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ESSENTIALS Bleeding into the skin may occur for local reasons or as part of a sys- temic disorder. The distribution of lesions is important: widespread lesions suggest a systemic problem, whereas regional lesions suggest that local factors predominate. Widespread flat purpura without erythema should prompt a search for underlying haematological abnormalities such as platelet disorders. Larger (>1 cm) areas of purpura or bruising usually result from coagulation dysfunction. Palpable purpuric lesions, or those with a blanching component, suggest an associated inflammation as can be seen with vasculitis. In patients with acute peripheral ischaemia, it is important to ex- clude embolism. A pressure ulcer (decubitus ulcer, bedsore, pressure sore) is due to localized injury to the skin and/or underlying tissue as a result of pressure alone, or in combination with shear and/or fric- tion. The presence of moisture, particularly relevant in an incontinent patient, leads to a macerated (and therefore more vulnerable) skin. Faecal soiling results in chemical damage to the skin. Acute deep venous thrombosis (see Chapter 16.16.1) may be silent but usually results in skin erythema and limb oedema. Consequences of post-thrombotic vein damage include further deep venous thrombosis, superficial thrombophlebitis, oedema, skin changes, and eventually ulceration. Approximately 70% of leg ulcers are venous in origin; the other 30% resulting from coexistent arterial disease, diabetes, and other skin disease. Most ulcers occur in the gaiter region at or above the level of the malleoli, where the per- sistently elevated ambulatory venous pressure has an adverse effect on the upstream capillary microcirculation. Nearly half of all venous ulcers are associated with deep vein valvular incompetence, usually secondary to previous deep venous thrombosis, while the remainder result from incompetence of the superficial or communicating veins (primary varicose veins). Introduction Vasculogenesis represents the formation of new blood

and lymph- atic vessels from endothelial precursors which share an origin with haemopoietic precursors. This process is not confined to the embryo. Adult bone marrow-derived haemopoietic cells extravasate around nascent vessels and stimulate growth of resident vessels by releasing angiogenic factors. These cells can also function as haemangioblasts, producing both haemopoietic and endothelial progenitors that give rise to new blood vessels (probably not lymphatic vessels). Angiogenesis is the growth of blood vessels through a process of sprouting and remodelling from existing vessels. The lymphatic system develops differently as most lymphatics differentiate from veins. Both blood and lymphatic vessels are crucial for organ growth in the embryo, as witnessed by mutations in some of the key genes in programming for cardiovascular and lymphatic development. For example, deletion of FLT4 (VEGFR3, vascular endothelial growth factor receptor 3, the gene most responsible for lymphangiogenesis) leads to defects in blood vessel remodelling and embryonic death at mid-gestation, indicating an early blood vascular function. The formation of blood and lymphatic vessels is a complex process con- trolled by numerous genes and molecular players. For example, members of the Notch family drive the arterial gene programme; the orphan receptor COUP-TF11 regulates venous specification; and PROX1 commits venous endothelial cells to lymphatic lineage. The vascular endothelial growth factor (VEGF) family of proteins seem most important for vascular and lymphatic endothelial cell sprouting, whereas platelet-derived growth factor (PDGF) and the angiopoietins are responsible for subsequent remodelling, matur- ation, and stability of the newly formed vessels. Close links exist between vessels and nerves; for example, axon-guidance signals such as ephrins and semaphorins allow vessels to navigate to their targets. Skin has been one of the most investigated tissues for under- standing mechanisms of (lymph) angiogenesis, largely because it is so accessible. Angiogenesis is reactivated physiologically during wound healing and repair. In some circumstances—for example, malignancy—the (lymph) angiogenesis activation becomes excessive and harmful so promoting the tumour growth and facilitating metastatic spread. Conversely, in arterial ischaemia the angiogenic switch is insuf- ficient, preventing revascularization and healing of skin ulcers. In recent years, angiogenesis promoters and inhibitors have served as therapeutic targets. For example, the anti-VEGF antibody bevacizumab conveys survival benefit in the treatment of meta- static colorectal, breast, and lung cancer when combined with 23.12 Blood and lymphatic vessel disorders Peter S. Mortimer and Roderick J. Hay

section 23 Disorders of the skin 5710 conventional chemotherapy but not as a monotherapy. One side ef- fect is impaired wound healing. Cutaneous manifestation of blood vessel disorders As the main organ interacting with the environment, the skin vas- culature has to be adaptive. The blood supply has a generous re- serve to meet the requirements of wounding and repair as well as thermoregulation. Skin disorders invariably involve the vasculature, if only because inflammation drives an increase in blood (and lymph) flow. A rash is red (erythema) because of an increase in blood flow. Surface pres- sure, by emptying the compressible venules and veins and reducing capillary inflow, will blanch the skin. Purpura represents extrava- sation of red cells from microvessels into the dermis and cannot be blanched. Simple purpura is not raised, but if it is associated with inflammatory changes of the blood vessels (vasculitis), the mass of cells and oedema makes the purpura palpable. More extensive release of red cells into the skin and subcutis (haemorrhage) will result in a bruise (ecchymosis). Differences between purpura and bruising are simply a matter of degree or depth of haemorrhage. The cause may be due to: thrombophilia; excessive intravascular pres- sure; weakness of the blood vessel wall or surrounding stroma (as seen with steroid therapy). Petechiae are pinpoint lesions of purpura (<2 mm diameter).

Gravitational forces, by increasing venous and consequently capillary pressure, are likely to make purpura more evident in the lower limbs. Telangiectases (named from Greek words meaning ‘end’, ‘vessel’, and ‘extension or dilatation’) are chronically widened capillaries or small vessels. They appear on the skin and mucous membranes as small, dull red, linear, stellate, or punctate markings. Telangiectases (telangiectasias) represent expansion of pre-existing vessels without any obvious new vessel growth (angiogenesis). Unfortunately, clinical appearance may vary greatly according to the site, depth, and type of blood vessel involved. For example, the macular (flat) telangiectases seen in scleroderma, generalized essential telangiectasia, and port- wine stain are produced by dilatation of the postcapillary venules of the uppermost vascular plexus in the dermis. The common raised cherry angioma (Campbell de Morgan spot) is produced by spher- ical and tubular dilatations of capillary loops in the dermal papillae. Telangiectases are discussed in more detail next. Angiokeratomas (as seen in Fabry’s disease and the more common, harmless scrotal angiokeratoma) have the ultrastructure of collecting venules that contain valves and are dark red to black in colour. A spider angioma (spider naevus) represents high flow filling of surface capillaries by a single feeding dilated arteriole which, if blanched, will obliterate the whole spider naevus. The cutaneous le- sions of hereditary haemorrhagic telangiectasia represent small ar- teriovenous anastomoses. Mottling (marbling) of the skin is a physiological response to cold. Vasoconstriction to the skin results in desaturation of the slow flowing blood, leading to bluish (cyanotic) discoloration overlying the polygonal plexus of superficial venules and veins; warming re- stores normal flow and colour. If a similar reduction in flow occurs for pathological reasons, for example, intravascular thrombosis in antiphospholipid syndrome or vasculitis in polyarteritis nodosa, the mottling is fixed and broken up in pattern (livedo reticularis). Necrosis of the skin occurs following vascular occlusion due to intravascular coagulation, vasculitis, emboli, hyperviscosity syn- dromes, or vessel wall thickening. Purpura Simple macular purpura/petechiae Bleeding into the skin may occur for local reasons or as part of a systemic disorder (Box 23.12.1). Widespread flat (macular) pur- pura without erythema (no associated inflammation) should prompt a search for underlying haematological abnormalities such as platelet disorders. Larger (>1 cm) areas of purpura with or without ecchymoses usually result from coagulation dysfunction. The distribution of lesions is important: widespread lesions sug- gest a systemic problem, whereas regional lesions suggest that local factors predominate. For example, purpura confined to the lower limbs would suggest venous hypertension (acute following a deep venous thrombosis (DVT) or chronic from long-standing varicose veins); purpura in chronically sun damaged skin, such as the backs of hands and forearms in older people result from weakness in the supporting collagen of the dermis, particularly in those on steroids; eyelid purpura occurs acutely with raised intravascular pressure from coughing/vomiting or chronically with systemic amyloidosis (panda sign, Fig. 23.12.1). Box 23.12.1 Causes of simple purpura/ecchymoses • Platelet disorders — Thrombocytopenia (in isolation or with myeloproliferative disorders) — Abnormal platelet function/antiplatelet drugs (aspirin, chemotherapy) — Thrombocytosis • Coagulation disorders — Haemophilia and other clotting factor deficiencies — Drugs (anticoagulants) — Thrombophilia (protein C and S deficiency) — Disseminated intravascular coagulation and purpura fulminans — Liver disease (decreased clotting factor synthesis) • Microvascular occlusion — Dysproteinaemias (e.g. hypergammaglobulinaemic purpura) — Cryoproteinaemias — Emboli (cholesterol, oxalate, fat, myoma, septic) — Sickle cell disease • Mechanical — Chronic sun damage (‘senile’ purpura) — Corticosteroids — Scurvy — Amyloid — Inherited collagen disorders (Ehlers–Danlos, pseudoxanthoma elasticum) — Easy bruising syndrome/pinch purpura/’bite’/exercise purpura • Raised intravascular pressure — Coughing, vomiting, Valsalva manoeuvre — Tourniquet — ‘Stasis’

from chronic venous disease (varicose veins, post- thrombotic syndrome) and dependency syndrome

