2 The function and structure of the skin

The skin – the interface between humans and their environment – is the largest organ in the body. It weighs an average of 4 kg and covers an area of 2 m^2. It acts as a barrier, protecting the body from harsh external conditions and preventing the loss of important body constituents, especially water. A death from destruction of skin, as in a burn or in toxic epidermal necrolysis (p. 127), and the misery of unpleasant acne, remind us of its many important functions, which range from the vital to the cosmetic (Table 2.1).

The skin has three layers. The outer one is the *epidermis*, which is firmly attached to, and supported by connective tissue in the underlying *dermis*. Beneath the dermis is loose connective tissue, the *subcutis/hypodermis*, which usually contains abundant fat (Fig. 2.1).

Epidermis

The epidermis consists of many layers of closely packed cells, the most superficial of which are flattened and filled with keratins; it is therefore a stratified squamous epithelium. It adheres to the dermis partly by the interlocking of its downward projections (*epidermal ridges* or *pegs*) with upward projections of the dermis (*dermal papillae*) (Fig. 2.1).

The epidermis contains no blood vessels. It varies in thickness from less than 0.1 mm on the eyelids to nearly 1 mm on the palms and soles. As dead surface squames are shed (accounting for some of the dust in our houses), the thickness is kept constant by cells dividing in the deepest (*basal* or *germinative*) layer. A generated cell moves, or is pushed by underlying mitotic activity, to the surface, passing through the *prickle* and *granular cell layers* before dying in the *horny layer*. The journey from the basal layer to the surface (epidermal turnover or transit time) takes 30 to 60 days. During this time the appearance of the cell changes. A vertical section through the epidermis summarizes the life history of a single epidermal cell (Fig. 2.2).

The *basal layer*, the deepest layer, rests on a basement membrane, which attaches it to the dermis. It is a single layer of columnar cells, whose basal surfaces sprout many fine processes and hemidesmosomes, anchoring them to the *lamina densa* of the basement membrane.

In normal skin some 30% of basal cells are preparing for division (growth fraction). Following mitosis, a cell enters the G_1 phase, synthesizes RNA and protein, and grows in size (Fig. 2.3). Later, when the cell is triggered to divide, DNA is synthesized

Table 2.1 Functions of the skin.

| Function	Structure/cell involved
Protection against:	
chemicals, particles	Horny layer
ultraviolet radiation	Melanocytes
antigens, haptens	Langerhans cells
microbes	Langerhans cells
Preservation of a balanced internal environment	Horny layer
Prevents loss of water, electrolytes and macromolecules	Horny layer
Shock absorber	Dermis and subcutaneous fat
Strong, yet elastic and compliant	
Temperature regulation	Blood vessels
	Eccrine sweat glands
Insulation	Subcutaneous fat
Sensation	Specialized nerve endings
Lubrication	Sebaceous glands
Protection and prising	Nails
Calorie reserve	Subcutaneous fat
Vitamin D synthesis	Keratinocytes
Body odour/pheromones	Apocrine sweat glands
Psychosocial, display	Skin, lips, hair and nails
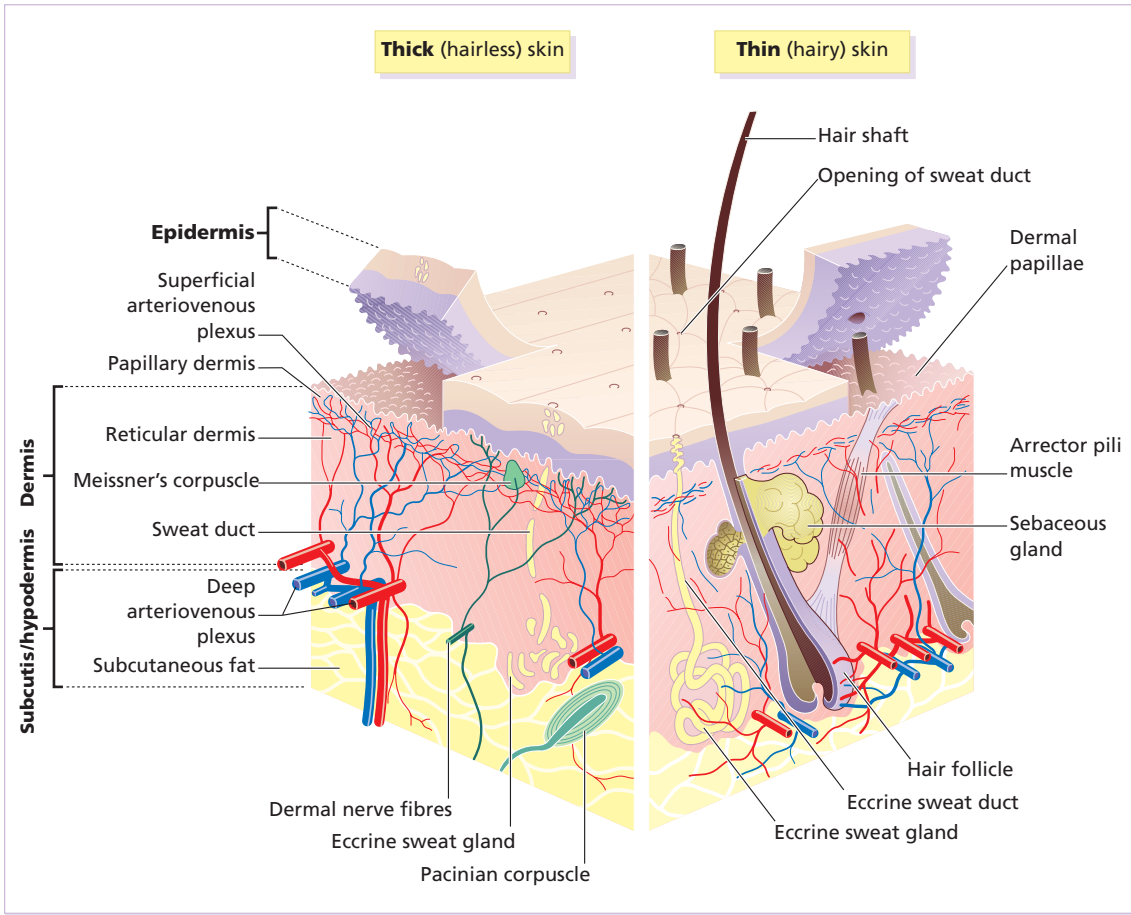
Fig. 2.1 Three-dimensional diagram of the skin, including a hair follicle.

(S phase) and chromosomal DNA is replicated. A short post-synthetic (G_2) phase of further growth occurs before mitosis (M). DNA synthesis continues through the S and G_2 phases, but not during mitosis. The G_1 phase is then repeated, and one of the daughter cells moves into the suprabasal layer. It then differentiates (Fig. 2.2), having lost the capacity to divide, and synthesizes keratins. Some basal cells remain inactive in a so-called G_0 phase but may re-enter the cycle and resume proliferation. The cell cycle time in normal human skin is controversial; estimates of 50–200 h reflect differing views on the duration of the G_1 phase. Stem cells reside amongst these interfollicular basal cells and also amongst the cells of the external root sheath at the bulge in the hair follicle at the level of attach-

ment of the arrector pili muscle. Stem cells cannot be identified by histology but experimentally can be identified by their ability to retain radioactive thymidine incorporated into their DNA for long periods of time. These cells divide infrequently, but can generate new proliferative cells in the epidermis and hair follicle in response to damage.

Keratinocytes

The *spinous* or *prickle cell* layer (Fig. 2.4) is composed of *keratinocytes.* These differentiating cells, which synthesize keratins, are larger than basal cells. Keratinocytes are firmly attached to each other by small interlocking cytoplasmic processes, by abundant desmosomes and by other cadherins p. 26 and

