard texture	3.3	NS
Tender	0.4	1.3
Fixed node	10.9	NS
3 or fewer nodes	0.04	—
5 or 6 nodes	5.1	—
7 or more nodes	21.9	—

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

Axillary nodes

To palpate these, the examiner raises the patient's arm and, using the left hand for the right side, pushes his or her fingers as high as possible into the axilla. The patient's arm is then brought down to rest on the examiner's forearm. The opposite is done for the other side (Figure 8.5).

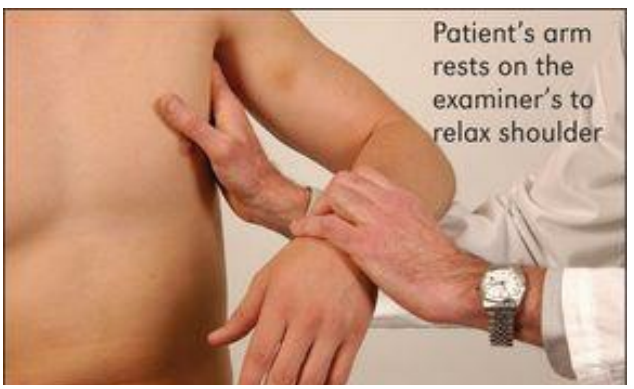


Figure 8.5 Feeling for the axillary lymph nodes

There are five main groups of axillary nodes: (i) central; (ii) lateral (above and lateral); (iii) pectoral (medial); (iv) infraclavicular; and (v) subscapular (most inferior) (Figure 8.6). An effort should be made to feel for nodes in each of these areas of the axilla.

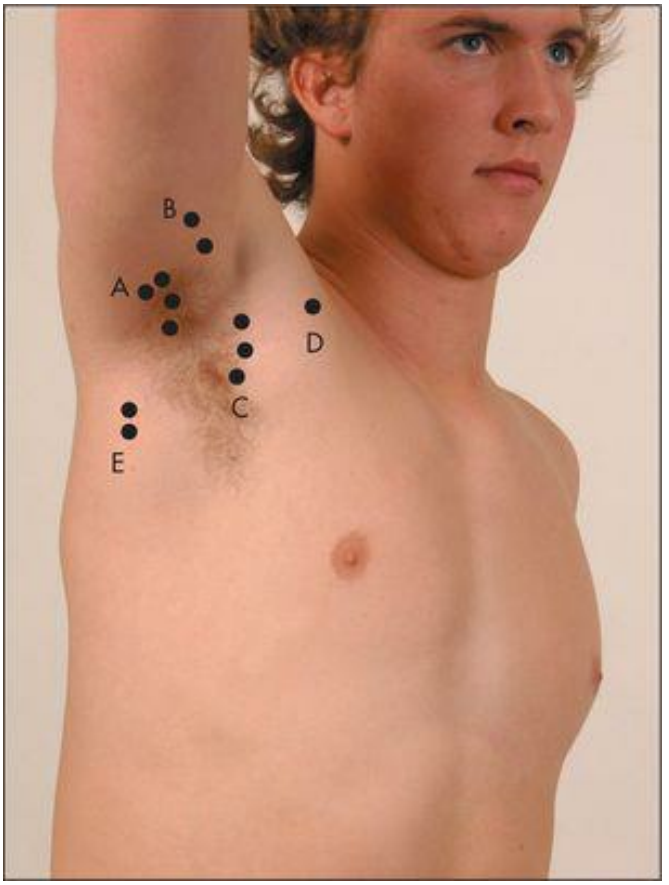


Figure 8.6 The main groups of axillary lymph nodes
A = central; B = lateral; C = pectoral; D = infraclavicular; E = subscapular.

The face

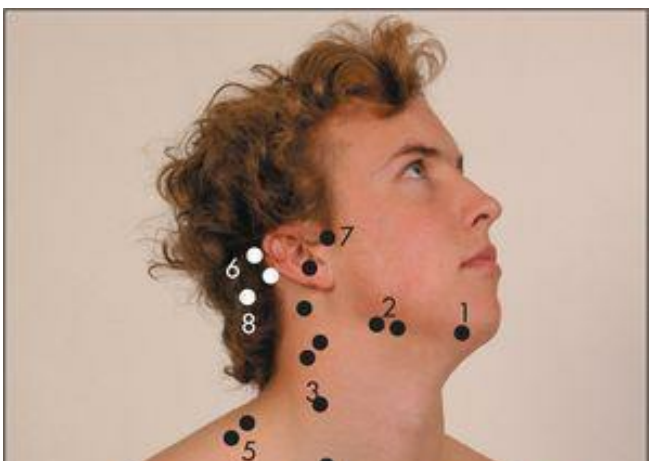
The *eyes* should be examined for the presence of scleral jaundice, haemorrhage or injection (due to increased prominence of scleral blood vessels, as in polycythaemia). Conjunctival pallor suggests anaemia and is more reliable than examination of the nail beds or palmar creases.[3] In northern Europeans the combination of prematurely grey hair and blue eyes may indicate a predisposition to the autoimmune disease *pernicious*

anaemia, where there is a vitamin B_{12} deficiency due to lack of intrinsic factor secretion by an atrophic gastric mucosa.