23.12 Blood and lymphatic vessel disorders 5711 Palpable purpura Palpable purpuric lesions, or those with a blanching component, suggest an associated inflammation. Care should be taken to evaluate new purpura as old lesions may show secondary inflammatory changes. Palpable purpura suggests vasculitis or some degree of vessel damage. In dysproteinaemic purpura, hypergammaglobulinaemic purpura, and cryoproteinaemia, a range of purpura may develop from macular purpura to larger necrotic lesions depending upon the size and type of blood vessel involved. Distribution may be widespread or limited to colder or more de- pendent peripheries (lower legs). Larger vessel involvement may produce cutaneous necrosis or livedo reticularis. Vasculitis Vasculitis refers to inflammation and necrosis of any blood vessel (Box 23.12.2; also see Chapter 21.10.2). Minor inflammation of a capillary (capillaritis) may simply increase permeability, resulting in only purpura, whereas involvement of arteries and veins will af- fect tissue perfusion. Vasculitis may be local or systemic, primary, or secondary. Many systemic vasculitides have a cutaneous compo- nent. That cutaneous component will usually be a palpable purpura with multiple lesions distributed symmetrically and usually worse in the lower limbs. More severe inflammation from neutrophil in- filtration will often manifest with pustule formation on top of the purpura. Necrosis of the lesion will produce a small black eschar after a few days. More extensive necrosis and punched out ulceration will ensue. ‘Vasculitic’ is a term inappropriately used to describe focal nec- rotic skin lesions that result from small infarcts due to micro- vascular occlusion. To understand the cause and guide treatment, a skin biopsy is essential in order to distinguish an inflamma- tory vasculitis responsive to systemic steroids from a vasculitis with marked fibrinoid wall changes where steroids are unlikely to be helpful. Other investigations that should be performed include measurement of complement (C4), antiphospholipid antibodies (which cause microvascular thrombosis and a sec- ondary vasculitis), antiendothelial cell antibodies (AECA), and antineutrophilic cytoplasmic antibodies (ANCA), as well as serological tests for connective tissue disorders and screening for distant infection. Microvascular occlusion/cutaneous necrosis Microvascular occlusion may occur for several reasons (Box 23.12.3). While purpura can be the only clinical manifestation, the usual consequences are focal areas of necrosis secondary to failed perfusion, such as the digital finger tip infarcts seen in scleroderma. Disturbances in blood rheology may arise from aggregation of blood contents. Alternatively, the fault may lie with the endothelial wall or lack of blood vessel conformation. If vascular occlusion is extensive or involves larger ves- sels, then well-demarcated areas of skin are infarcted and a black eschar forms. Terminal vessel involvement will cause peripheral gangrene. Purpura fulminans results from Fig. 23.12.1 Amyloid (panda sign). Box 23.12.2 Working classification of systemic vasculitis Small vessel vasculitis • Henoch–Schönlein purpura • Essential mixed cryoglobulinaemia • Waldenström’s hypergammaglobulinaemia • Vasculitis associated with systemic lupus erythematosus and other connective tissue disorders and antiphospholipid syndrome • Urticarial vasculitis • Septic vasculitis • Eosinophilic vasculitis • Drug-induced • Reactive leprosy • Bowel-associated dermatosis–arthritis syndrome (BADAS) • Fungal infection of vessels (immunocompromized) • Behçet’s disease Larger vessel vasculitis • Polyarteritis nodosa — Systemic (including microscopic polyarteritis) — Cutaneous limited • Granulomatous vasculitis — Granulomatosis with polyangiitis (formerly Wegener’s) — Churg–Strauss allergic granulomatosis • Giant cell arteritis — Temporal — Takayasu’s Box 23.12.3 Disorders of microvascular occlusion Intravascular • Platelet plugging (myeloproliferative disorders) • Cryoprecipitates

(cryoglobulinaemia, cryofibrinogenaemia, cold agglutins) • Emboli (cholesterol, crystals, septic) • Sickle cell disease Vessel wall • Raynaud’s disease • Scleroderma, rheumatoid arthritis, dermatomyositis • Fibrinoid vasculopathy/atrophie blanche

section 23 Disorders of the skin 5712 extensive vascular occlusion, the most important cause of which is meningococcaemia. Livedo reticularis Livedo (Box 23.12.4; also Fig. 23.12.2) describes a reticulate network of slow blood flow in the deep skin vascular plexus. When fixed and broken up in its pattern it is always pathological, usually representing thrombosis or vasculitis. In areas of livedo where perfusion is most compromised, purpura and necrosis will occur. Erythema ab igne is a hyperpigmented fixed mottling resulting from prolonged application of heat to the skin. It occurs from sit- ting too close to a fire or from the use of heat pads applied for pain relief. Arterial and peripheral ischaemic disorders Arterial disease will generally compromise skin perfusion only in its advanced stages. Nevertheless, it may present with a dusky red to blue discolouration of skin in the peripheries (hand or foot) or frank ulceration. If the ischaemia is marked, limb elevation above heart level causes skin pallor, while dependency results in delayed but exaggerated hyperaemia. In such circumstances, a history of cardiovascular risk factors, intermittent claudication, and rest pain should be sought. A gross general rule is that arterial disease will cause foot ulceration particularly at sites of pressure including be- tween the toes, whereas venous disease will cause leg ulceration (see next). If peripheral pulses cannot be palpated, simple assessment of peripheral arterial pressure can be undertaken by measuring the ankle brachial pressure index or toe pressures. Arterial pressure in the foot or ankle vessels should be the same or slightly greater than in the arm. If lower limb pressure is less than 80% of the arm, then arterial disease should be considered. Measurements can be unreli- able in diabetes where calcification of the arterial wall prevents oc- clusion by the sphygmomanometer cuff and a false high reading may be obtained. Toe pressures are more reliable in such circumstances. Significant arterial disease demanding investigation is un- common when the foot pulses are easily palpable. Covert arterial disease may manifest with a reduction in oxygen delivery from an- aemia, cardiac dysrhythmias, or any circumstances where cardiac output is reduced. In patients with acute peripheral ischaemia it is important to ex- clude embolism. Thromboangiitis obliterans (Buerger’s disease) may be difficult to distinguish from atherosclerosis. Rarer causes of ischaemia include external arterial compression (popliteal en- trapment or a cervical rib), dissecting or thrombosed aneurysms, ergot poisoning, intra-arterial injections, coagulation disorders, and vasculitis. Management of atherosclerosis includes correction of underlying cardiovascular risk factors where possible. The vast majority of pa- tients with arterial disease die from medical comorbidities, such as myocardial infarction. Small vessel calcification (calciphylaxis) Calcification of arteries is common, but when it affects small ar- terioles, as occasionally happens with hyperparathyroidism, par- ticularly in chronic renal failure, it results in complete vascular occlusion of dermal arterioles (Fig. 23.12.3). Surrounding an area of skin infarction there is extensive livedo reticularis, as well as sub- cutaneous induration from fat necrosis. The pathogenesis is unex- plained. Uraemia and hyperphosphataemia are often more obvious Box 23.12.4 Livedo reticularis • Vasculitis (large vessel) — Polyarteritis nodosa — Mixed cryoglobulinaemia • Antiphospholipid syndrome • Sneddon’s syndrome (livedo with cerebrovascular accident) • Calciphylaxis • Disseminated intravascular coagulation and thrombophilia Fig. 23.12.2 Livedo reticularis. Fig. 23.12.3 Calciphylaxis.