12 Chapter 2

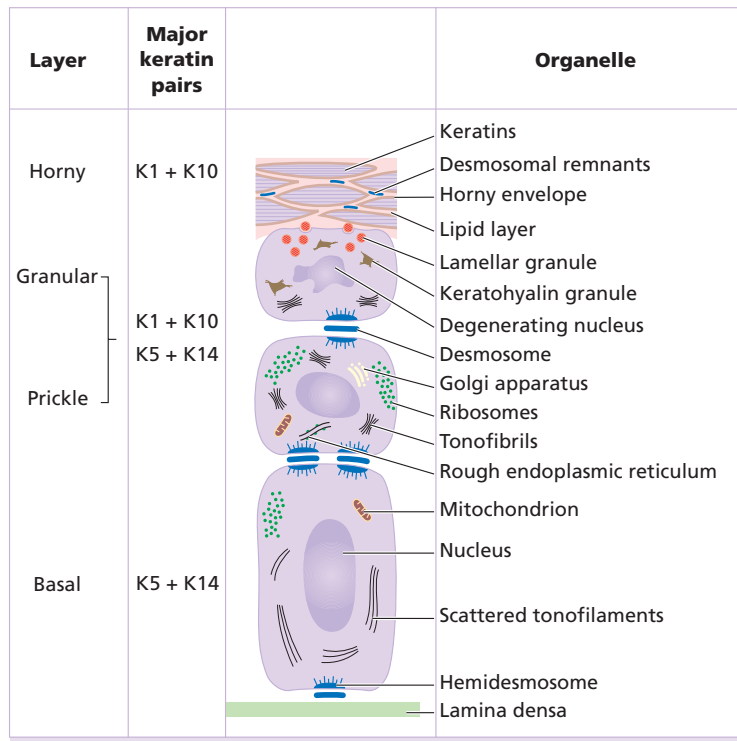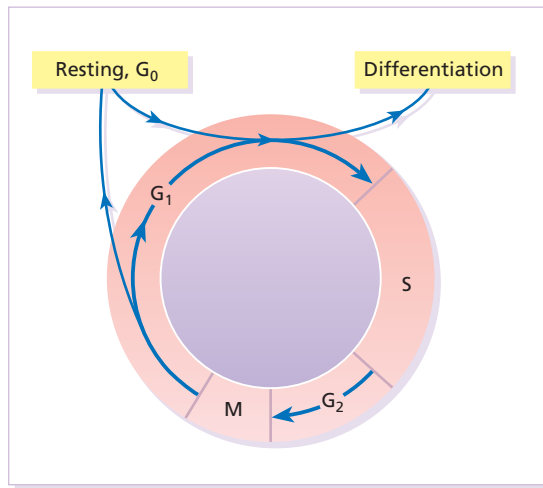| Layer	Major keratin pairs		Organelle
Horny	K1 + K10		Keratins Desmosomal remnants Horny envelope Lipid layer Lamellar granule Keratohyalin granule Degenerating nucleus Desmosome Golgi apparatus Ribosomes Tonofibrils Rough endoplasmic reticulum Mitochondrion Nucleus Scattered tonofilaments Hemidesmosome Lamina densa
Granular	K1 + K10 K5 + K14		
Prickle			
Basal	K5 + K14		

Fig. 2.2 Changes during keratinization.

Fig. 2.3 The cell cycle.

table 2.5 separated by an intercellular layer of glyco-proteins and lipoproteins. Under the light microscope, the desmosomes look like 'prickles'. They are specialized attachment plaques that have been characterized biochemically. They contain desmoplakins, desmogleins and desmocollins. Autoantibodies to these proteins are found in pemphigus (p. 120), when they are responsible for the detachment of keratinocytes from one another and so for intra-epidermal blister formation. Cytoplasmic continuity between keratinocytes occurs at *gap junctions*, specialized areas on opposing cell walls. Tonofilaments are small fibres running from the cytoplasm to the desmosomes. They are more numerous in cells of the spinous layer than of the basal layer, and are packed into bundles called *tonofibrils*. Many *lamellar granules* (otherwise known as membrane-coating granules, Odland bodies or keratinosomes), derived from the Golgi apparatus, appear in the superficial keratinocytes of this layer. They contain polysaccharides, hydrolytic enzymes and stacks of lipid lamellae composed of phospholipids, cholesterol and glucosylceramides. Their contents are discharged into the intercellular space of the granular cell layer to become precursors of the lipids in the intercellular space of the horny layer (p. 13).

Cellular differentiation continues in the granular layer, which normally consists of two or three layers of cells that are flatter than those in the spinous layer, and have more tonofibrils. As the name of
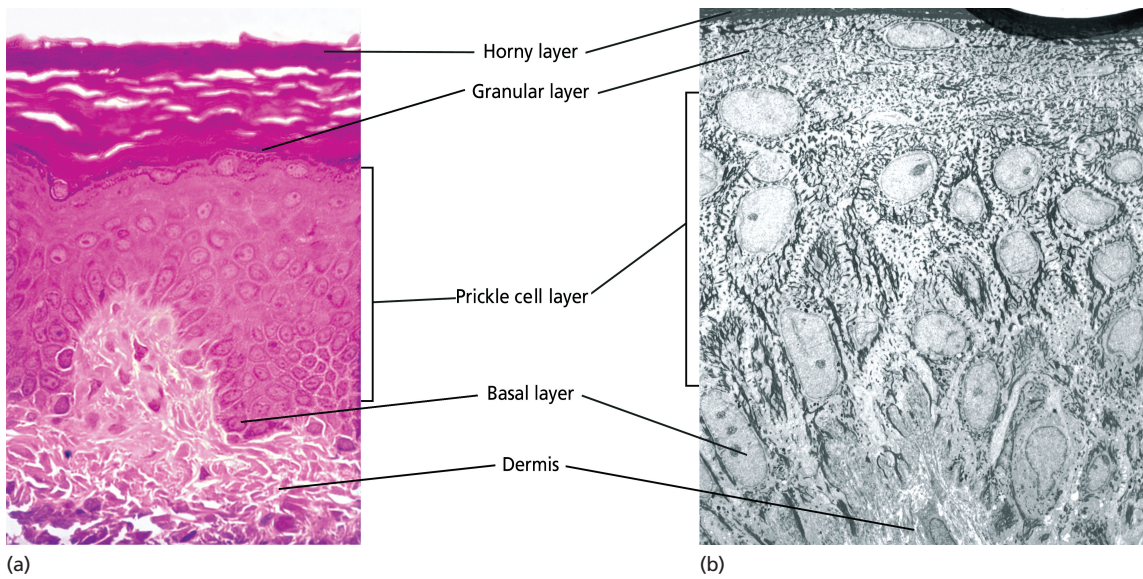
Fig. 2.4 Layers of the epidermis. (a) Light microscopy and (b) electron micrograph.

the layer implies, these cells contain large irregular basophilic granules of *keratohyalin*, which merge with tonofibrils. These keratohyalin granules contain proteins, including involucrin, loricrin and profilaggrin, which is cleaved into filaggrin by specific phosphatases as the granular cells move into the horny layer.

As keratinocytes migrate out through the outermost layers, their keratohyalin granules break up and their contents are dispersed throughout the cytoplasm. Filaggrin peptides aggregate the keratin cytoskeleton, collapsing it, and thus converting the granular cells to flattened squames. These make up the thick and tough peripheral protein coating of the *horny envelope*. Its structural proteins include loricrin and involucrin, the latter binding to ceramides in the surrounding intercellular space under the influence of transglutaminase. Filaggrin, involucrin and loricrin can all be detected histochemically and are useful as markers of epidermal differentiation.

The *horny layer* (stratum corneum) is made of piled-up layers of flattened dead cells (corneocytes) – the bricks – separated by lipids – the mortar – in the intercellular space. Together these provide an effective barrier to water loss and to invasion by infectious agents and toxic chemicals. The corneocyte cytoplasm is packed with keratin filaments, embedded in a matrix and enclosed by an envel-

ope derived from the keratohyalin granules. This envelope, along with the aggregated keratins that it encloses, gives the corneocyte its toughness, allowing the skin to withstand all sorts of chemical and mechanical insults. Horny cells normally have no nuclei or intracytoplasmic organelles, these having been destroyed by hydrolytic and degrading enzymes found in lamellar granules and the lysosomes of granular cells.

Keratinization

All cells have an internal skeleton made up of microfilaments (7 nm diameter; actin), microtubules (20–35 nm diameter; tubulin) and intermediate filaments (10 nm diameter). Keratins (from the Greek *keras* meaning 'horn') are the main intermediate filaments in epithelial cells and are comparable to vimentin in mesenchymal cells, neurofilaments in neurones and desmin in muscle cells. Keratins are not just a biochemical curiosity, as mutations in their genes cause a number of skin diseases including simple epidermolysis bullosa (p. 128) and bullous ichthyosiform erythroderma (p. 49).

The keratins are a family of more than 30 proteins, each produced by different genes. These separate into two gene families: one responsible for basic and the other for acidic keratins. The keratin polypeptide

has a central helical portion with a non-helical N-terminal head and C-terminal tail. Individual keratins exist in pairs so that their double filament always consists of one acidic and one basic keratin polypeptide. The intertwining of adjacent filaments forms larger fibrils.

Different keratins are found at different levels of the epidermis depending on the stage of differentiation and disease; normal basal cells make keratins 5 and 14, but terminally differentiated suprabasal cells make keratins 1 and 10 (Fig. 2.2). Keratins 6 and 16 become prominent in hyperproliferative states such as psoriasis.

During differentiation, the keratin fibrils in the cells of the horny layer align and aggregate, under the influence of filaggrin. Cysteine, found in keratins of the horny layer, allows cross-linking of fibrils to give the epidermis strength to withstand injury.

Cell cohesion and desquamation

Firm cohesion in the spinous layer is ensured by 'stick and grip' mechanisms. A glycoprotein intercellular substance acts as a cement, sticking the cells together, and the intertwining of the small cytoplasmic processes of the prickle cells, together with their desmosomal attachments, accounts for the grip. The cytoskeleton of tonofibrils also maintains the cell shape rigidly.

The typical 'basket weave' appearance of the horny layer in routine histological sections is artefactual and deceptive. In fact, cells deep in the horny layer stick tightly together and only those at the surface flake off; this is in part caused by the activity of cholesterol sulphatase. This enzyme is deficient in X-linked recessive ichthyosis (p. 48), in which poor shedding leads to the piling up of corneocytes in the horny layer. Desquamation is normally responsible for the removal of harmful exogenous substances from the skin surface. The cells lost are replaced by newly formed corneocytes; regeneration and turnover of the horny layer are therefore continuous.