The *mouth* should be examined for hypertrophy of the gums, which may occur with infiltration by leukaemic cells, especially in acute monocytic leukaemia, or with swelling in scurvy. Gum bleeding must also be looked for, and ulceration, infection and haemorrhage of the buccal and pharyngeal mucosa noted. Atrophic glossitis occurs with megaloblastic anaemia or iron deficiency anaemia. Multiple telangiectasiae may appear around the mouth or in the mouth in patients with *hereditary haemorrhagic telangiectasia*. Look to see if the tonsils are enlarged. *Waldeyer's ring*[f] is a circle of lymphatic tissue in the posterior part of the oropharynx and nasopharynx, and includes the tonsils and adenoids. Sometimes non-Hodgkin's lymphoma will involve Waldeyer's tonsillar ring, but Hodgkin's disease rarely does.

Cervical and supraclavicular nodes

Sit the patient up and examine the cervical nodes from behind. There are eight groups. Attempt to identify each of the groups of nodes with your fingers (Figure 8.7). First palpate the submental node, which lies directly under the chin, and then the submandibular nodes, which are below the angle of the jaw. Next palpate the jugular chain, which lies anterior to the sternomastoid muscle, and then the posterior triangle nodes, which are posterior to the sternomastoid muscle. Palpate the occipital region for occipital nodes and then move to the postauricular node behind the ear and the preauricular node in front of the ear. Finally from the front, with the patient's shoulders slightly shrugged, feel in the supraclavicular fossa and at the base of the sternocleidomastoid muscle for the supraclavicular nodes. Causes of lymphadenopathy, localised and generalised, are given in Table 8.7. Note that small cervical nodes are often palpable in normal young people.[4,5]



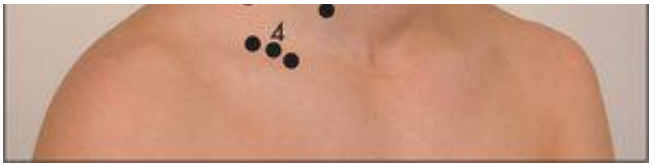


Figure 8.7 Cervical and supraclavicular lymph nodes
1 = submental; 2 = submandibular; 3 = jugular chain; 4 = supraclavicular; 5 = posterior triangle; 6 = postauricular; 7 = preauricular; 8 = occipital.

TABLE 8.7 Causes of lymphadenopathy

Generalised lymphadenopathy
Lymphoma (rubbery and firm)
Leukaemia (e.g. chronic lymphocytic leukaemia, acute lymphocytic leukaemia)
Infections: viral (e.g. infectious mononucleosis, cytomegalovirus, HIV), bacterial (e.g. tuberculosis, brucellosis, syphilis), protozoal (e.g. toxoplasmosis)
Connective tissue diseases: e.g. rheumatoid arthritis, systemic lupus erythematosus
Infiltration: e.g. sarcoid
Drugs: e.g. phenytoin (pseudolymphoma)
Localised lymphadenopathy
Local acute or chronic infection
Metastases from carcinoma or other solid tumour
Lymphoma, especially Hodgkin's disease

The detection of lymphadenopathy should lead to a search of the area

drained by the enlarged nodes. This may reveal the likely cause (see Table 8.6).

Bone tenderness

While the patient is sitting up, tap over the spine with the fist for bony tenderness. This may be caused by an enlarging marrow due to infiltration by myeloma, lymphoma or carcinoma, or due to malignant disease of the bony skeleton. Also gently press the sternum and both clavicles with the heel of the hand and then test both shoulders by pushing them towards each other with your hands.

The abdominal examination

Lay the patient flat again. Examine the abdomen carefully, especially for splenomegaly[6] (Table 8.8, *Good signs guide 8.2*), hepatomegaly, para-aortic nodes (rarely palpable), inguinal nodes and testicular masses. Remember that a central deep abdominal mass may occasionally be due to enlarged para-aortic nodes. Para-aortic adenopathy strongly suggests lymphoma or lymphatic leukaemia. The rectal examination may reveal evidence of bleeding or a carcinoma.

TABLE 8.8 Causes of splenomegaly

Massive
Common
Chronic myeloid leukaemia
Myelofibrosis
Rare
Malaria

Kala azar

Primary lymphoma of spleen

Moderate

The above causes

Portal hypertension

Lymphoma

Leukaemia (acute or chronic)

Thalassaemia

Storage diseases, e.g. Gaucher's disease*

Small

The above causes

Other myeloproliferative disorders:
- polycythaemia rubra vera
- essential thrombocythaemia

Haemolytic anaemia

Megaloblastic anaemia (rarely)

Infection:
- viral (e.g. infectious mononucleosis, hepatitis)
- bacterial (e.g. infective endocarditis)
- protozoal (e.g. malaria)

Connective tissue diseases:
- rheumatoid arthritis
- systemic lupus erythematosus
- polyarteritis nodosa

Infiltrations:

- e.g. amyloid, sarcoid

Splenomegaly may be found in 3%–12% of the normal population.