23.12 Blood and lymphatic vessel disorders 5713 than hypercalcaemia. Women are more often affected. An X-ray will reveal extensive vessel calcification and a skin biopsy will dem- onstrate

calcium replacing dermal vessels. The prognosis is poor and treatment unsatisfactory. The management of any renal failure and normalization of the calcium phosphate product are essential. Parathyroidectomy is only indicated if hyperparathyroidism is proven. Thromboangiitis obliterans (Buerger's disease) This appears a distinct condition, usually in young men who are heavy smokers. The aetiology is unknown, but antiendothelial cell antibodies can be present in high titre in active disease. Pathological examination shows that the arterial walls are invaded by inflam- matory cells with changes being segmental or focal and resulting in thrombosis. Nerves and veins may be involved and fibrosis oc- curs in the later stages. Pain is usually the presenting feature because of muscle or nerve ischaemia or thrombophlebitis. Claudication of the foot is especially characteristic. Ulceration or gangrene de- velops early, especially around the sides of the nails or tips of digits. Recurrent superficial or deep venous thrombosis is also common. The proximal pulses (e.g. brachial or popliteal), are usually present while the distal pulses are absent. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are usually raised, antiendothelial cell antibodies are often present, and arteriography is usually diagnostic (normal proximal vessels but multiple stenoses and occlusions in distal vessels with collateralization). The differ- ential diagnosis is early-onset atherosclerosis, embolism, diabetic vasculopathy, and connective tissue disorders. Strict abstinence from smoking is essential. Infusion of a prosta- cyclin analogue has been shown to be effective, but medical treat- ment is otherwise unhelpful and referral to a vascular surgeon is recommended. Sickle cell disease Perimalleolar, painful leg ulcers develop in association with sickle cell disease. While the ulceration may be attributed to sickling of erythrocytes causing microvascular occlusion and skin infarction, similar ulcers have been reported in other forms of chronic haemo- lytic anaemia. Low, steady state levels of haemoglobin, intensity of haemolysis, and sickle cell anaemia with thalassaemia genotypes ap- pear associated with ulceration. Leucocyte adhesion may initiate occlusion episodes in a manner similar to venous ulceration (in the same site); indeed, gravitational factors or venous disease may contribute to nonhealing of sickle cell ulcers. Secondary infection may also discourage healing, particu- larly in tropical climates. Treatment is unsatisfactory. Spontaneous healing may occur after some weeks irrespective of intervention; otherwise, bed rest and local compression may be necessary. Raynaud's phenomenon/syndrome Raynaud's phenomenon is defined as episodic digital ischaemia occurring in response to cold, emotional stimuli, or vibration. It is characterized by sequential colour changes: white—blue—red. Pallor is essential for the diagnosis but may be short-lived and be succeeded by prolonged cyanosis, making distinction from acro- cyanosis difficult. Raynaud's phenomenon may be primary (idio- pathic), when it is referred to as Raynaud's disease, or secondary to a range of diseases, most notably connective tissue disorders. Perniosis/acrocyanosis (cold injury) Chilblains (perniosis) are localized, tender, red, and often itchy le- sions which may blister or ulcerate. They occur as an abnormal re- sponse to cold. Perniosis of fingers and toes can be associated with cryoglobulinaemia, myelodysplastic disorders, lupus erythematosus ('chilblain' lupus), and anorexia or malnutrition. In contrast to per- ipheral (acral) chilblains, perniosis can occur overlying extensive subcutaneous fat (e.g. thighs), because the skin is more vulnerable to cold as a result of insulation by the fat. Acrocyanosis is a persistent bluish mottled discoloration of the skin, usually over hands and feet. Unlike Raynaud's phenomenon where digital artery vasoconstriction occurs, it arises due to dila- tation of small venules resulting in extremely slow venous flow fol- lowing physiological vasoconstriction of arteriolar inflow in response to cold. The backs of the hands and fingers look blue and puffy (from oedema). While connective tissue disorders, antiphospholipid syn- drome, neuropathies, and cryoglobulinaemia should be considered, the vast majority of cases are constitutional. Frostbite is the result of acute freezing of

tissues including the blood vessels. Hands, feet, ears, nose, and cheeks are most often af- fected. After the initial pain, the affected part becomes pain-free and the skin becomes shiny and white. Reperfusion injury occurs on warming with necrosis of tissue. Long-term scarring and abnormal autonomic nerve responses may occur. Trench or (cold) immersion feet are similar, but the tissues do not freeze. Vascular occlusion results in tissue necrosis and neuropathic changes. The syndrome is not uncommon in the homeless popula- tion living in the United Kingdom. Erythromelalgia (erythermalgia) This is a condition of painful red extremities in which the sensation of burning is induced by warmth. Patients will complain of intolerable burning relieved only by dunking their feet in cold water or wrapping in towels kept in the freezer. There is consequently a danger of cold immersion injury. The term erythermalgia was introduced to sep- arate primary cases (erythermalgia) from those (erythromelalgia) secondary to underlying disorders such as thrombocythaemia and other myeloproliferative disorders. The fundamental cause is now known to be a fault in sodium channels discovered by identifying mutations in the gene SCN9A, which encodes the voltage-gated so- dium channel NaV1.7. Mutations alter channel gating behaviour in a manner that increases nociceptive neuron excitability. Cooling re- duces the threshold of activation of the abnormal sodium channels. Although fundamentally a neuropathy, involvement of skin blood vessels results in persistent vasodilatation. Treatment with carba- mazepine and similar drugs acting on sodium channels can help. Complex regional pain syndrome (reflex sympathetic dystrophy, causalgia, Sudeck’s atrophy) This is a syndrome of chronic pain with altered or heightened sen- sation, hyperhidrosis, and swelling. Allodynia is characteristic. The increased blood flow combined with a reluctance to use the limb (movement triggers pain) results in deep redness of the skin and swelling. Increased blood flow is an important diagnostic feature of early complex regional pain syndrome and can often be dem- onstrated on a three-phase bone scan. Treatments include graded physical therapy and neuropathic pain relief.

section 23 Disorders of the skin 5714 Arteriovenous fistulae Persistent arteriovenous shunts cause local venous hypertension and skin changes as a result. Arteriovenous fistulae consist of direct connections between large arteries and veins and are always pathological. Congenital forms result from a failure of embryo- logical differentiation. Acquired forms are almost always traumatic and, if large, can cause significant cardiovascular effects. Increased warmth of the skin together with signs of increased venous pres- sure result (e.g. varicose veins). A palpable thrill and murmur on auscultation may be detected. Duplex ultrasonography is the in- vestigation of choice. Embolization may be the best therapeutic option. Pressure ulcers A pressure ulcer (decubitus ulcer, bedsore, pressure sore) is due to localized injury to the skin and/or underlying tissue as a result of pressure alone or in combination with shear and/or friction. The presence of moisture, particularly relevant in an incontinent patient, leads to a macerated, and therefore more vulnerable, skin. Faecal soiling results in chemical damage to the skin. Sustained pressure occurs most commonly when an individual is debilitated or paralysed and therefore cannot move to relieve pres- sure. Neurological deficit predisposes to a lack of movement or a lack of sensory feedback to pain, as well as impaired autonomic con- trol. Observations on patients with amyotrophic lateral sclerosis, a condition in which pressure sores are rarer, suggest a role for ciliary neutrophic factor. Defective collagen synthesis may be promoted in anaesthetic skin as well as by certain drugs such as corticosteroids. Other factors contributing to the development of pressure ulcers in- clude arterial ischaemia, hypotension, dehydration, malnutrition, cachexia of cancer, prolonged pyrexia, hypermetabolic states, and hypoalbuminaemia. Patients undergoing extracorporeal circulation are particularly at risk. Different classifications exist, but that of the National Pressure Ulcer Advisory Panel is