Epidermal barrier

The horny layer prevents the loss of interstitial fluid from within, and acts as a barrier to the penetration of potentially harmful substances from outside. Solvent extraction of the epidermis leads to an increased permeability to water, and it has been known for years that essential fatty acid deficiency causes poor cutaneous barrier function. These facts implicate ceramides, cholesterol, free fatty acids (from lamellar granules; p. 12), and smaller quantities of other lipids, in cutaneous barrier formation. Natural moisturizing factor (NMF), predominantly made up of amino acids and their metabolites, also helps maintain the properties of the stratum corneum. Barrier function is impaired when the horny layer is removed – experimentally, by successive strippings with adhesive tape, or clinically, by injury or skin disease. It is also decreased by excessive hydration or dehydration of the horny layer and by detergents.

The relative impermeability of the stratum corneum and 'moving staircase' effect of continually shedding the outer corneocytes provide a passive barrier to infective organisms. In addition to this, protection is given by the various antimicrobial peptides (AMPs) found on epithelial surfaces. The two major families of AMPs are the defensins and the cathelicidins which have a broad range of antimicrobial activity and form the first line of immune defence of the body.

The speed at which a substance penetrates through the epidermis is directly proportional to its concentration difference across the barrier layer, and indirectly proportional to the thickness of the horny layer. A rise in skin temperature aids penetration. A normal horny layer is slightly permeable to water, but relatively impermeable to ions such as sodium and potassium. Some other substances (e.g. glucose and urea) also penetrate poorly, whereas some aliphatic alcohols pass through easily. The penetration of a solute dissolved in an organic liquid depends mainly on the qualities of the solvent.

Epidermopoiesis and its regulation

Both the thickness of the normal epidermis and the number of cells in it remain constant, as cell loss at the surface is balanced by cell production in the basal layer. Locally produced polypeptides (cytokines), growth factors and hormones stimulate or inhibit epidermal proliferation, interacting in complex ways to ensure homoeostasis. Nitric oxide, a gaseous free radical produced on the skin surface by nitrate reduction and also by constitutive enzymes within the

Table 2.2 Some cytokines produced by keratinocytes.

Designation	Cytokine	Function
Interleukins		
IL-1	Interleukin 1	Lymphocyte activation
		Langerhans cell activation
		Acute phase reactions
IL-3	Interleukin 3	Colony-stimulating factor
IL-6	Interleukin 6	B-cell differentiation
IL-8	Interleukin 8	Chemotaxis
		Angiogenesis
IL-10	Interleukin 10	Inhibition of Th1 T cells
IL-12	Interleukin 12	Induction of Th1 T cells
Colony-stimulating factors		
GM-CSF	Granulocyte–macrophage colony-stimulating factor	Proliferation of granulocytes and macrophages
G-CSF	Granulocyte colony-stimulating factor	Proliferation of granulocytes
M-CSF	Macrophage colony-stimulating factor	Proliferation of macrophages
Others		
TGF	Transforming growth factors	Inhibit inflammation
TNF-α	Tumour necrosis factor α	Induces inflammatory response and
		amplifies Th1 response
		Induces apoptosis
IFN-α	α-Interferon	Antiviral state
IFN-γ	γ-Interferon	Amplification of type IV reactions

epidermis, affects the balance between keratinocyte differentiation and proliferation. This is dose dependent and involves direct interactions with enzymes containing transition elements such as zinc and iron. Cytokines and growth factors (Table 2.2) are produced by keratinocytes, Langerhans cells, fibroblasts and lymphocytes within the skin. After these bind to high affinity cell surface receptors, DNA synthesis is controlled by signal transduction, involving protein kinase C or inositol phosphate. Catecholamines, which do not penetrate the surface of cells, influence cell division via the adenosine 3′,5′-cyclic monophosphate (cAMP) second messenger system. Steroid hormones bind to receptor proteins within the cytoplasm, and then pass to the nucleus where they influence transcription.

Vitamin D synthesis

The steroid 7-dehydrocholesterol, found in keratino-cytes, is converted by sunlight to cholecalciferol. The vitamin becomes active after 25-hydroxylation in the kidney. Kidney disease and lack of sun, particularly in dark-skinned peoples, can both cause vitamin D deficiency and rickets. A few authors have recently raised concerns that low vitamin D levels may be associated with some internal cancers and suggested that we should encourage more sun exposure. However, the link between sun protection, low vitamin D and cancer remains unproven, and if it were found to be true dietary supplementation raises serum levels of vitamin D without the risks of skin cancer and ageing associated with sunbathing.

Other cells in the epidermis

Keratinocytes make up about 85% of cells in the epidermis, but three other types of cell are also found there: melanocytes, Langerhans cells and Merkel cells (Fig. 2.5).
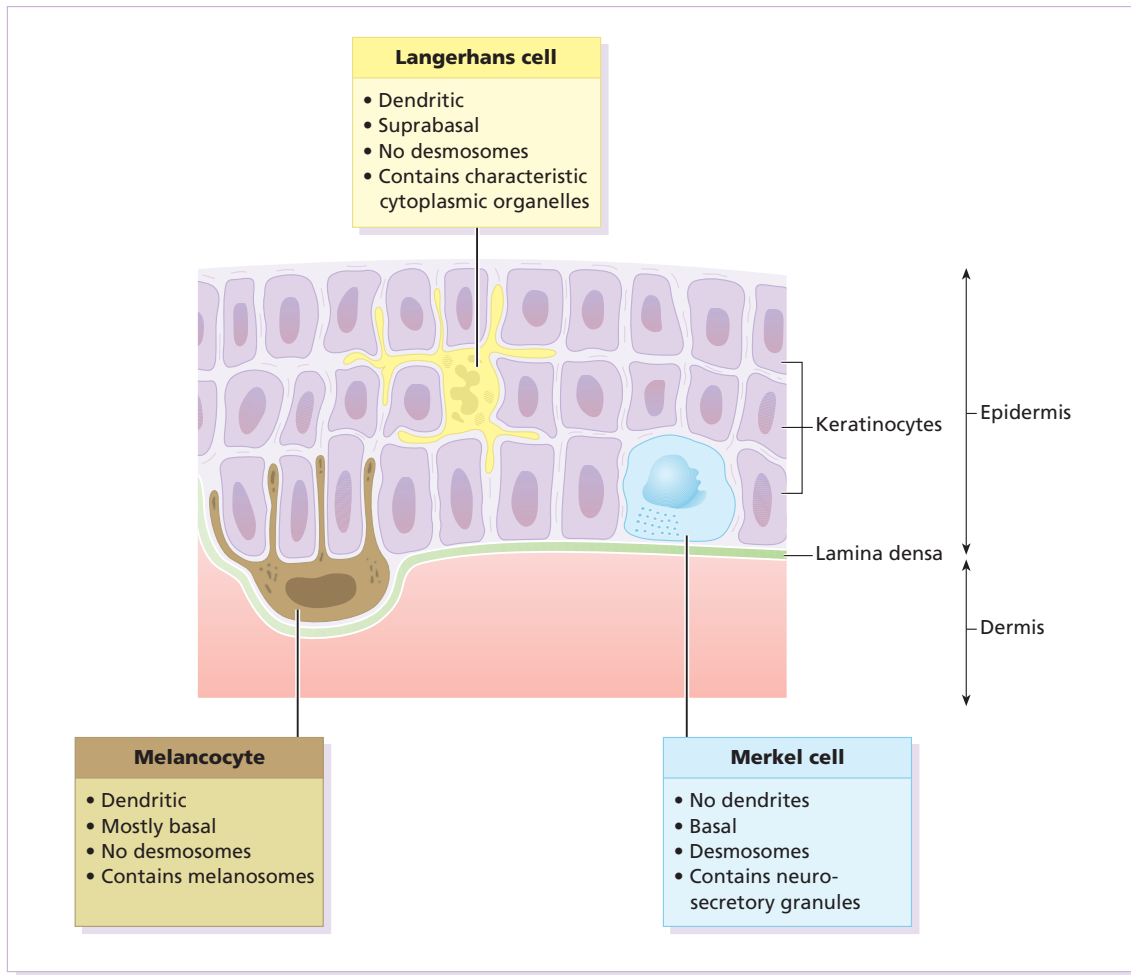
Fig. 2.5 Melanocyte, Langerhans cell and Merkel cell.

Melanocytes

Melanocytes are the only cells that can synthesize melanin. They migrate from the neural crest into the basal layer of the ectoderm where, in human embryos, they are seen as early as 8 weeks' gestation. They are also found in hair bulbs, the retina and pia arachnoid. Each dendritic melanocyte associates with a number of keratinocytes, forming an 'epidermal melanin unit' (Fig. 2.5). The dendritic processes of melanocytes wind between the epidermal cells and end as discs in contact with them. Their cytoplasm contains discrete organelles, the *melanosomes*, containing varying amounts of the pigment melanin (Fig. 2.6). This is 'injected' into surrounding keratinocytes to provide them with pigmentation to help protect the skin against damaging ultraviolet radiation.