Note: Secondary carcinomatosis is a very *rare* cause of splenomegaly.

* Phillipe Charles Ernest Gaucher (1854–1918), who described this in 1882, was physician and dermatologist at the Hôpital St-Louis, Paris.

GOOD SIGNS GUIDE 8.2 Splenomegaly

Finding	Positive LR	Negative LR
Spleen palpable	8.5	0.5
Spleen percussion positive	1.7	0.7

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

Assessment of the patient with suspected malignancy is presented in Table 8.9.[7]

TABLE 8.9 Assessing the patient with suspected malignancy

1 Palpate all draining lymph nodes
2 Examine all remaining lymph node groups
3 Examine the abdomen, particularly for hepatomegaly and ascites
4 Feel the testes
5 Perform a rectal examination and pelvic examination
6 Examine the lungs
7 Examine the breasts
8 Examine all the skin and nails for melanoma

Inguinal nodes

There are two groups—one along the inguinal ligament and the other along the femoral vessels. Small, firm mobile nodes are commonly found in otherwise normal subjects (Figure 8.8).

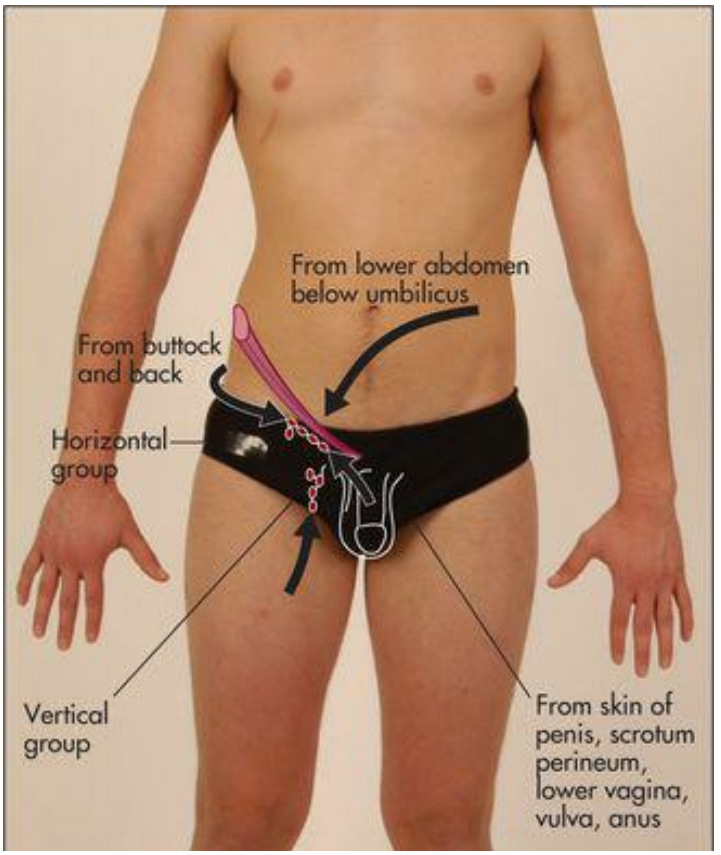


Figure 8.8 The groups of inguinal lymph nodes, their drainage areas and the position of the spleen

Adapted from Epstein O et al, Clinical Examination, 4th edn, Edinburgh: Mosby, 2008.

The legs

Inspect for any bruising, pigmentation or scratch marks. Palpable purpura over the buttocks and legs are present in Henoch-Schönlein purpura[g] (Figure 8.9). Leg ulcers may occur above the medial or lateral malleolus in association with haemolytic anaemia (including sickle cell anaemia and hereditary spherocytosis), probably as a result of tissue infarction due to abnormal blood viscosity. Leg ulcers can also occur with thalassaemia, macroglobulinaemia, thrombotic thrombocytopenic purpura and polycythaemia, as well as in Felty's syndrome. Chronic use of hydroxyurea for myeloproliferative disorders can cause malar ulcers.