simple to use. Stage I is nonblanchable ery- thema over a bony prominence; stage II partial thickness loss of dermis; stage III is ulceration into subcutaneous fat; stage IV is ex- posure of muscle, bone, or joint. Deep sores will often result in more necrosis of fat or muscle than skin, so a cavity wound with under- mined edges occurs. Prevention should involve recognition of the at-risk patient. Several risk scales exist with the Norton scale being the best known. All at-risk patients should have a pressure-relieving mat- tress in addition to frequent repositioning. Static support systems mould around the patient so distributing pressure over a greater area, while dynamic support systems vary the pressure distribu- tion by, for example, the use of air-fluidized and low air loss beds. The lateral position must be avoided and nursing in the prone position is advised. Any medical conditions should be controlled and the nutritional status assessed; spasticity should be relieved where possible. When pressure is relieved, necrotic tissue will sep- arate naturally but eschar is best removed surgically. In principle, wounds heal best when moist and clear of infection and when exudate is absorbed away from wound surfaces. The choice of dressing depends upon the stage and state of the wound. Surgical debridement is necessary for removal of necrotic tissue and radical excision with reconstruction may be needed for extensive cavity wounds. Venous disorders Chronic venous disease Veins are responsible for venous return. Muscles in the calf and foot compress and empty veins thereby lowering venous pressure. Valves prevent the reflux of blood. Valve failure results in min- imal respite from high venous pressures during exercise. Venous pressure at the ankle is normally 70–100 mm Hg dropping to 0– 30 mm Hg on exercise and remaining at approximately 55 mm Hg while sitting. Long periods spent sitting with legs dependent, reduced exercise levels, and obesity encourage venous hyperten- sion with sustained pressures of 50–100 mg Hg. Venous reflux due to valve failure will result from inherent vein or valve weak- ness in primary varicose veins, or damage to veins usually from deep venous thrombosis. Persistently elevated venous pressure af- fects capillary pressure and endothelial function that results in a complex train of events which adversely affects skin viability in the gaiter region. The clinical consequences are varicose veins, oedema, haemosiderin skin pigmentation, varicose eczema, lipodermatosclerosis, and ulceration signs that are used for the CEAP Classification (class, aetiology, anatomy, pathophysiology) of chronic venous disease (CVD). Deep venous thrombosis (DVT), post-thrombotic syndrome, and venous obstruction Acute deep venous thrombosis (DVT) may be silent but usually re- sults in skin erythema and limb oedema. Iliac vein thrombosis may be easily missed on compression ultrasonography but should be sus- pected if whole limb swelling is associated with a mottled erythema. Post-thrombotic (postphlebitic) syndrome complicates 50–75% of DVTs. The more proximal the deep venous thrombosis, the greater the risk. Consequences of post-thrombotic vein, and particularly valve, damage include further deep venous thrombosis, superficial thrombophlebitis, oedema, skin changes, and eventually ulceration. Lipodermatosclerosis and prominent perforating veins are characteristic skin changes. Lipodermatosclerosis refers to a com- bination of skin and subcutaneous changes seen with chronic con- gestion, due to venous or lymphatic hypertension. Fat inflammation (panniculitis) combined with phlebitis and dermatitis results, over time, in fat atrophy and fibrosis which manifests as hardening and retraction of the skin, leading to the appearance of an inverse champagne-bottle shape to the gaiter region. The most common cause of deep vein obstruction is deep venous thrombosis but nonthrombotic causes include iliac vein compres- sion from pelvic tumours or aneurysms, tumours, or aneurysms compressing the deep femoral vein, and a Baker’s cyst may com- press the popliteal vein. Abdominal obesity interferes with venous drainage, particularly in the sitting position. Retroperitoneal fibrosis can obstruct the iliac veins. Superficial thrombophlebitis Thrombosis in a superficial vein usually develops because of slow flow within a

varicose vein. Pain, heat, and tenderness over a palp- able nodule or cord is characteristic. Cellulitis may extend for

23.12 Blood and lymphatic vessel disorders 5715 some distance, sometimes making distinction from infection dif- ficult. In the absence of any varicose veins, superficial thrombo- phlebitis usually occurs from trauma due to an intravenous cannula with or without extravasation of an irritating substance (e.g. chemotherapeutic agent). When recurrent or widespread, consider- ation should be given to the possibility of a thrombophilic state such as protein C or S deficiency, antiphospholipid syndrome, Behçet's syndrome, or underlying cancer (thrombophlebitis migrans). Mondor's disease is diagnosed when palpable tender cords de- velop around the axilla, breast, or chest wall. Such cords, which may represent thrombosed veins or lymphatics, may 'bowstring' across the axilla (axillary web syndrome) and extend down the arm, cre- ating a 'guttering' effect with the limb outstretched. Leg ulcers Approximately 70% of leg ulcers are venous in origin; the other 30% result from coexistent arterial disease, diabetes, and rarer skin disorders (Box 23.12.5). Most ulcers occur in the gaiter re- gion, at or above the level of the malleoli, where the persistently elevated ambulatory venous pressure has an adverse effect on the upstream capillary microcirculation. The consequent changes to the microvasculature and interstitium result in a failure of wound healing after trauma. Nearly half of all venous ulcers are associ- ated with deep vein valvular incompetence, usually secondary to previous DVT, while the remainder results from incompetence of the superficial or communicating veins (primary varicose veins). Community surveys suggest an overall prevalence of 0.2% of the population with the highest rates in older women. Once treated, up to 72% can recur. Capillary congestion conveys a bluish erythema to the skin often with purpura and oedema. Over time, the purpura turns to a brown 'rust' discoloration due to haemosiderin deposition. Scratching (due to 'varicose' eczema) or other trauma will lead to skin break- down. Once ulceration has occurred, wound exudation will further damage surrounding skin, promoting more skin inflammation (ec- zema/dermatitis) and necrosis. Underlying oedema will further fuel the exudation process. Indeed, leg oedema is an invariable associ- ation of a venous ulcer and always a sign of inadequate treatment. The 'congestion' resulting from the venous hypertension and oe- dema can cause a persistent redness to the skin resembling cellulitis from which clinical distinction can be difficult. The diagnosis of a venous ulcer is essentially clinical. Venous du- plex Doppler ultrasound examination can be normal in obese pa- tients who spend long periods in a chair, whereupon 'functional venous hypertension' occurs. Nevertheless, venous duplex Doppler is essential for identifying ulcers due to surgically correctable superficial venous incompetence. Arterial ischaemia can be ex- cluded by measuring the ankle brachial pressure index, although it is unreliable in diabetes and other circumstances where compres- sion by a sphygmomanometer cuff is not possible due to arterial wall calcification. Falsely high readings may be obtained and arterial duplex Doppler may be needed. Sensory testing is always important in dia- betic patients, not just because impaired sensation can lead to ul- ceration but also because compression therapy applied unwittingly may contribute to ulceration. Any ulcer with a raised border or one that does not respond to therapy should undergo biopsy to exclude malignancy. First-line therapy for venous ulceration is compression therapy and exercise. The concept is to reduce venous pressure, particularly during walking, by improving calf muscle pump function and by opposing gravitational venous reflux. Exercise and movement are to be encouraged and preferred to rest. Long periods spent sitting and standing are discouraged, but when resting the leg(s) should be ele- vated, ideally with the ulcer just above heart level, to ensure the max- imum reduction in venous pressure. Falling asleep in a chair with the legs elevated on a stool is of no use. Obesity should be

tackled effectively. Heart failure must be controlled, as right-sided failure further elevates leg venous pressures. Severe anaemia should be cor- rected, although chronic leg ulcers will result in a degree of chronic anaemia. Graduated, multilayer, high-compression bandage regimens cap- able of sustaining compression for a week at a time should be the first line of treatment. In general, it is treatment of the leg rather than the wound that is important. Nevertheless, eczema and exudation must be controlled. Antibiotics, topical or oral, are of no value unless there is clear evidence of clinical infection or if streptococci are colonizing Box 23.12.5 Cutaneous necrosis • Venous disease — Stasis, congenital, post-thrombotic • Coagulation defects — Disseminated intravascular coagulopathy — Purpura fulminans — Protein C and S deficiency, antithrombin III deficiency • Infection — Viral, gas gangrene, Buruli ulcer, tuberculosis, leprosy, swimming pool granuloma, Meleney's anaerobic ulcer, synergistic gangrene, streptococcal, superficial or deep fungus, syphilis, yaws, leishman- iasis, Haemophilus ducreyi, Fusobacterium ulcerans • Blood disorders — Hyperviscosity, dysglobulinaemia, sickle cell anaemia, spherocytosis, polycythaemia • Vasculitis • Pyoderma gangrenosum • Vasculopathy — Arterial disease, Buerger's disease — Antiphospholipid syndrome — Raynaud's disease — Calciphylaxis • Emboli • Metabolic — Hyperhomocysteinaemia • Venoms (snake and spider bites) • Neuropathic — Leprosy, diabetes • Drugs — Anticoagulants — Ergot — Chemotherapy infusions — Illicit drugs • Malignancy (or paraneoplastic) — Melanoma, squamous cell carcinoma, Kaposi's sarcoma, leu- kaemia, secondary deposits • Physical damage from contact