Melanogenesis is described at the beginning of Chapter 19 on disorders of pigmentation.

Langerhans cells

The Langerhans cell is a dendritic cell (Figs 2.5 and 2.7) like the melanocyte. It also lacks desmosomes and tonofibrils, but has a lobulated nucleus. The specific granules within the cell look like a tennis racket when seen in two dimensions in an electron micrograph (Fig. 2.8), or like a sycamore seed
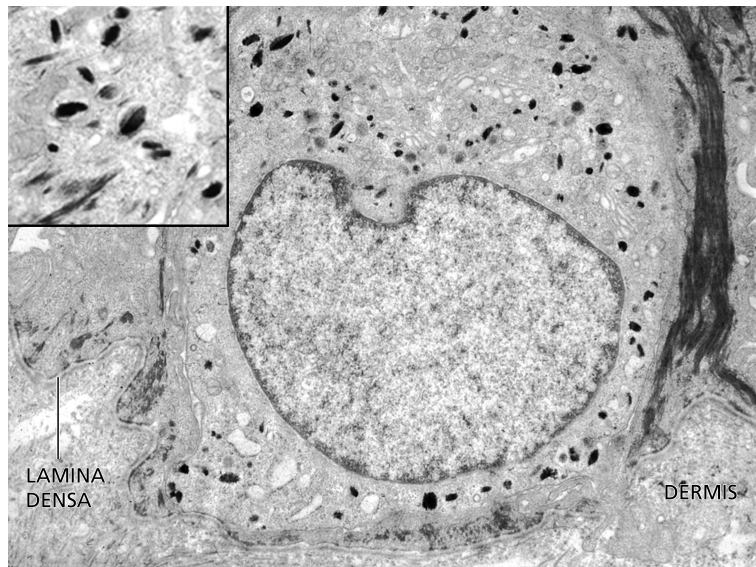
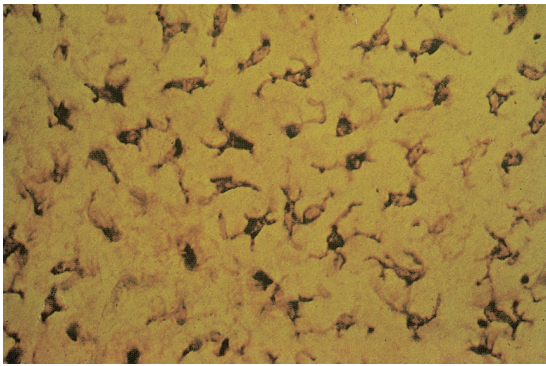**Fig. 2.6** Melanocyte (electron micrograph), with melanosomes (inset).

Fig. 2.7 Adenosine triphosphatase-positive Langerhans cells in an epidermal sheet: the network provides a reticulo-epithelial trap for contact allergens.

when reconstructed in three dimensions. They are plate-like, with a rounded bleb protruding from the surface.

Langerhans cells come from a mobile pool of precursors originating in the bone marrow. There are approximately 800 Langerhans cells per mm^2 in human skin and their dendritic processes fan out to form a striking network seen best in epidermal sheets (Fig. 2.7). Langerhans cells are alone among epidermal cells in possessing surface receptors for C3b and the Fc portions of immunoglobulin G (IgG) and IgE, and in bearing major histocompatibility complex (MHC) class II antigens (HLA-DR, -DP and -DQ). They are best thought of as highly specialized macrophages.

Langerhans cells have a key role in many immune reactions. They take up exogenous antigen, process it and present it to T lymphocytes either in the skin or in the local lymph nodes (p. 31). They probably play a part in immunosurveillance for viral and tumour antigens. In this way, ultraviolet radiation can induce skin tumours both by causing mutations in the epidermal cells, and by decreasing the number of epidermal Langerhans cells, so that cells bearing altered antigens are not recognized or destroyed by the immune system. Topical or systemic glucocorticoids also reduce the density of epidermal Langerhans cells. The Langerhans cell is the principal cell in skin allografts to which the T lymphocytes of the host react during rejection; allograft survival can be prolonged by depleting Langerhans cells.

Merkel cells

Merkel cells are found in normal epidermis (Fig. 2.5) and act as transducers for fine touch. They are non-dendritic cells, lying in or near the basal layer, and are of the same size as keratinocytes. They are concentrated in localized thickenings of the epidermis near hair follicles (hair discs), and contain membrane-bound spherical granules, 80–100 nm in diameter, which have a core of varying density, separated from
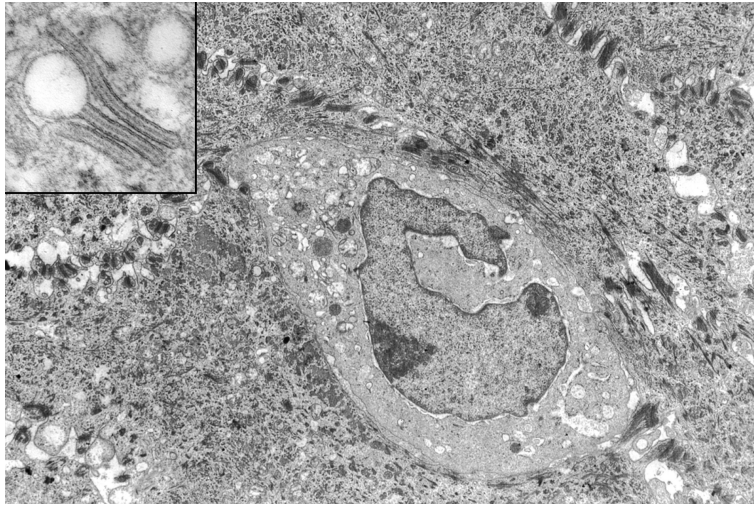
Fig. 2.8 Langerhans cell (electron micrograph), with characteristic granule (inset).

the membrane by a clear halo. Sparse desmosomes connect these cells to neighbouring keratinocytes. Fine unmyelinated nerve endings are often associated with Merkel cells, which express immunoreactivity for various neuropeptides.

Epidermal appendages

The skin appendages are derived from epithelial germs during embryogenesis and, except for the nails, lie in the dermis. They include hair, nails and sweat and sebaceous glands. They are described, along with the diseases that affect them, in Chapters 12 and 13, respectively.

Dermo-epidermal junction

The basement membrane lies at the interface between the epidermis and dermis. With light microscopy it can be highlighted using a periodic acid–Schiff (PAS) stain, because of its abundance of neutral mucopolysaccharides. Electron microscopy (Fig. 2.9) shows that the *lamina densa* (rich in type IV collagen) is separated from the basal cells by an electron-lucent area, the *lamina lucida*. The plasma membrane of basal cells has *hemidesmosomes* (containing bullous pemphigoid antigens, collagen XVII and α6 β4 integrin). The lamina lucida contains the adhesive macromolecules, laminin-1, laminin-5 and entactin.

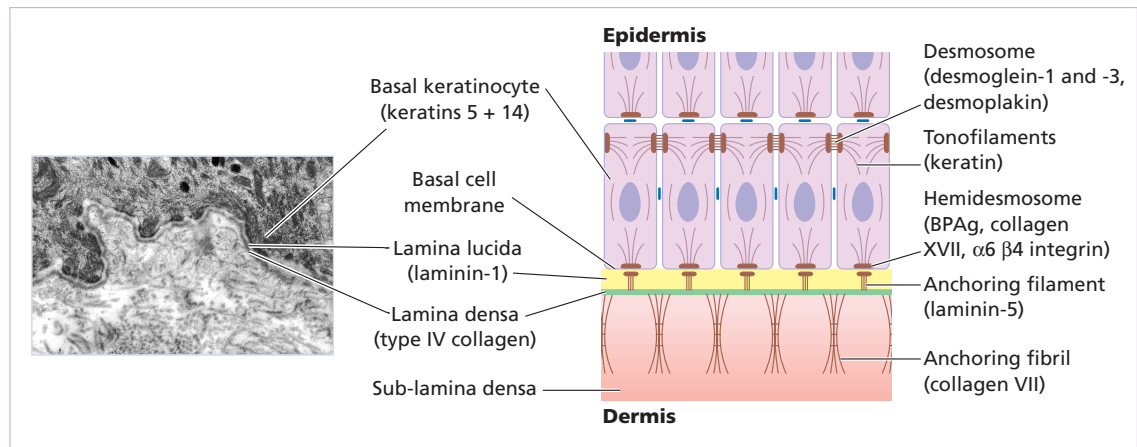**Fig. 2.9** Structure and molecular composition of the dermo-epidermal junction.

Table 2.3 Functions of some resident dermal cells.