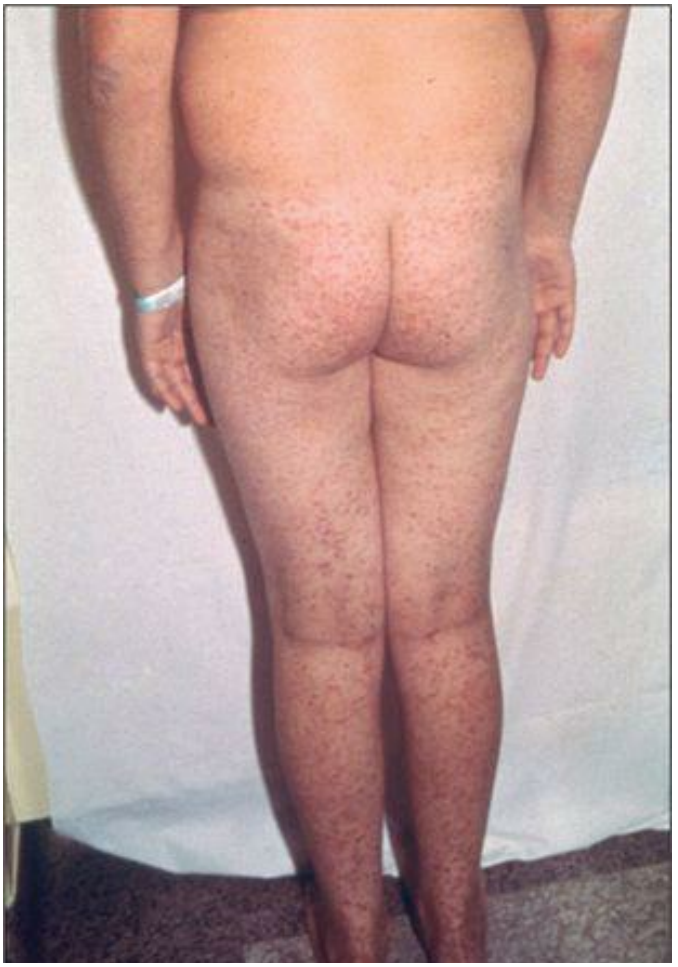


Figure 8.9 Henoch-Schönlein purpura

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

Very occasionally, popliteal nodes may be felt in the popliteal fossa.

The legs should also be examined for evidence of the neurological abnormalities caused by vitamin B_{12} deficiency: peripheral neuropathy and subacute combined degeneration of the spinal cord. Vitamin B_{12} is an essential cofactor in the conversion of homocysteine to methionine; in B_{12} deficiency, the lack of methionine impairs methylation of myelin basic protein. Deficiency of vitamin B_{12} can also result in optic atrophy and mental changes. Lead poisoning causes anaemia and foot (or wrist) drop.

The fundi

Examine the fundi. An increase in blood viscosity, which occurs in diseases such as macroglobu, myeloproliferative disease or chronic granulocytic leukaemia, can cause engorged retinal vessels and later papilloedema. Haemo may occur because of a haemostatic disorder. Retinal lesions (multiple yellow-white patches) may be present in toxoplasmosis (see Figure 16.5) and cytomegalovirus infections (see Figure 16.6).

Examination of the peripheral blood film

This is a simple and useful clinical investigation.

A properly made peripheral blood film is one of the simplest, least invasive and most readily accessible forms of ‘tissue biopsy’, and can be a very useful diagnostic tool in clinical medicine. An examination of the patient’s blood film can (i) assess whether the morphology of red cells, white cells and platelets is normal; (ii) help to characterise the type of anaemia; (iii) detect the presence of abnormal cells and provide clues about quantitative changes in plasma proteins—e.g. paraproteinaemia; and (iv) help to make the diagnosis of an underlying infection, malignant infiltration of the bone marrow or primary proliferative haematological disorder. The following pages present illustrated examples of some clinical problems diagnosed by examination of the blood film (Figures 8.10 to 8.22).

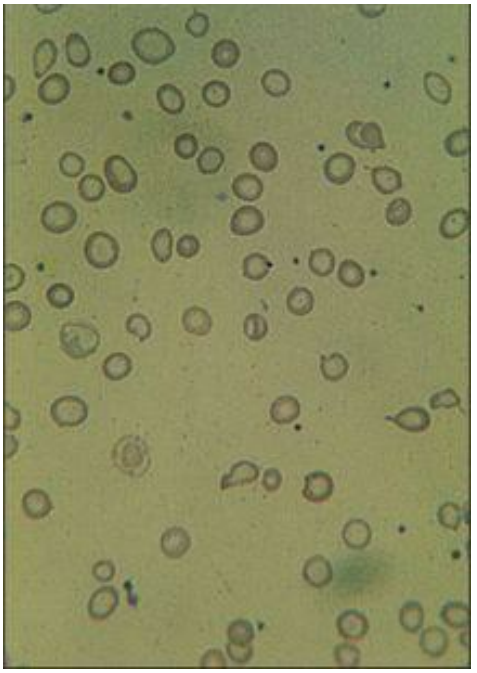


Figure 8.10 Iron-deficiency anaemia
Red cells show varying shape and size and are generally hypochromic.