 the ulcer. Beneath the compression, a simple low adherent wound dressing is advisable. Foot ulcers It is unusual to see ulcers of purely venous origin below the line of the edge of the shoes, although atrophie blanche/livedoid vasculopathy (Fig. 23.12.4) can occur on the foot. Vasoconstriction operates more powerfully in the feet than the legs and it is here that the earliest effects of arterial insufficiency or neuropathy manifest. Pressure or friction points suffer first. In populations who do not wear pro- tective shoes, the foot is prone to infection. It was previously thought that microangiopathic arteriolar occlusion disease was responsible for the tissue necrosis in the diabetic foot. Tissue necrosis and ul- ceration are now believed to result from narrowing and occlusion of the main arteries of the leg below the knee, complicated by septic oc- clusive vasculitis of the terminal arteries. Consequently, correction of the occlusive artery disease by angioplasty and the infection by aggressive antibiotic treatment and debridement are recommended. Telangiectasis Telangiectases (Box 23.12.6) are chronically expanded capillaries or small venules. They usually appear in the skin as spidery red lines, as on the facial cheeks, but can be punctate, as in hereditary haemor- rhagic telangiectasis (HHT), or be flat red macules as seen in the mat telangiectasis of scleroderma. Telangiectases represent enlargement of pre-existing vessels without any apparent angiogenesis (con- versely angiomas imply a vascular malformation due to an anomaly of embryological development or alternatively a form of tumour). Secondary telangiectases Telangiectases commonly represent the effect of wear and tear on the skin and are particularly frequent on ageing, light-exposed skin. Atrophy of the skin and the resulting lack of dermal support to the microvasculature will result in telangiectases, as may follow smoking and ultraviolet (UV) radiation. Prolonged vasodilatation may be followed by permanent telangiectases as in rosacea. Varicose veins are frequently the cause of telangiectases of the leg where an arborizing pattern may result. The colour of the telangiectases depends on the calibre of the dilated venule. Large dilatations (<1 mm) are dark blue and palpable. The smallest (0.1 mm), most superficial telangiectases are red and barely empty when the leg is raised. Telangiectases around the lower border of the ribs are virtually physiological in older age groups. There are increasing

reports of telangiectases associated with calcium channel blocking drugs. Connective tissue disorders The presence of telangiectases is an important diagnostic sign in lupus erythematosus, dermatomyositis, scleroderma, and overlap syndromes. Nailfold telangiectases can usually be seen with the naked eye, but an ophthalmoscope will reveal fewer but larger, tortuous capillaries often with haemorrhage. Scleroderma results in mat telangiectases which can mimic the telangiectases of HHT both in appearance and distribution (face and hands), but in heredi- tary haemorrhagic telangiectasis they are more obvious on mucous membranes. Telangiectases can occur with cutaneous mastocytosis and angiotropic (intravascular) lymphoma. Spider naevi (arterial spider, spider angioma) Spider telangiectases occur in up to 15% of a normal population and are even more common in children and pregnant women. They are char- acteristically found in liver disease of which they may be a presenting sign. A relationship to high oestrogen levels has been suggested. The main vessel of the spider is an arteriole. The high blood flow fills the capillaries radiating from the vessel. Occlusion of the ar- teriole with a pin head blanches the whole lesion; refilling occurs first from the arteriole and is pulsatile. Spider naevi are only seen above heart level (e.g. upper body). Cherry angiomas (Campbell de Morgan spots) These are common in middle age, but disappear in extreme old age. They can be confused with petechiae when small and flat because they do not blanch. Larger angiomas are raised and dome- shaped. They have no known medical associations. Fig. 23.12.4 Atrophie blanche represented by red dots (enlarged tortuous capillaries) between which are areas of white scarring. Box 23.12.6 Elangiectasia Secondary • Prolonged vasodilatation (e.g. rosacea, varicose veins) • Photoageing (sun damage, smoking) • Spider naevi • Radiotherapy • Topical steroids • Connective tissue disorders (scleroderma, lupus erythematosus, dermatomyositis) • Mastocytosis • Cutaneous lymphoma Primary • Vascular birthmarks (e.g. port-wine stain) • Hereditary haemorrhagic telangiectasia • Ataxia—telangiectasia • Generalized essential telangiectasia

 Venous lakes (phlebectasia) Greatly dilated, thin-walled venules occur on the face, lips, and ears of older patients. Because they contain desaturated blood, venous lakes are dark blue to black and can be confused with melanoma until compressed and emptied. Rosacea and flushing Rosacea is a diagnostic term applied to a spectrum of abnormal- ities in the skin and eyes. Cutaneous features include persistent redness of exposed skin (usually the face) with telangiectases, flushing, oedema, erupting small inflammatory papules (pimples) and pustules, and, in chronic cases, hypertrophy of the sebaceous glands with fibrosis (rhinophyma). Ocular changes occur in more than 50% of patients and range from the common blepharitis and conjunctivitis to the rare, sight-threatening keratitis. The onset is usually between 30 and 50 years old and more common in women and in patients with fair skin. Ambient heat, alcohol, sunlight, hot drinks, spicy food, and stress appear to exacerbate the condition. The use of topical fluorinated steroids and tacrolimus can trigger a rosacea-like eruption. Persistent central facial erythema is the most common feature. Telangiectases are prominent and, together with inflammation, cause the red complexion. Appearances may mimic the ‘butterfly’ rush of lupus erythematosus, but a skin biopsy will confirm the presence of ectatic capillaries (and lymphatics) in the dermis. Inflammation may be minimal but, if present, is usually follicular (folliculitis). Photo (sun) damage and oedema frequently coexist. Flushing is usually provoked by ambient temperature, alcohol, hot or spicy food, menopause, or anxiety. Prolonged episodes of severe flushing accompanied by sweating, flushing, sweating not limited to the face, and associated systemic symptoms such as diarrhoea, wheezing, headache, or palpitations should prompt investigation for carcinoid syndrome, phaeochromocytoma, or mastocytosis. Treatment of the

erythema and flushing component of rosacea is difficult. A therapeutic six-week trial of antiacne-type antibiotics (e.g. oxytetracycline 500 mg twice daily or metronidazole 200 mg twice daily) is worthwhile to resolve any underlying inflammation contributing to symptoms. Such first-line treatment usually works well for any papules or pustules. If telangiectases are prominent, laser therapy can be helpful. Because relapse of rosacea is common, avoidance of exacerbating factors, such as alcohol, is advised and topical metronidazole cream has proved effective. Perioral dermatitis is a persistent erythematous eruption con- sisting of tiny papules and pustules primarily distributed around the mouth. It occurs predominantly in younger women and is associ- ated with the use of topical steroids. Indeed, the steroid potency as- sociates with risk of disease and it is important to stop steroid usage. Response to treatment with four weeks of oral tetracycline is usually excellent. Topical tetracycline and topical metronidazole can also be effective. Primary telangiectases Hereditary haemorrhagic telangiectasia (HHT, Osler–Rendu– Weber disease) Hereditary haemorrhagic telangiectasis is an autosomal dominant disorder characterized by epistaxis, cutaneous telangiectases, and visceral arteriovenous malformations (AVMs). Mutations in at least two genes are responsible. Endoglin (ENG) on chromosome 9 is the gene for HHT1, where there is a higher preva- lence of cerebral and pulmonary arteriovenous malformationss, while activin receptor-like kinase 1 (ACVRL1 or ALK1) on chromo- some 12 causes HHT2 which has a milder, later onset phenotype with an increased number of hepatic arteriovenous malformationss. ENG and ALK both encode a homodimeric integral membrane glycoprotein which is the surface receptor for TGFβ. Recurrent epistaxis is usually the presenting symptom at, or just after, puberty but onset may begin in childhood. Telangiectases are punctate, or sometimes papular, and most commonly seen on the lips, mucous membranes, and fingers. They represent micro- vascular arteriovenous anastomoses causing the visible dilatation of postcapillary venules. Lesions occur on the nasal septum, naso- pharynx, and throughout the gastrointestinal tract where they may be demonstrated by endoscopy or magnetic resonance angiography, but not by barium studies. Pulmonary arteriovenous malformationss cause dyspnoea, cyanosis, and clubbing and are seen on chest X-ray. Liver enlargement and cirrhosis can occur (HHT2). An association with juvenile polyposis has been described. The diagnosis is based on family history and clinical phenotype. Molecular genetic testing de- tects mutations in 60–80% of individuals. Prenatal testing is available. In mild cases, no treatment is usually needed except the control of any anaemia, possibly including iron replacement. Tranexamic acid, by regulating the ALK1/endoglin pathway, may be beneficial in some patients. Symptomatic skin or mucous membrane lesions can be destroyed by cautery or laser. Recurrent nasal bleeding and pul- monary arteriovenous malformationss may demand more extensive surgery or embolism approaches. Antibiotic prophylaxis is recom- mended for dental and invasive procedures. Ataxia-telangiectasia (Louis-Bar syndrome) Ataxia-telangiectasia syndrome is a rare recessive disease with pleio- tropic involvement of nervous and lymphoid systems caused by mu- tations in the ataxia-telangiectasia-mutated (ATM) gene. Defective excision repair of DNA damaged by ultraviolet (UV) light, γ, or X-rays is responsible. The syndrome presents with telangiectases, progressive cerebellar ataxia, combined immuno- deficiency, and a marked susceptibility to cancer. A diminished level, or absent, IgA is characteristic. Telangiectases may be present as early as the second year and first appear on the bulbar conjunctiva and subsequently on the ears, eyelids, and the butterfly area of the cheeks. Bleeding is un- common. Recurrent sinus and pulmonary infections are frequent and may dominate the clinical picture. X-ray investigation should be restricted. The laboratory diagnosis relies on increased serum α-fetoprotein levels and cellular sensitivity to ionizing radiation. Molecular, genetic, and prenatal testing for the presence of the ab- normal ATM gene is available. No proven treatment exists. Antioxidants such as vitamin E