Fibroblast	Synthesis of collagen, reticulin, elastin, fibronectin, glycosaminoglycans, collagenase
Mononuclear phagocyte	Mobile: phagocytoses and destroys bacteria Secretes cytokines
Lymphocyte	Immunosurveillance
Langerhans cell and dermal dendritic cell	In transit between local lymph node and epidermis Antigen presentation
Mast cell	Stimulated by antigens, complement components, and other substances to release many inflammatory mediators including histamine, heparin, prostaglandins, leukotrienes, tryptase and chemotactic factors for eosinophils and neutrophils
Merkel cell	Acts as transducer for fine touch

Fine *anchoring filaments* (of laminin-5) cross the lamina lucida and connect the lamina densa to the plasma membrane of the basal cells. *Anchoring fibrils* (of type VII collagen), dermal microfibril bundles and single small collagen fibres (types I and III), extend from the papillary dermis to the deep part of the lamina densa.

Laminins, large non-collagen glycoproteins produced by keratinocytes, aided by entactin, promote adhesion between the basal cells above the lamina lucida and type IV collagen, the main constituent of the lamina densa, below it. The laminins act as a glue, helping to hold the epidermis onto the dermis. Bullous pemphigoid antigens (of molecular weights 230 and 180 kDa) are synthesized by basal cells and are found in close association with the hemidesmosomes and laminin. Their function is unknown but antibodies to them are found in pemphigoid (p. 123), a subcutaneous blistering condition.

The structures within the dermo-epidermal junction provide mechanical support, encouraging the adhesion, growth, differentiation and migration of the overlying basal cells, and also act as a semipermeable filter that regulates the transfer of nutrients and cells from dermis to epidermis.

Dermis

The dermis lies between the epidermis and the subcutaneous fat. It supports the epidermis structurally and nutritionally. Its thickness varies, being greatest in the palms and soles and least in the eyelids and penis. In old age, the dermis thins and loses its elasticity.

The dermis interdigitates with the epidermis (Fig. 2.1) so that upward projections of the dermis, the dermal papillae, interlock with downward ridges of the epidermis, the rete pegs. This interdigitation is responsible for the ridges seen most readily on the fingertips (as fingerprints). It is important in the adhesion between epidermis and dermis as it increases the area of contact between them.

Like all connective tissues the dermis has three components: cells, fibres and amorphous ground substance.

Cells of the dermis

The main cells of the dermis are fibroblasts, but there are also small numbers of resident and transitory mononuclear phagocytes, lymphocytes, Langerhans cells and mast cells. Other blood cells (e.g. polymorphs) are seen during inflammation. The main functions of the resident dermal cells are listed in Table 2.3 and their role in immunological reactions is discussed later in this chapter.

Fibres of the dermis

The dermis is largely made up of interwoven fibres, principally of collagen, packed in bundles. Those in the papillary dermis are finer than those in the deeper reticular dermis. When the skin is stretched, collagen, with its high tensile strength, prevents tearing, and the elastic fibres, intermingled with the collagen, later return it to the unstretched state.

Collagen makes up 70–80% of the dry weight of the dermis. Its fibres are composed of thinner

Collagen type	Tissue distribution
I	Most connective tissues including tendon and bone Accounts for approximately 85% of skin collagen
II	Cartilage
III	Accounts for about 15% of skin collagen Blood vessels
IV	Skin (lamina densa) and basement membranes of other tissues
V	Ubiquitous, including placenta
VII	Skin (anchoring fibrils) Foetal membranes

Table 2.4 Distribution of some types of collagen.

fibrils, which are in turn made up of microfibrils built from individual collagen molecules. These molecules consist of three polypeptide chains (molecular weight 150 kDa) forming a triple helix with a non-helical segment at both ends. The alignment of the chains is stabilized by covalent cross-links involving lysine and hydroxylysine. Collagen is an unusual protein as it contains a high proportion of proline and hydroxyproline and many glycine residues; the spacing of glycine as every third amino acid is a pre-requisite for the formation of a triple helix. Defects in the enzymes needed for collagen synthesis are responsible for some skin diseases, including the Ehlers–Danlos syndrome (Chapter 24), and conditions involving other systems, including lathyrism (fragility of skin and other connective tissues) and osteogenesis imperfecta (fragility of bones).

There are many, genetically distinct, collagen proteins, all with triple helical molecules, and all rich in hydroxyproline and hydroxylysine. The distribution of some of them is summarized in Table 2.4.

Reticulin fibres are fine collagen fibres, seen in foetal skin and around the blood vessels and appendages of adult skin.

Elastic fibres account for about 2% of the dry weight of adult dermis. They have two distinct protein components: an amorphous elastin core and a surrounding 'elastic tissue microfibrillar component'. Elastin (molecular weight 72 kDa) is made up of polypeptides (rich in glycine, desmosine and valine) linked to the microfibrillar component through their desmosine residues. Abnormalities in the elastic tissue cause cutis laxa (sagging inelastic skin) and pseudoxanthoma elasticum (Chapter 24).

Ground substance of the dermis

The amorphous ground substance of the dermis consists largely of two glycosaminoglycans (hyaluronic acid and dermatan sulphate) with smaller amounts of heparan sulphate and chondroitin sulphate. The glycosaminoglycans are complexed to core protein and exist as proteoglycans.

The ground substance has several important functions:
- it binds water, allowing nutrients, hormones and waste products to pass through the dermis;
- it acts as a lubricant between the collagen and elastic fibre networks during skin movement; and
- it provides bulk, allowing the dermis to act as a shock absorber.

Muscles

Both smooth and striated muscle are found in the skin. The smooth arrector pili muscles (see Fig. 13.1) are used by animals to raise their fur and so protect them from the cold. They are vestigial in humans, but may help to express sebum. Smooth muscle is also responsible for 'goose pimples' (bumps) from cold, nipple erection, and the raising of the scrotum by the dartos muscle. Striated fibres (e.g. the platysma) and some of the muscles of facial expression are also found in the dermis.

Blood vessels

Although the skin consumes little oxygen, its abundant blood supply regulates body temperature. The
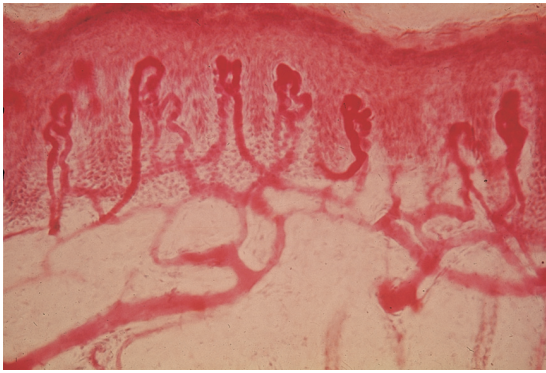
Fig. 2.10 Blood vessels of the skin (carmine stain).

blood vessels lie in two main horizontal layers (Fig. 2.10). The deep plexus is just above the sub-cutaneous fat, and its arterioles supply the sweat glands and hair papillae. The superficial plexus is in the papillary dermis and arterioles from it become capillary loops in the dermal papillae. An arteriole arising in the deep dermis supplies an inverted cone of tissue, with its base at the epidermis.

The blood vessels in the skin are important in thermoregulation. Under sympathetic nervous control, arteriovenous anastomoses at the level of the deep plexus can shunt blood to the venous plexus at the expense of the capillary loops, thereby reducing surface heat loss by convection.

Cutaneous lymphatics

Afferent lymphatics begin as blind-ended capillar-ies in the dermal papilla and pass to a superficial lymphatic plexus in the papillary dermis. There are also two deeper horizontal plexuses, and collecting lymphatics from the deeper one run with the veins in the superficial fascia.

Nerves

The skin is liberally supplied with an estimated 1 million nerve fibres. Most are found in the face and extremities. Their cell bodies lie in the dorsal root ganglia. Both myelinated and non-myelinated fibres exist, with the latter making up an increasing proportion peripherally. Most free sensory nerves end in the dermis; however, a few non-myelinated nerve endings penetrate into the epidermis. Some

of these are associated with Merkel cells (p. 17). Free nerve endings detect the potentially damag-ing stimuli of heat and pain (nocioceptors), while specialized end organs in the dermis, Pacinian and Meissner corpuscles, register deformation of the skin caused by pressure (mechanoreceptors) as well as vibration and touch. Autonomic nerves supply the blood vessels, sweat glands and arrector pili muscles.

Itching is an important feature of many skin dis-eases. It follows the stimulation of fine free nerve endings lying close to the dermo-epidermal junction. Areas with a high density of such endings (itch spots) are especially sensitive to itch-provoking stimuli. Impulses from these free endings pass centrally in two ways: quickly along myelinated A fibres, and more slowly along non-myelinated C fibres. As a result, itch has two components: a quick localized pricking sensa-tion followed by a slow burning diffuse itching.

Many stimuli can induce itching (electrical, chem-ical and mechanical). In itchy skin diseases, prurito-genic chemicals such as histamine and proteolytic enzymes are liberated close to the dermo-epidermal junction. The detailed pharmacology of individual diseases is still poorly understood but prostaglandins potentiate chemically induced itching in inflammat-ory skin diseases.

> **Learning points**
>
> **1** More diseases are now being classified by abnormal-ities of function and structure rather than by their appearance.
> **2** Today's patients are inquisitive and knowledgeable. If you understand the structure and function of the skin, your explanations to them will be easier and more convincing.