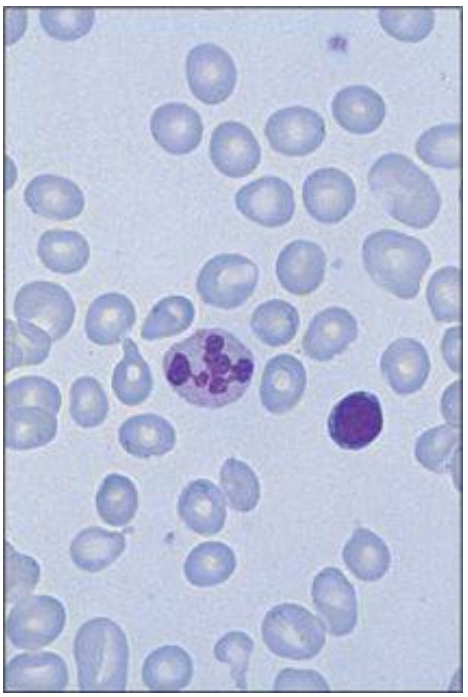


Figure 8.11 Megaloblastic anaemia
Red cells are macrocytic with many oval forms and the neutrophil is hypersegmented.

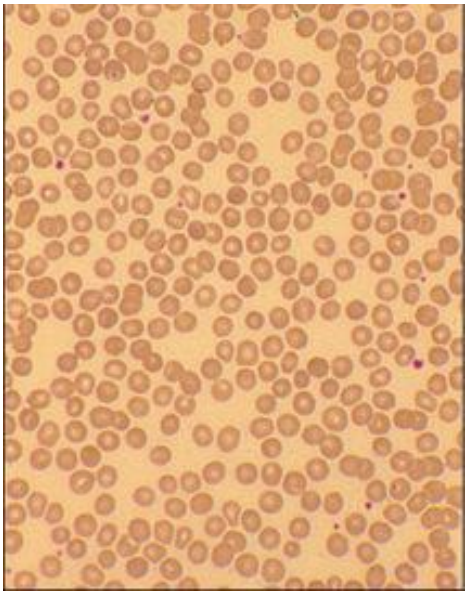


Figure 8.12 Spherocytic anaemia
Hereditary spherocytosis or autoimmune haemolytic anaemia. The numerous red blood cells which are small, round and lack central pallor are spherocytes (the big red blood cells are probably reticulocytes).

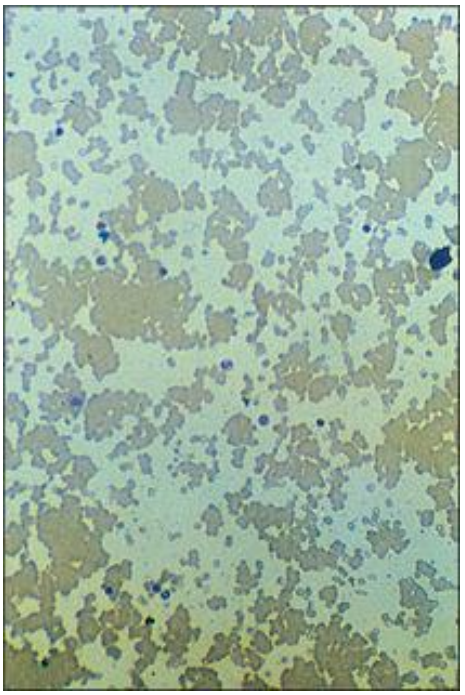


Figure 8.13 Autoagglutination
Cold haemagglutinin disease. Film shows clumping of red cells (low power).

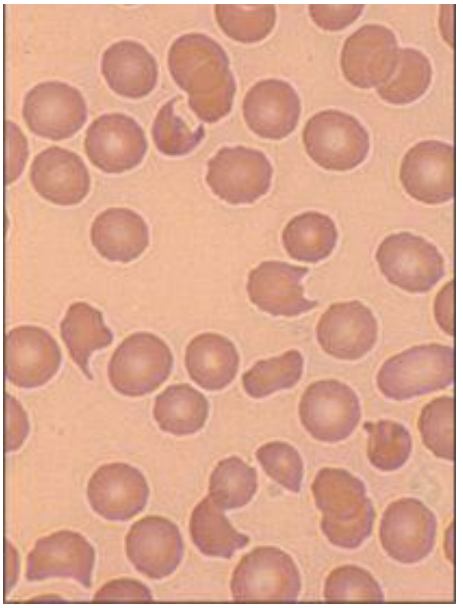


Figure 8.14 Microangiopathic haemolysis (e.g. disseminated intravascular coagulation)
Frequent fragmented (bitten) red cells.