and α-lipoic acid are recommended. Intravenous immunoglobulin ap- pears to reduce the number of infections. Vascular birthmarks Vascular birthmarks usually develop during childhood and are therefore naevoid in origin (naevus is Latin for ‘maternal impression’

section 23 Disorders of the skin 5718 or ‘birthmark’). Many, possibly all, birthmarks represent clones of genetically altered cells arising from mosaicism during somatic mu- tation. It is important to distinguish between haemangiomas and vascular malformations, although it may prove difficult on clinical grounds. Haemangiomas are proliferative blood vessel tumours, whereas vascular malformations represent structural defects arising from vascular development. Vascular malformations can be high flow (arterial or arterio- venous fistulas) or low flow (capillary, venous, lymphatic, or mixed) types. In general, vascular malformations possess no endothelial proliferation, are present at birth, and do not involute. Port-wine stain (naevus flammeus) These are characterized clinically by persistent macular erythema from birth, and pathologically by ectasia of superficial dermal capil- laries. Port-wine stains have a greatly diminished density of perivas- cular nerves. Associated eye and brain abnormalities occur in 8–15% of port-wine stains on the head and neck. The most significant ocular problem is glaucoma, particularly if the eyelids are involved. The Sturge–Weber syndrome represents involvement of the leptomenin- geal vasculature giving rise to epilepsy and neurological deficit. Klippel–Trénaunay syndrome The association of a port-wine stain with tissue overgrowth and vein abnormalities usually affecting one hindquarter is termed the Klippel–Trénaunay syndrome. The port-wine stain is present from birth with excessive longitudinal bone growth occurring during childhood. Increased limb girth suggests soft tissue overgrowth. Vein abnormalities, particularly aberrant veins such as the lateral thigh vein (embryological remnant), progress from puberty. Lymphatic abnormalities (lymphoedema and lymphangioma) are not un- common. Sometimes the whole of one side of the body is affected with hemihypertrophy. There is a high rate of thrombosis involving both superficial and deep veins. Venous ulceration may occur. The differential diagnosis includes the Parkes Weber syndrome in which limb hypertrophy is associated with multiple arteriovenous anastomoses. The Proteus syndrome is highly variable (protean) in its clinical presentation. Mandatory general criteria include mosaic distribution of lesions, a progressive course, and a sporadic occur- rence. Connective tissue naevi are pathognomonic and epidermal naevi, tissue overgrowth, lipodystrophy, and vascular malforma- tions (including lymphatic) may occur. Mutations in PTEN may be present. The Proteus-like syndrome is undefined and refers to the presence of significant clinical features falling short of diagnostic criteria. The Servelle–Martorell syndrome encompasses vascular malformations associated with limb hypoplasia (shortening). Cutis marmorata (reticulate vascular naevus) This is a combined capillary and venous birthmark form of livedo reticularis. Appearances are very similar in that a fixed mottled or marbled look to the skin results from an uneven perfusion and slow flow in the venous component. Atrophy of skin and subcutaneous tissue makes the reticulate pattern even more livid. Limbs are most commonly involved, in which case hypoplasia of underlying bones may occur. A range of other abnormalities can occur including glau- coma, macrocephaly, and cardiac abnormalities. Because of natural improvement with time, treatment is rarely needed. Blue rubber bleb naevus syndrome The most typical lesions are small, compressible, blue to purple rub- bery nodules occurring anywhere on the body surface as well as on lips, mouth, and penis and within the gastrointestinal tract where they frequently bleed. The resulting anaemia may be profound. Other organs including the lung and the central nervous system may be involved. Nodular blue lesions under the tongue are charac- teristic. Onset is usually during childhood but may be in adult life. Once developed, lesions persist for life. Treatment is directed at con- trolling

bleeding and anaemia. Maffucci’s syndrome (dyschondroplasia with haemangiomas) Despite the name, the soft, bluish cutaneous protrusions are not haemangiomas but small venous malformations. They persist and may grow into large lesions resembling a bunch of red grapes. Hard nodules arising from the bones, especially on the hands and feet, represent enchondromas which are radiologically translucent. Bone growths are delayed and pathological fractures occur with slow re- covery. Deformity of the hands and feet may be gross. Malignancy is common, particularly chondrosarcoma but also angiosarcoma and ovarian cancer. Dyschondroplasia can occur without the vascular malformations (Ollier’s disease). Patients require careful follow-up with imaging or biopsy of any lesions that enlarge or cause symptoms. Angiokeratoma corporis diffusum (Fabry’s disease) Angiokeratomas are characterized clinically by the presence of dark red to black, flat to slightly raised, vascular lesions which are most commonly seen on the scrotum where they are harmless. Histology reveals superficial vascular ectasia (expanded capillaries) with an overlying increase in surface keratin and so they represent capillary malformations rather than haemangiomas. Anderson–Fabry disease should be considered when lesions are clustered as small telangi- ectatic spots between the umbilicus and the knees. This is an X-linked disorder (MIM 301 500) in which deficiency of lysosomal hydrolase and galactosidase leads to deposition of globotriaosylceramide in cells throughout the body. It causes severe, painful neuropathy with progressive renal, car- diovascular, and cerebrovascular dysfunction and early death. The surface angiokeratomas affect both skin and mucous membranes and usually appear shortly before puberty. Lesions can be up to 4 mm across but do not blanch on pressure due to the presence of red cells trapped within the ectatic capillaries. Their persistence distinguishes the lesions from purpura. Skin biopsy will confirm an angiokeratoma. The finding of albuminuria or haematuria and, more specifically, ‘mulberry-like’ cells in the urinary sediment sug- gests a diagnosis of Fabry’s disease, but the finding of decreased X-galactosidase A in plasma or isolated leucocytes is diagnostic. Disease causing mutations in the GLA gene can be found in all af- fected individuals and in most carriers. Vascular tumours Infantile haemangioma Usually appearing in the first year of life, these common haemangi- omas characteristically have an initial proliferative and then a later

23.12 Blood and lymphatic vessel disorders 5719 involutional phase. Although previously known as a ‘strawberry’ naevus or haemangiomas, the terms strawberry, capillary, and cav- ernous have been abandoned for the preferred superficial, deep, and mixed haemangiomas. Over 60% will develop on the head and neck. The principal features distinguishing infantile haemangiomas from vascular malformations are that they are not present at birth and that they undergo spontaneous resolution. Few associations exist, but posterior fossa brain abnormalities may occur as in the PHACE(S) syndrome (posterior fossa malformations, haemangiomas, arterial anomalies, coarctation of the aorta and other cardiac defects, eye abnormalities, and sternal abnormalities). Lumbosacral haemangi- omas can be a marker of spinal dysraphism. Glomus tumour (glomangioma) Glomus cells are modified smooth muscle cells found in glomus bodies which are believed to function as temperature receptors. Solitary glomus tumours are characteristically found in finger tips and in nail beds and are exquisitely tender. Multiple glomangiomas can be familial. Pyogenic granuloma (lobular capillary haemangioma) Pyogenic granuloma is a misnomer. Neither pyogenic nor granu- lomatous, the lobular capillary haemangiomas are benign vascular tumours that represent excessive production of granulation tissue usually in response to injury. Bleeding can be profuse and persistent. They can be indistinguishable clinically from amelanotic melan- omas and should be treated by excision biopsy, although curettage will suffice if confident of the diagnosis. Kaposi’s sarcoma Kaposi’s sarcoma (KS) is a multifocal tumour characterized by dysregulated angiogenesis,