The skin immune system

The skin acts as a barrier to prevent injury of under-lying tissues and to prevent infections from entering the body. Simply put, it keeps the inside in and the outside out. The horny layer is a physical barrier that minimizes the loss of fluid and electrolytes, and also stops the penetration of harmful substances and trauma (p. 10). It is a dry mechanical barrier from which contaminating organisms and chem-icals are continually being removed by washing and

desquamation. Only when these breach the horny layer do the cellular components, described below, come into play.

The skin is involved in so many immunological reactions seen regularly in the clinic (e.g. urticaria, allergic contact dermatitis, psoriasis, vasculitis) that special mention has to be made of the peripheral arm of the immune system based in the skin – the skin immune system (SIS). It includes the cutaneous blood vessels and lymphatics with their local lymph nodes and contains circulating lymphocytes and resident immune cells. Although it is beyond the scope of this book to cover general immunology, this section outlines some of the intricate ways in which the skin defends itself and the body, and how antigens are recognized by specialized skin cells, mainly the Langerhans cells. It also reviews the ways in which antibodies, lymphocytes, macrophages and polymorphs elicit inflammation in skin.

Some cellular components of the skin immune system

Keratinocytes (p. 11)

Their prime role is to make the protective horny layer (p. 10) and to support the outermost epithelium of the body, but they also have immunological functions in their own right. Keratinocytes produce large numbers of cytokines (Table 2.2), and can be induced by γ-interferon to express HLA-DR. They release large amounts of interleukin-1 (IL-1) after injury, and this initiates various immune and inflammatory cascades (Fig. 2.11). Keratinocytes play a central part in healing after epidermal injury by self-regulating epidermal proliferation and differentiation (Fig. 2.11). They can also produce α-melanocyte-stimulating hormone (p. 278), which is immunosuppressive.
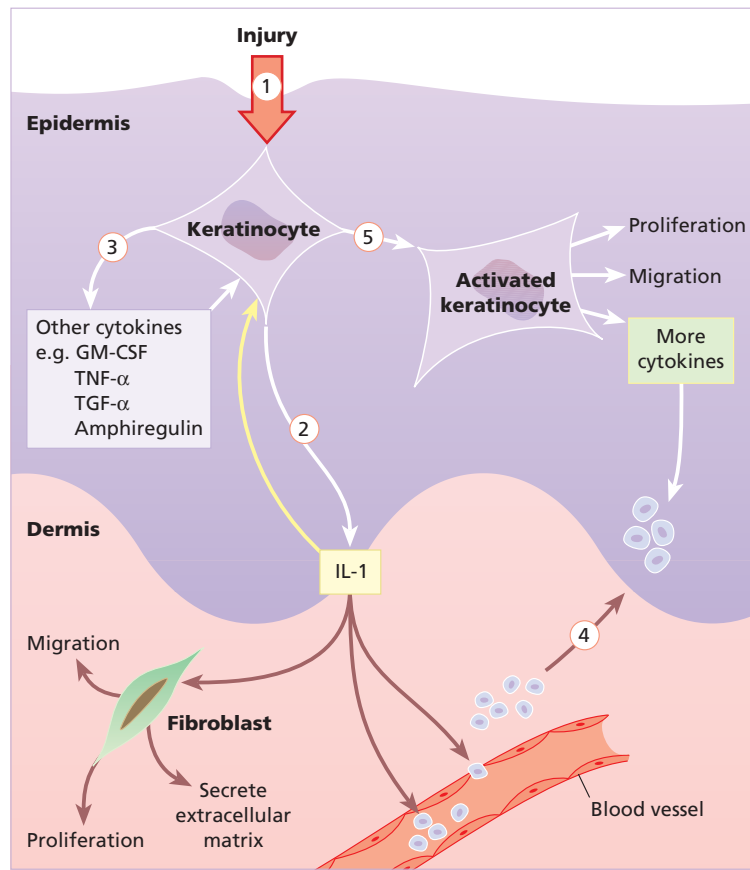
Fig. 2.11 The keratinocyte and wound healing. The injured keratinocyte turns on wound healing responses. When a keratinocyte is injured (1), it releases interleukin-1 (IL-1) (2). IL-1 activates endothelial cells causing them to express selectins that slow down lymphocytes passing over them. Once lymphocytes stop on the endothelial cells lining the vessels, IL-1 acts as a chemotactic factor to draw lymphocytes into the epidermis (4). At the same time, IL-1 activates keratinocytes by binding to their IL-1 receptors. Activated keratinocytes produce other cytokines (3). Among these is tumour necrosis factor α (TNF-α) that additionally activates keratinocytes and keeps them in an activated state (5). Activation of keratinocytes causes them to proliferate, migrate and secrete additional cytokines.

Langerhans cells (p. 16)

These dendritic cells come from the bone marrow and move into the epidermis where they remain. Their dendrites intercalate between keratinocytes. They can be identified in tissue sections by demonstrating their characteristic surface markers (e.g. CD1a antigen, MHC class II antigens, adenosine triphosphatase) or S-100 protein in their cytoplasm (also found in melanocytes). Langerhans cells have a key role in antigen presentation.

Dermal dendritic cells

These poorly characterized cells are found around the tiny blood vessels of the papillary dermis. They bear MHC class II antigens on their surface and, like Langerhans cells, probably function as antigen-presenting cells.

T lymphocytes

Like T cells elsewhere, these develop and acquire their antigen receptors (T-cell receptors; TCR) in the thymus. They differentiate into subpopulations, recognizable by their different surface molecules (CD meaning cluster of differentiation markers), which are functionally distinct. T lymphocytes that express CD4 on their surfaces work to induce immune reactions and elicit inflammation. T cells that express CD8 are cytotoxic and can lyse infected, grafted and cancerous cells.

Thelper (Th) cells, CD4 (helper) cells are subdivided into Th1 cells that produce IL-2 (T-cell growth factor), γ-interferon, and other cytokines not produced by Th2 cells. Th2 cells produce other interleukins such as IL-4, IL-5, IL-9 and IL-13. The amounts of IL-12 and IL-4 secreted by antigen-processing cells seem important in determining exactly which path of differentiation is followed. A third subset of CD-4 cells has recently been called, somewhat confusingly, Th17 cells. IL-23 directs these to release IL-17 and IL-22.

Th1 cells induce cell-mediated immune reactions in the skin (e.g. allergic contact dermatitis and delayed hypersensitivity reactions) and are involved in elicitation reactions as well. Th2 cells help B cells produce antibody. Th17 cells are involved in the clearance of infectious agents, and also mediate autoimmune inflammation and psoriasis. Th cells recognize antigen in association with MHC class II molecules (Fig. 2.12) and, when triggered by antigen, release cytokines that attract and activate other inflammatory cells (Fig. 2.13).

Some skin diseases display a predominantly Th1 response (e.g. psoriasis), others a mainly Th2 response (e.g. lepromatous leprosy).

T-cytotoxic (Tc) cells

These lymphocytes are capable of destroying allogeneic, tumour and virally infected cells, which they recognize by the MHC class I molecules on their surface. They express CD8.

T-cell receptor (TCR) and T-cell gene receptor rearrangements

Most TCRs are composed of an α and a β chain, each with a variable (antigen binding) and a constant domain, which are associated with the CD3 cell surface molecules (Fig. 2.12). The amino acid sequence of the variable portion determines its antigen-binding specificity – different sequences bind different antigens. To provide diversity and the ability to bind almost any antigen, the genes coding for the amino acid sequence undergo rearrangement. Antigenic stimulation results in expansion of appropriate clones carrying TCRs capable of binding to the antigen. Most inflammatory responses are polyclonal. However, malignant transformation is associated with proliferation of a unique clone. In fact, an analysis of the degree of clonality of rearrangements of the gene for the receptor can be used to determine whether a T-cell infiltrate in skin is likely to be malignant or reactive.

Other (non-T, non-B) lymphocytes

Some lymphocytes express neither CD4 nor CD8. These leucocytes have some properties of T lymphocytes and some properties of myelomonocytic cells. Most have receptors for FcIgG. This subpopulation contains natural killer (NK) and killer (K) cells.