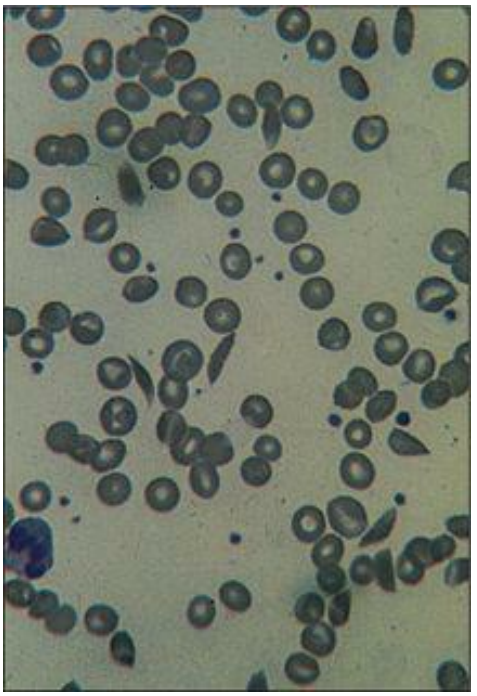
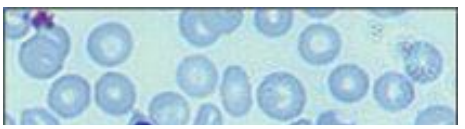


Figure 8.15 Sickle cell anaemia
Film shows several sickle-shaped cells with target cells probably secondary to the 'autosplenectomy' that occurs in this disease.



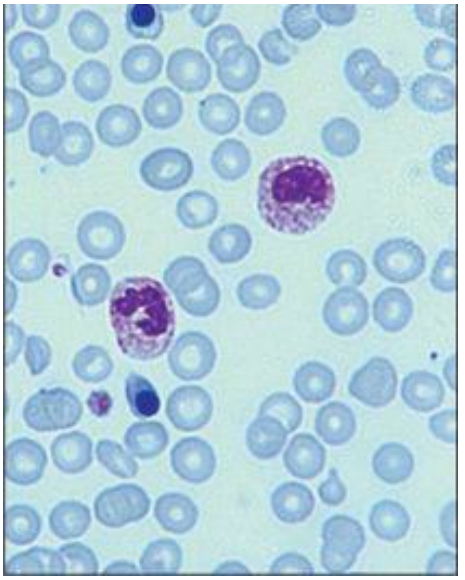


Figure 8.16 Leucoerythroblastic film
Film indicative of bone marrow infiltration. Shows circulating nucleated red blood cells and immature white cells.

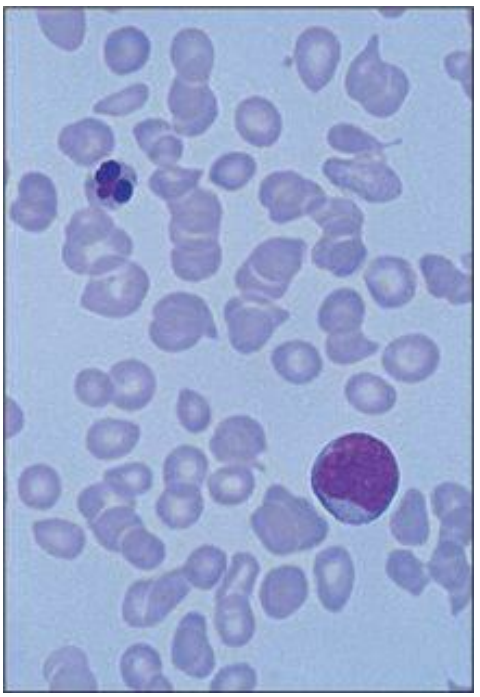
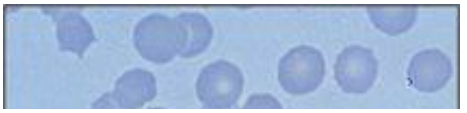


Figure 8.17 Myelofibrosis
Film shows a dysplastic nucleated red blood cell, frequent tear-drop poikilocytes and a primitive granulocyte.



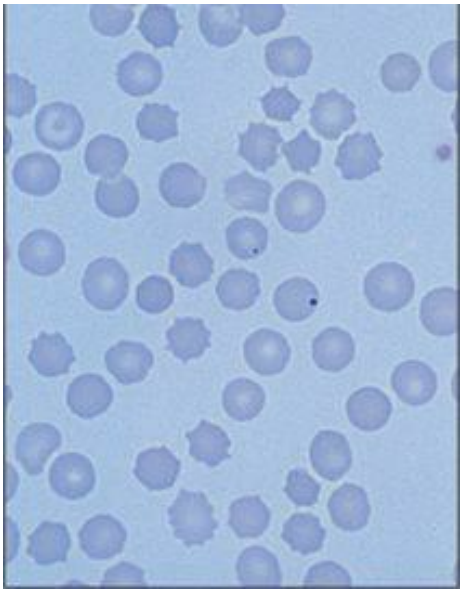


Figure 8.18 Postsplenectomy picture
Film shows several Howell-Jolly bodies, target cells and crenated cells.