a proliferation of spindle cells, and ex- travasation of inflammatory cells and erythrocytes. Human herpes- virus 8 appears causal. Kaposi's sarcoma is the most common cancer in HIV-infected individuals and in sub-Saharan Africa. There are four clinically distinct subsets of Kaposi's sarcoma: (1) classic forms, as described originally by Kaposi, are found mainly in older men. Red to purple lesions appear on the feet and spread proximally. Usually flat patches (like purpura or purple stain) or slightly raised lesions can progress to plaques or nodules. Limb oedema (lymphoedema) fre- quently coexists. The characteristic colour, slow development, and multifocal distribution should suggest the diagnosis. (2) Endemic Kaposi's sarcoma is found in equatorial Africa. Crops of cutaneous vascular lesions develop, usually on the lower limbs, associated with gross oedema, lymphadenopathy, and sometimes visceral involvement. (3) Iatrogenic forms result from immunosuppres- sion in transplant patients and after cytotoxic chemotherapy. Both systemic and cutaneous involvement occurs. (4) HIV-associated Kaposi's sarcoma occurs most commonly in homosexual men where dark red to purple stains may appear rapidly and occur any- where on the skin surface or mucous membranes, particularly in the soft palate. Skin biopsy is characteristic, demonstrating a proliferation of jagged, irregular lymphatic-like vascular channels lined by a single layer of bland endothelial cells. An inflammatory infiltrate is as- sociated with red cell extravasation and haemosiderin deposition (explaining the purple to brown skin discoloration on blanching). A network of bland spindle cells develops. Staining for HHV-8 should be positive in all tumour cells. HIV testing should be under- taken. The differential diagnosis would include causes of purpura, venous disease (lower limb only), and angiosarcoma. No treatment may be required in asymptomatic indolent classical forms. Superficial radiotherapy is rapid and effective for localized diseases. Cases related to AIDS may regress with HAART (highly ac- tive antiretroviral therapy). Doxorubicin, bleomycin, and vincristine chemotherapy is widely regarded as first-line treatment, although liposomal anthracyclines have also proved effective in advanced dis- ease. A reduction of immunosuppressant therapy will often resolve lesions in transplant patients, but this is not always possible without jeopardizing the transplant. Sirolimus inhibits the progression of dermal Kaposi's sarcoma in kidney transplant recipients while pro- viding effective immunosuppression. Angiosarcoma (lymphangiosarcoma) This is a malignant vascular tumour arising from both vascular (and lymphatic) endothelium which occurs in three settings: (1) as a pri- mary event on the face, scalp, or neck usually in older people; (2) as- sociated with lymphoedema (although best described following mastectomy (Stewart–Treves syndrome)) lymphangiosarcoma can occur in any long- standing lymphoedema); and (3) postirradiation. In all types of (lymph) angiosarcoma, the first sign may be a bruise. Dark red to black plaques and nodules appear, spreading rapidly. Oedema and haemorrhage are common. The diagnosis is through skin biopsy. Defining the limits of the tumour is difficult and imaging is unhelpful. Consequently, wide excision, if possible, is the only treatment and the prognosis is poor. Lymphatic disorders The lymphatic system has long been a neglected area of medicine largely because, lymphoma excepting, it has not produced any life- threatening diseases nor has the technology been available to indi- cate the contribution of lymphatics to pathology. See Section 16 for further descriptions of lymphatic disease. The recent discovery of specific genes and proteins, however, has catapulted lymphatic biology onto the research agenda of cancer spread, infection and inflammation, asthma, organ transplant rejec- tion, and lymphoedema. The lymphatic system is essentially a drain, returning to the blood circulation protein and fluid unwanted by the tissues. This com- pletes the extravascular circulation of fluid and protein and main- tains tissue volume homeostasis. Lymph drainage is also an essential part of the body's immune defence. Cells such as extravasated leuco- cytes and activated antigen-presenting cells enter the initial lymph- atics and are transported to lymph nodes where specific

immune responses to foreign materials are generated. Lymphatic capillaries are thin-walled vessels but capacious and potentially larger than nearby blood capillaries. Lymphatic capil- laries absorb protein and fluid from the interstitial space and initiate lymph drainage and hence are referred to as ‘initial lymphatics’. They drain into downstream ‘collecting lymphatics’ which, unlike initial lymphatics, possess a smooth muscle layer and valves. Intermittent changes in tissue pressures, external to initial lymphatics, are mainly responsible for lymph absorption and transport. Lymph within

section 23 Disorders of the skin 5720 collecting lymphatics, however, is propelled forward by mural smooth muscle contraction with valves preventing backflow. Lymphangiogenesis Lymphatic vessels were discovered before the blood circulation, but the first growth factors and molecular markers specific for lymph- atics were discovered only 15 years ago. The gene PROX1 commits endothelial cells from a venous to a lymphatic phenotype. Vascular endothelial growth factor (VEGF) C and D and their receptor VEGFR3 are mainly responsible for lymphatic vessel sprouting and growth. Subsequently, a signal transduction system is responsible for lymphatic endothelial cell growth, migration, maturation, and survival. Lymph sacs appear at six to seven weeks in embryos with lymph- atic endothelial cells sprouting from embryonic veins in the jugular and perimesonephric areas under the influence of VEGFC. From here they migrate to form primary lymph sacs and the primary lymphatic plexus. Antibodies to cell surface markers LYVE1, VEGFR3, podoplanin (D2-40), and PROX1 enable distinction be- tween blood and lymphatic endothelial cells. Lymphoedema A failure of lymph drainage causes a build-up of protein and fluid within the tissues (lymphoedema). When this occurs in the skin and subcutis the tissues become swollen and undergo character- istic changes. An increase of intralymphatic pressure (lymphatic hypertension) results in enlargement of the dermal initial lymph- atics. If compliance permits, distended lymphatics bulge like blisters on the skin surface (lymphangiectasia), leading to leakage of lymph fluid (lymphorrhoea). If disruption to lymph drainage involves the lymphatics draining the intestinal lacteals, then rerouting/backflow of chylous lymph can result in leaking of milky chyle from the skin surface, particularly after a fatty meal. Chronic distension of dermal lymphatics and accumulation of protein-rich fluid within the skin results in a cobble stone appear- ance to the skin (papillomatosis) and a build-up of surface keratin (hyperkeratosis). This combination of features is referred to as ele- phantiasis (Fig. 23.12.5) because of its resemblance to elephant skin. In tropical medicine and parasitology, the term elephantiasis is syn- onymous with lymphoedema resulting from filarial infection, but elephantiasis skin changes can occur with any form of lymphoedema irrespective of cause. If left untreated, elephantiasis progresses to marked fibrosis with little evidence of pitting oedema. Most swelling with lymphoedema occurs in the more compliant subcutis. Fat and fibrous tissue accumulates as much as protein-rich fluid. Indeed, the pathology of lymphoedema is complex involving proliferation of inflammatory cells, adipocytes, fibroblasts, and blood vessels (angiogenesis). Lymphoedema is also discussed in Chapter 16.18. Infection and lymphatic failure Recurrent infection (e.g. tinea pedis, cellulitis) is a common event in lymphoedema. It is likely that disturbances to the trafficking of im- munologically active cells, such as lymphocytes and dendritic cells, compromise tissue immunosurveillance, but the exact mechanism is not known. Lymphatic vessels participate in the regulation of an in- flammatory response through their role in transport of lymphocytes to and from lymph nodes. Migration of dendritic cells is mediated in part by the chemokine receptor CCR7, with lymphatic vessels ex- pressing the ligand CCL21. Lymphangitis The lymphatic system has evolved in humans as a host defence mech- anism. Noxious agents and predators such as bacteria, if not dealt with at the point

of entry to the host, access the lymphatic system. Lymphatic vessels, together with adjoining lymph nodes, effectively act as a second line of defence preventing further onward spread and limiting systemic involvement (e.g. septicaemia). Lymphangitis represents inflammation of the lymphatic collectors and is clinically seen as tender red streaks spreading up the limb corresponding to the inflamed vessels. Inflammation of downstream lymph nodes, known as lymphadenitis, manifests with painful, tender, swollen glands. Lymphangitis is not easily seen in the pres- ence of oedema and a more diffuse erythema is observed, making distinction from cellulitis impossible. Cellulitis (erysipelas, acute inflammatory episodes, dermatolymphangioadenitis) Cellulitis can result from the impaired local host defence mech- anism associated with lymphatic insufficiency but, conversely, can damage lymph drainage routes and cause lymphoedema. A vicious cycle of recurrent cellulitis and worsening swelling can arise. In one epidemiological study, 64 (29%) of 218 patients identified with lymphoedema had suffered at least one attack of cellulitis within the previous 12 months with 16 (8%) experiencing more than three episodes. Any patient with recurrent attacks of cellulitis in the same leg almost certainly has compromised lymph drainage in that leg. Unlike conventional cellulitis (in an immunocompetent site), the first sign of illness is usually constitutional upset with flu-like symptoms, fever, rigors, or vomiting. Only some hours later may a blotchy rash, pain, and increased swelling appear with Fig. 23.12.5 Elephantiasis resulting from underlying lymphoedema. Elephantiasis refers to the thickened skin with papillomatosis and hyperkeratosis.