Natural killer cells

These are large granular leucocytes that can kill virally infected cells, or tumour cells that have not previously been sensitized with antibody. They

24 Chapter 2
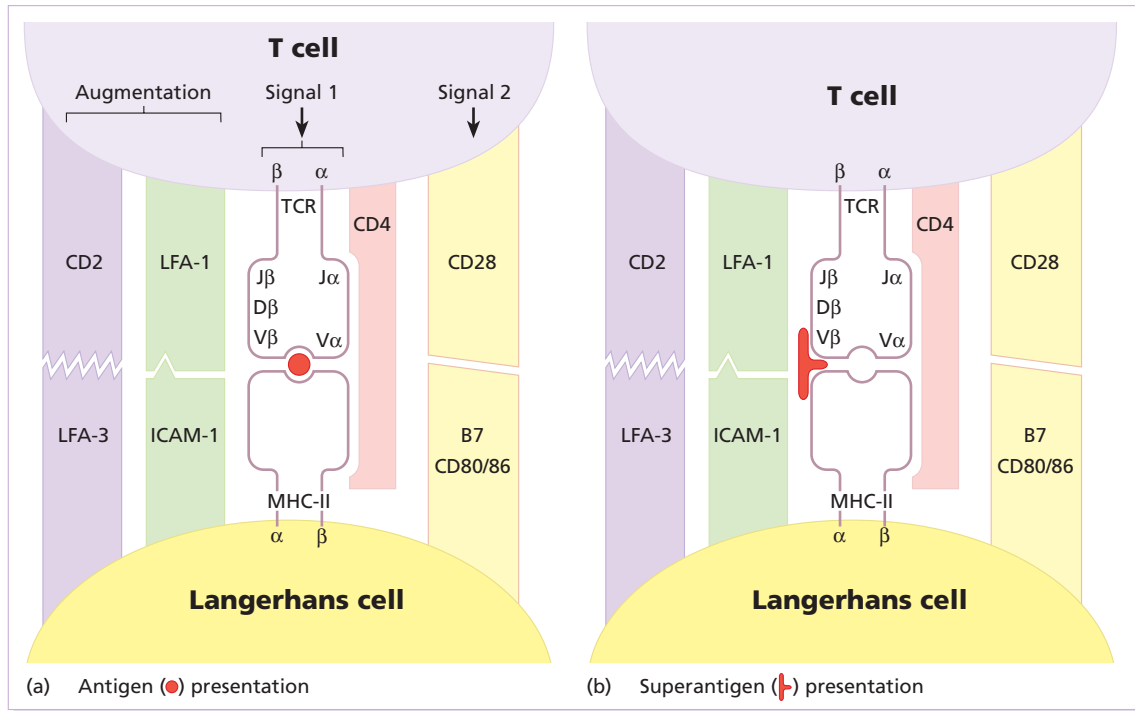
Fig. 2.12 T-lymphocyte activation by (a) antigen and (b) superantigen. When antigen has been processed it is presented on the surface of the Langerhans cell in association with major histocompatibility complex (MHC) class II. The complex formation that takes place between the antigen, MHC class II and T-cell receptor (TCR) provides signal 1, which is enhanced by the coupling of CD4 with the MHC molecule. A second signal for T-cell activation is provided by the interaction between the co-stimulatory molecules CD28 (T cell) and B7 (Langerhans cell). CD2–LFA-3 and LFA-1–ICAM-1 adhesion augment the response to signals 1 and 2. Superantigen interacts with the TCR Vβ and MHC class II without processing, binding outside the normal antigen binding site. Activated T cells secrete many cytokines, including IL-1, IL-8 and γ-interferon, which promote inflammation (Fig. 2.13).

Fig. 2.13 Characteristics of Th1, Th2 and Th17 responses.

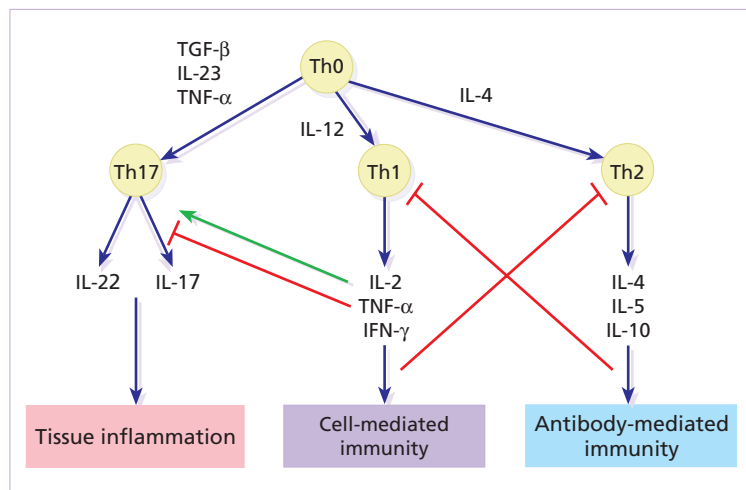develop in the bone marrow, but have no antigen-specific receptors, reacting instead with self antigens. They especially kill tumour and virally infected cells. These cells can sometimes recognize glycolipid antigens using CD1 surface molecules that do not require presentation by antigen-presenting cells.

Killer cells

These are cytotoxic T cells, NK cells or monocytic leucocytes that can kill target cells sensitized with antibody. In antibody-mediated cellular cytotoxicity, antibody binds to antigen on the surface of the target cell; the K cell binds to the antibody at its other (Fc) end by its Fc receptor and the target cell is then lysed.

Mast cells

These are present in most connective tissues, predominantly around blood vessels. Their numerous granules contain inflammatory mediators (see Fig. 8.1). In rodents – and probably in humans – there are two distinct populations of mast cells: connective tissue and mucosal, which differ in their staining properties, content of inflammatory mediators and proteolytic enzymes. Skin mast cells play a central part in the pathogenesis of urticaria (p. 104).

Molecular components of the skin immune system

Antigens

Antigens are molecules that are recognized by the immune system thereby provoking an immune reaction, usually in the form of a humoral or cell-mediated immune response. The immune system can usually identify its own molecules, so that it does not direct a reaction against them. If it does, 'autoimmune reactions' occur. Otherwise the skin immune system readily responds to 'non-self' antigens, such as chemicals, proteins, allografted cells and infectious agents. The process of recognizing antigens and developing immunity is called induction or sensitization.

Superantigens

Some bacterial toxins (e.g. those released by *Staphylococcus aureus*) are prototypic superantigens. They align with MHC class II molecules of antigen-presenting cells outside their antigen presentation groove and, without any cellular processing, may directly induce massive T-cell proliferation and cytokine production leading to disorders such as the toxic shock syndrome (p. 225). Streptococcal toxins act as superantigens to activate T cells in the pathogenesis of guttate psoriasis.

Antibodies (immunoglobulins)

Antibodies are immunoglobulins (Ig) that react with antigens.
● IgG is responsible for long-lasting humoral immunity. It can cross the placenta, and binds complement to activate the classic complement pathway. IgG can coat neutrophils and macrophages (by their FcIgG receptors), and acts as an opsonin by cross-bridging antigen. IgG can also sensitize target cells for destruction by K cells.
● IgM is the largest immunoglobulin molecule. It is the first antibody to appear after immunization or infection. Like IgG it can fix complement, but unlike IgG it cannot cross the placenta.
● IgA is the most common immunoglobulin in secretions. It acts as a protective paint in the gastrointestinal and respiratory tracts. It does not bind complement but can activate it via the alternative pathway.
● IgE binds to Fc receptors on mast cells and basophils, where it sensitizes them to release inflammatory mediators in type I immediate hypersensitivity reactions (Fig. 2.14).

Cytokines

Cytokines are small proteins secreted by cells such as lymphocytes and macrophages, and also by keratinocytes (Table 2.2). They regulate the amplitude and duration of inflammation by acting locally on nearby cells (paracrine action), on those cells that secreted them (autocrine) and occasionally on distant target cells (endocrine) via the circulation. The term cytokine covers interleukins, interferons, colony-stimulating factors, cytotoxins and growth factors. Interleukins are produced predominantly by leucocytes, have a known amino acid sequence and are active in inflammation or immunity.
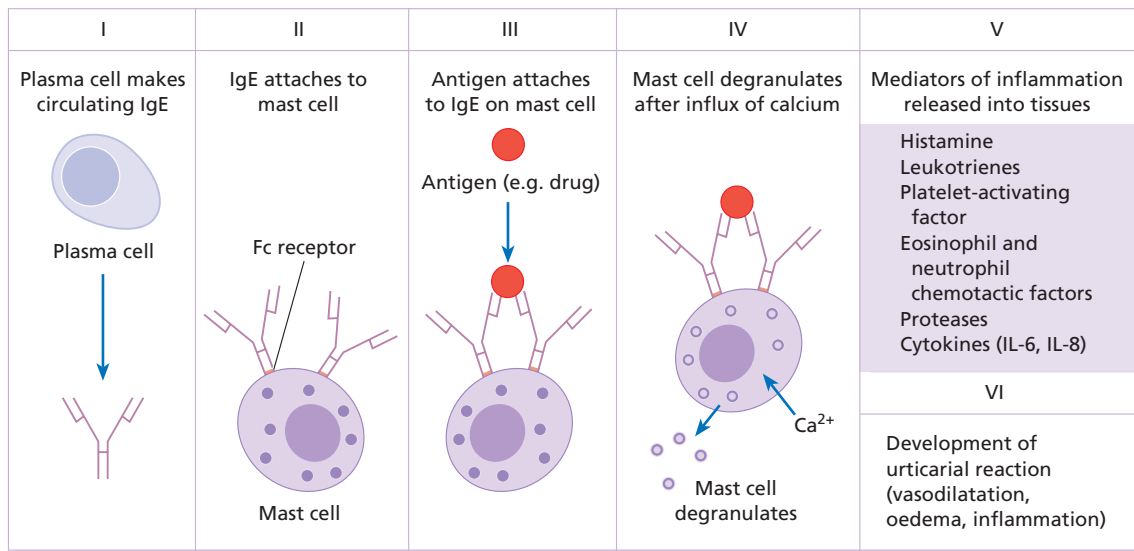
I	II	III	IV	V
Plasma cell makes circulating IgE	IgE attaches to mast cell	Antigen attaches to IgE on mast cell	Mast cell degranulates after influx of calcium	Mediators of inflammation released into tissues

Plasma cell

Fc receptor

Antigen (e.g. drug)

Mast cell

Ca²⁺

Mast cell degranulates

V (continued)
Histamine
Leukotrienes
Platelet-activating factor
Eosinophil and neutrophil chemotactic factors
Proteases
Cytokines (IL-6, IL-8)

VI
Development of urticarial reaction (vasodilatation, oedema, inflammation)

Fig. 2.14 Urticaria: an immediate (type I) hypersensitivity reaction.