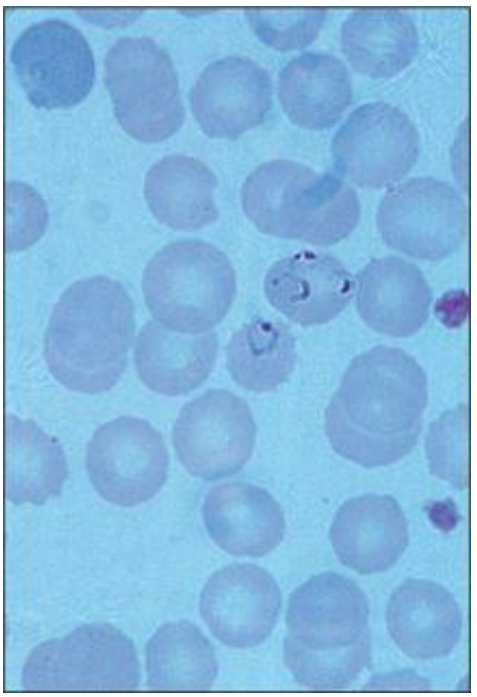
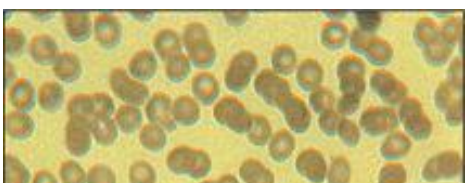


Figure 8.19 Malaria
The two red cells in the centre show the trophozoite.



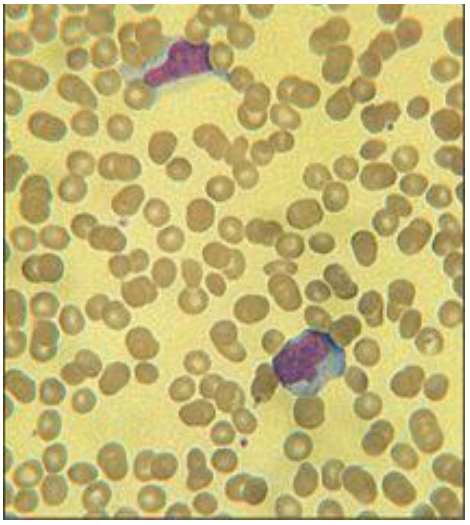


Figure 8.20 Viral illness (e.g. infectious mononucleosis)
Film shows two atypical or 'switched-on' lymphocytes.

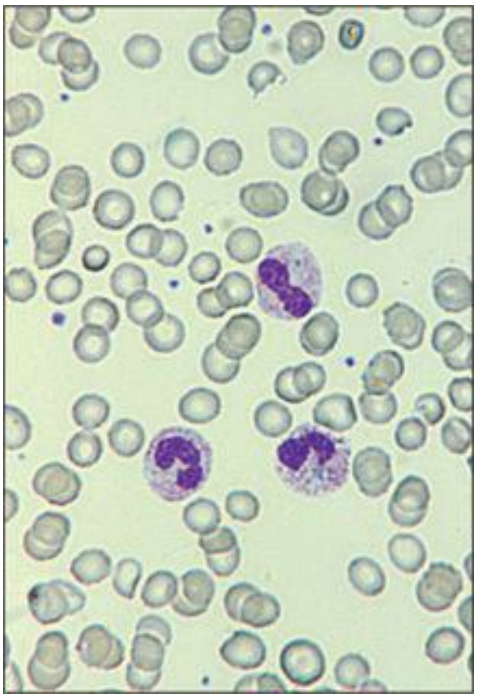
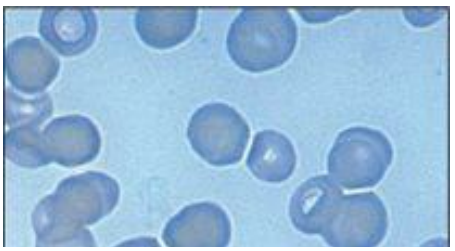


Figure 8.21 Bacterial infection (e.g. pneumonia, infective endocarditis)
The white cell in the centre is a band form with prominent 'toxic' granules.



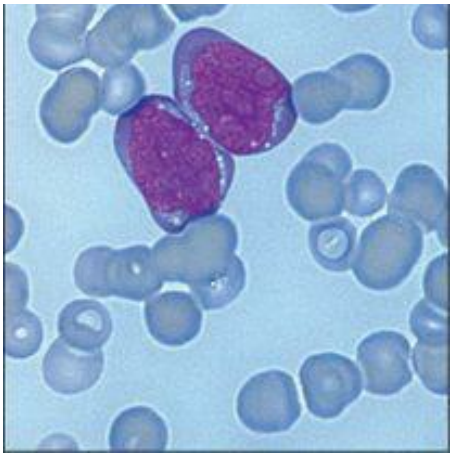


Figure 8.22 Acute leukaemia
The film shows two very primitive white cells with prominent nucleoli.