 the diagnosis becoming clear. The typical advancing border of a spreading cellulitis is not seen with lymphoedema. Streptococcal infection is considered the likely culprit, but it is unusual to be able to isolate an organism. A consensus document on the management of cellulitis in lymphoedema emphasizes the need to correct risk factors (e.g. skin wounds, dermatitis, tinea pedis), and the need for longer courses of antibiotics as insufficient treatment will often result in early relapse of cellulitis. When attacks occur more than twice a year, prophylactic antibiotics are indicated, such as penicillin V (phenoxymethylpenicillin) 500 mg daily. Prophylaxis for two years is recommended, although it is not unusual for cellulitis to recur as soon as antibiotics are discontinued suggesting relapse rather than the development of a new infection. In such circumstances, lifelong prophylaxis is suggested. Tropical lymphoedemas Lymphatic filariasis Adenitis and lymphangitis are major acute manifestations of lymphatic filariasis. Two events may present in a similar manner. ‘True’ filarial adenolymphangitis is caused by the death of the adult worm, whereas acute dermatolymphangioadenitis (ADLA) is equivalent to cellulitis/lymphangitis secondary to bacterial infection (usually streptococcal). Recurrent ADLA/cellulitis is a major risk factor for progression to elephantiasis. Treatment with diethylcarbamazine (DEC) has no effect on the outcome of ADLA, but scrupulous attention to skin hygiene and/or prophy- lactic penicillin significantly reduces the number of attacks. Podoconiosis Similar secondary lymphoedema is seen, together with ADLA, in podoconiosis, a chronic reaction to certain soil types seen in those going barefoot in some tropical regions (e.g. Ethiopia). Tumour metastasis Lymphatic spread is the preferential route of metastasis for most human cancers, with sentinel lymph node assessment as the most important prognostic indicator in, for example, melanoma and vulval and penile cancers, where growth factor stimulation of lymphatic vessels enhances lymphatic metastasis. Melanoma cells expressing VEGFC induce local lymphangiogenesis at the tumour margin. Some evidence exists to suggest that lymphatic endothe- lium actively attracts certain cells, by secreting chemokines such as CCL21 whose receptor CCR7 is expressed on some tumour cells. Lymph containing VEGFC stimulates downstream lymphatics to di- late and

facilitate spread of clumps of tumour cells. Carcinoma erysipeloides (carcinoma telangiectatica) Carcinoma erysipeloides (Fig. 23.12.6) manifests clinically with a fixed erythematous patch or plaque resembling cellulitis/erysipelas but without fever. The inflamed area may show a distinct raised com- ponent due to palpable infiltrated lymphatics and oedema. Congenital lymphatic malformations Lymphangioma Simple sustained dilatation of otherwise normal lymphatic vessels is termed lymphangiectasia, but when lymphatics are distended due to structural abnormalities of a tumour-like nature the term lymphangioma is best used. The most important feature of all con- genital lymphangiomas is that they are not part of the normal lymph conducting system. Lymphangioma circumscriptum, as the name implies, is localized to an area of skin, subcutaneous tissue, and sometimes muscle. It consists of lymph (and sometimes blood) filled vesicles which bulge on the skin surface (Fig. 23.12.7). The lymphangiomas may resemble blisters or may take on a more warty appearance and be mistaken for viral warts, except they can leak lymph fluid. There may or may not be swelling depending upon extension into deeper tissues, but pitting oedema is absent. The term ‘circumscriptum’ may be misleading because deeper compo- nents may be extensive, making surgical excision difficult. Although lymphangioma circumscriptum is usually evident at or soon after Fig. 23.12.6 Carcinoma erysipeloides indicating infiltration of breast carcinoma within dermal lymphatics. Usually associated with local oedema because of lymphatic obstruction. Fig. 23.12.7 Cutaneous lymphangioma as demonstrated by lymph blisters on skin surface.

 birth, it may present later. Radical surgery offers the only chance of cure, but a conservative approach with simple electrocautery to cor- rect the weeping (lymphorrhoea) is advised. Diffuse lymphangioma indicates a more extensive malformation which may involve an entire hindquarter. Limb swelling may be due either to lymphoedema or to gross dilatation of abnormal lymphatic channels, while skin surface lymphangiomas may coexist with blood vascular malformations. Diffuse lymphangiomas may form part of the Klippel–Trénaunay syndrome with limb and tissue overgrowth. If the lymphangioma involves underlying bone, osteoid tissue may resorb leading to pathological fractures (Gorham’s disease). Maffucci’s syndrome consists of diffuse, multiple haemoly mphangiomas accompanied by severe deformities of bone and cartilage. Cystic hygroma (cystic lymphangioma) Cystic hygromas are large lymph cysts considered remnants of primitive lymph sacs, which is why they are found most often in the neck, groin, or retroperitoneum. Although usually present at birth, some present in adulthood after a local disturbance stimu- lates lymph absorption. if large, a cystic hygroma may interfere with breathing or swallowing. Episodes of infection occur in 25% of both cystic hygromas and lymphangiomas. Cystic hygromas are strik- ingly translucent. Repeated aspiration, sclerotherapy, or excision are treatment options. Acquired lymphatic abnormalities Acquired lymphangiectases (acquired lymphangioma) Acquired or secondary lymphangiectases arise following damage to previously normal deep lymphatic vessels. Obstruction to drainage leads to back pressure and dermal backflow with subsequent dila- tation of upper dermal lymphatics. They develop most often in genital skin where they are easily mistaken for warts, but weeping of lymph distinguishes one from the other. Persistent leakage of lymph can be mistaken for urinary incontinence. They occur following cancer treatment (lymphadenectomy or radiotherapy) and scarring processes. Traumatic lymph cysts (lymphoceles) and fistulae Lymphatics severed by accidental trauma or surgery normally col- lapse and block with fibrin. If lymph continues to leak, it collects in the tissues forming a large pseudocyst or lymphocele (often wrongly called a ‘seroma’). Should the lymphocele burst through the over- lying wound, then a fistula with continuous lymph leakage can occur. Most

lymphoceles resolve spontaneously with or without re- peat aspiration. Chylous reflux/intestinal lymphangiectasia Chyle is lymph-rich in chylomicrons. The word chylous means juice and the milky whiteness comes from fat absorbed from intestinal lacteals. It is important to recognize that fluid in the lacteals is only white after a meal containing free fat; patients on a low- or non- fat diet have clear fluid in their lacteals. Chyle, like lymph, can es- cape into peritoneal (chylous ascites), pleural, or pericardial cavities, joints, vagina (chylous colporrhoea), or external genitalia as well as refluxing into a lower limb with chyle leaking from the skin. Where chyle refluxes is entirely dependent on the position of incompetent lymphatics or the site and degree of any obstruction to normal lymph flow. Primary chylous reflux arises from congenitally incompetent megalymphatics (lymphangiectasia with valve incompetence) or lymphatic hypoplasia when lymph/chyle is forced to reroute. Secondary (acquired) reflux is almost always caused by thoracic duct obstruction caused by filariasis, malignant disease, or trauma (accidental or surgery). Treatment involves reducing chyle produc- tion by following a strict, no fat diet supplemented with medium chain triglycerides and extra vitamins. When chyle cannot pass through the lacteals, cisterna chyli, and thoracic duct as usual, it refluxes back into the villi and diffuses back through the intestinal mucosa into the lumen of the bowel. The dis- tended intestinal lacteals are termed intestinal lymphangiectasia. A steady loss of protein, fat, and fat-soluble vitamins causes weight loss, steatorrhoea, diarrhoea, and a hypoproteinaemic oedema (protein-losing enteropathy). Intestinal lymphangiectasia usually occurs from a failure of lymphatic development in genetic forms of lymphoedema, but can rarely be acquired following radiotherapy. Lymphatic tumours The understanding of benign and malignant lymphatic tumours has been limited owing to a lack of specific lymphatic markers. Lymphangiosarcoma Lymphangiosarcoma is the only known malignant disease of lymph- atics. Although well known for its association with postmastectomy lymphoedema (Stewart–Treves syndrome), it is a rare but serious complication of any chronic lymphoedema irrespective of cause. Red-brown or purple discoloration, like a bruise, appears in the skin. Nodules or raised plaques may appear later and oedema deteriorates. Limits are poorly defined and progression is rapid. Radical surgery, if per- formed early, may offer cure. Kaposi’s sarcoma The phenotype of the endothelial cells of Kaposi’s sarcoma may be as much lymphatic as blood vascular, but its origins may lie with a primitive cell capable of either differentiation. It can arise in long- standing lymphoedema or indeed cause lymphoedema. FURTHER READING Angiogenesis/lymphangiogenesis Alitalo K, Tammela T, Petrova TV (2005). Lymphangiogenesis in de- velopment and human disease. Nature, 438, 946–53. Carmeliet P (2005). Angiogenesis in life, disease and medicine. Nature, 438, 932–6. Calciphylaxis Weeniq RH, et al. (2007). Calciphylaxis: natural history, risk factor analysis and outcome. J Am Acad Dermatol, 56, 569–79. Buerger’s disease Olin JW, Shih A (2006). Thrombangiitis obliterans (Buerger’s Disease). Curr Opin Rheumatol, 18, 18–24.

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