Correlation of physical signs and haematological disease

Anaemia

Anaemia is a reduction in the concentration of haemoglobin below 135 g/L in an adult man and 115 g/L in an adult woman. Anaemia is not a disease itself but results from an underlying pathological process (Table 8.10, page 235). It can be classified according to the blood film. Red blood cells with a low mean cell volume (MCV) appear small (microcytic) and pale (hypochromic). Those with a high MCV appear large and round or oval-shaped (macrocytic). Alternatively, the red blood cells may be normal in shape and size (normochromic, normocytic) but reduced in number.

TABLE 8.10 Causes of anaemia

Microcytic anaemia
Iron-deficiency anaemia (iron is essential for haem production) • chronic bleeding (commonest cause, usually from gastrointestinal or menstrual loss)

- malabsorption, e.g. gastrectomy, coeliac disease
- hookworm (blood loss)
- pregnancy (increased demand)

Note: Dietary inadequacy alone is rarely the sole cause.

Thalassaemia minor (an abnormal haemoglobin)

Sideroblastic anaemia (iron incorporation into haem is abnormal)

Long-standing anaemia of chronic disease

Macrocytic anaemia

Megaloblastic bone marrow (oval macrocytes on the blood film)

- vitamin B_{12} deficiency due to:
  - pernicious anaemia
  - gastrectomy
  - tropical sprue or bacterial overgrowth
  - ileal disease, e.g. Crohn's disease, ileal resection (>60 cm)
  - fish tapeworm (*Diphyllobothrium latum*) in Scandinavia especially
  - poor diet (vegans, very rare)
- folate deficiency due to:
  - dietary deficiency, especially alcoholics
  - malabsorption, especially coeliac disease
  - increased cell turnover, e.g. pregnancy, leukaemia, chronic haemolysis, chronic inflammation
  - antifolate drugs, e.g. phenytoin, methotrexate, sulfasalazine

Non-megaloblastic bone marrow (round macrocytes on the blood film)

- alcohol
- cirrhosis of the liver
- reticulocytosis, e.g. haemolysis, haemorrhage
- hypothyroidism

- hypothyroidism
- marrow infiltration
- myelodysplastic syndrome
- myeloproliferative disease

Normocytic anaemia

Bone marrow failure:

- aplastic anaemia (bone marrow fatty or empty), e.g. drugs (such as chloramphenicol, indomethacin, phenytoin, gold, sulfonamides, antineoplastics), radiation, systemic lupus erythematosus, viral hepatitis, pregnancy, Fanconi syndrome, idiopathic
- ineffective haematopoiesis (normal or increased bone marrow cellularity), e.g. myelodysplastic syndrome, paroxysmal nocturnal haemoglobinuria (PNH)
- infiltration, e.g. leukaemia, lymphoma, myeloma, granuloma, myelofibrosis

Anaemia of chronic disease:

- chronic inflammation, e.g. infection (abscess, tuberculosis), connective tissue disease
- malignancy
- endocrine deficiencies, e.g. hypothyroidism, hypopituitarism, Addison's disease
- liver disease
- chronic renal failure
- malnutrition

Haemolytic anaemia:

- intracorpuscular defects, e.g. hereditary spherocytosis, elliptocytosis; haemoglobinopathies—sickle cell anaemia, thalassaemia; paroxysmal nocturnal haemoglobinuria (PNH)
- extracorpuscular defects: e.g. immune–autoimmune (warm or cold antibody) incompatible blood transfusion; hypersplenism; trauma (marathon runners, prosthetic heart valves); microangiopathic—disseminated intravascular

valves); microangiopathic—disseminated intravascular coagulation); toxic—malaria

Signs of a severe anaemia of any cause include pallor, tachycardia, wide pulse pressure, systolic ejection murmurs due to a compensatory rise in cardiac output, and cardiac failure if myocardial reserve is reduced. There may be signs of the underlying cause.

Pancytopenia

Signs

There may be clinical evidence of anaemia, leucopenia (reduced numbers of white blood cells resulting in susceptibility to infection) and thrombocytopenia (petechiae and bleeding)—a deficiency in all three bone marrow cell lines. If confirmed on a blood count, this condition is called pancytopenia.

Causes

- **Aplastic anaemia:** severe hypoplasia of the erythroid, myeloid and platelet precursor cell lines in the bone marrow, resulting in a bone marrow that is fatty and empty of cells. The causes are listed in Table 8.10; 50% have no cause identified.

- **Marrow infiltration** by leukaemia, lymphoma, carcinoma, myeloma, myelofibrosis or granulomata.

- **Other:** acute leukaemia (subleukaemic phase), pernicious anaemia, hypersplenism, systemic lupus erythematosus, folate deficiency, paroxysmal nocturnal haemoglobinuria (PNH).

Acute leukaemia

Leukaemia is a neoplastic proliferation of one of the blood-forming cells. Acute leukaemia presents with marrow failure from progressive infiltration of the marrow with immature cells. The course is rapidly fatal without treatment. Acute leukaemias can be divided into two main types: acute lymphoblastic leukaemia and acute myeloid leukaemia.