There are many cytokines (Table 2.2), and each may act on more than one type of cell, causing many different effects. Cytokines frequently have overlapping actions. In any inflammatory reaction some cytokines are acting synergistically while others will antagonize these effects. This network of potent chemicals, each acting alone and in concert, moves the inflammatory response along in a controlled way. Cytokines bind to high-affinity (but not usually specific) cell surface receptors, and elicit a biological response by regulating the transcription of genes in the target cell via signal transduction pathways involving, for example, the Janus protein tyrosine kinase or calcium influx systems. The biological response is a balance between the production of the cytokine, the expression of its receptors on the target cells and the presence of inhibitors.

Adhesion molecules

Cellular adhesion molecules (CAMs) are surface glycoproteins that are expressed on many different types of cell; they are involved in cell–cell and cell–matrix adhesion and interactions. CAMs are fundamental in the interaction of lymphocytes with antigen-presenting cells (Fig. 2.12), keratinocytes and endothelial cells, and are important in lympho-cyte trafficking in the skin during inflammation (Fig. 2.11). CAMs have been classified into three families: immunoglobulin superfamily, integrins and selectins.

CAMs of special relevance in the skin are listed in Table 2.5.

Histocompatibility antigens

Like other cells, those in the skin express surface antigens directed by genes. The human leucocyte antigen (HLA) region lies within the major histocompatability (MHC) locus on chromosome 6. In particular, HLA-A, -B and -C antigens (the class I antigens) are expressed on all nucleated cells including keratinocytes, Langerhans cells and cells of the dermis. HLA-DR, -DP, -DQ and -DZ antigens (the class II antigens) are expressed only on some cells (e.g. Langerhans cells and B cells). They are usually not found on keratinocytes except during certain reactions (e.g. allergic contact dermatitis) or diseases (e.g. lichen planus). Helper T cells recognize antigens only in the presence of cells bearing class II antigens. Class II antigens are also important for certain cell–cell interactions. Class I antigens mark target cells for cell-mediated cytotoxic reactions, such as the rejection of skin allografts and the destruction of cells infected by viruses.

Table 2.5 Cellular adhesion molecules important in the skin.

Family	Nature	Example	Site	Ligand
Cadherins	Glycoproteins Adherence dependent on calcium	Desmoglein	Desmosomes in epidermis	Other cadherins
Immunoglobulin	Numerous molecules that are structurally similar to immunoglobulins	ICAM-1 CD2 VCAM-1	Endothelial cells Keratinocytes Langerhans cells T lymphocytes Some NK cells Endothelial cells	LFA-1 LFA-3
Integrins	Surface proteins comprising two non-covalently bound α and β chains	Very late activation proteins (β1-VLA) LFA-1 Mac-1	T lymphocyte T lymphocyte Macrophages Monocytes Granulocytes	VCAM ICAM-1 C3b component of complement
Selectins	Adhesion molecules with lectin-like domain which binds carbohydrate	E selectin	Endothelial cells	CD15

CD2, cluster of differentiation antigen 2; ICAM-1, intercellular adhesion molecule 1; LFA, leucocyte function antigen; Mac-1, macrophage activation 1; VCAM-1, vascular cell adhesion molecule 1.

Types of immune reactions in the skin

Innate immune system

The epidermal barrier is the major defence against infection in human skin. When it is breached, cells in the dermis and epidermis can telegraph the danger and engage the innate immunity and inflammatory systems. Innate immunity allows reaction to infectious agents and noxious chemicals, without the need to activate specific lymphocytes or use antibodies. This is fortunate. If an infected person had to wait for immunity to develop, the onset of the reaction might take a week or two, and by then the infection might be widespread or lethal.

For example, defensins in the epidermis inhibit bacterial replication there. Complement can be activated by many infectious agents via the alternative pathway without the need for antigen–antibody interaction. Complement activation generates C5a, which attracts neutrophils, and C3b and C5b, which opsonize the agents so they can be more readily engulfed and killed by the phagocytes when these

arrive. Chemicals such as detergents can activate keratinocytes to produce cytokines, leading to epidermal proliferation and eventual shedding of the toxic agent. After infection or stimulation, certain cells can non-specifically secrete chemokines that bring inflammatory cells to the area. The main effector cells of the innate immune system are neutrophils, monocytes and macrophages.

The antigen-presenting cells have a role in both innate and acquired immunity. They can recognize certain patterns of molecules or chemicals common to many infectious agents. The lipopolysaccharide of Gram-negative bacteria is an example of such a 'pathogen-associated molecular pattern'. The receptors for these reside on cell membranes and are genetically derived.

Toll-like receptors are expressed on Langerhans cells, macrophages and regulatory T cells in the skin and provide the innate immune system with a certain specificity. They are transmembrane proteins, which recognize patterns, and different Toll receptors recognize different patterns and chemicals. For example, Toll-like receptor 2 recognizes

lipoproteins, while Toll-like receptor 3 recognizes double-stranded RNA. Toll-like receptors also up-regulate the expression of co-stimulatory molecules that allow appropriate recognition and response of the adaptive immune system.

Adaptive immune system

Adaptive immunity is not only more specific, but is also long-lasting. It generates cells that can persist in a relatively dormant state. These are ready to react quickly and powerfully when they encounter their antigen again – even years later.

Specific immune responses allow a targeted and amplified inflammatory response. To induce such a response, an antigen must be processed by an antigen-presenting cell such as a Langerhans cell, and then be presented to a T cell, with unique receptor molecules on its surface, that can bind the antigen presented to it. To elicit an inflammatory response, this antigen processing, presentation and binding process is repeated but, this time, with the purpose of bringing in inflammatory, phagocytic and cytotoxic cells to control the inflammation within the area.

It is still helpful, if rather artificial, to separate these elicited specific immune responses into four main types using the original classification of Coombs and Gell. All of these types cause reactions in the skin.

Type I: immediate hypersensitivity reactions

These are characterized by vasodilatation and an outpouring of fluid from blood vessels. Such reactions can be mimicked by drugs or toxins, which act directly, but immunological reactions are mediated by antibodies, and are manifestations of allergy. IgE and IgG4 antibodies, produced by plasma cells in organs other than the skin, attach themselves to mast cells in the dermis. These contain inflammatory mediators, both in granules and in their cytoplasm. The IgE antibody is attached to the mast cell by its Fc end, so that the antigen-combining site dangles from the mast cell like a hand on an arm (Fig. 2.14). When specific antigen combines with the hand parts of the immunoglobulin (the antigen-binding site or Fab end), the mast cell liberates its mediators into the surrounding tissue. Of these mediators, histamine (from the granules) and leukotrienes (from the cell membrane) induce vasodilatation, and endothelial cells retract, allowing transudation into the extravascular space. The vasodilatation causes a pink colour, and the transudation causes swelling. Urticaria and angioedema (p. 104) are examples of immediate hypersensitivity reactions occurring in the skin.

Antigen may be delivered to the skin from the outside (as in a bee sting). This will induce a swelling in everyone by a direct pharmacological action. However, some people, with IgE antibodies against antigens in the venom, swell even more at the site of the sting as the result of a specific immunological reaction. If they are extremely sensitive, they may develop wheezing, wheals and anaphylactic shock (see Fig. 25.5), because of a massive release of histamine into the circulation.

Antigens can also reach mast cells from inside the body. Those who are allergic to shellfish, for example, may develop urticaria within seconds, minutes or hours of eating one. Antigenic material, absorbed from the gut, passes to tissue mast cells via the circulation, and elicits an urticarial reaction after binding to specific IgE on mast cells in the skin.

Type II: humoral cytotoxic reactions

In the main, these involve IgG and IgM antibodies, which, like IgE, are produced by plasma cells and are present in the interstitial fluid of the skin. When they meet an antigen, they fix and activate complement through a series of enzymatic reactions that generate mediator and cytotoxic proteins. If bacteria enter the skin, IgG and IgM antibodies bind to antigens on them. Complement is activated through the classic pathway, and a number of mediators are generated. Amongst these are the chemotactic factor, C5a, which attracts polymorphs to the area of bacterial invasion, and the opsonin, C3b, which coats the bacteria so that they can be ingested and killed by polymorphs when these arrive (Fig. 2.15). Under certain circumstances, activation of complement can kill cells or organisms directly by the 'membrane attack complex' (C5b6789) in the terminal complement pathway. Complement can also be activated by bacteria directly through the alternative pathway; antibody is not required. The bacterial cell wall causes more C3b to be produced by the alternative pathway factors B, D and P
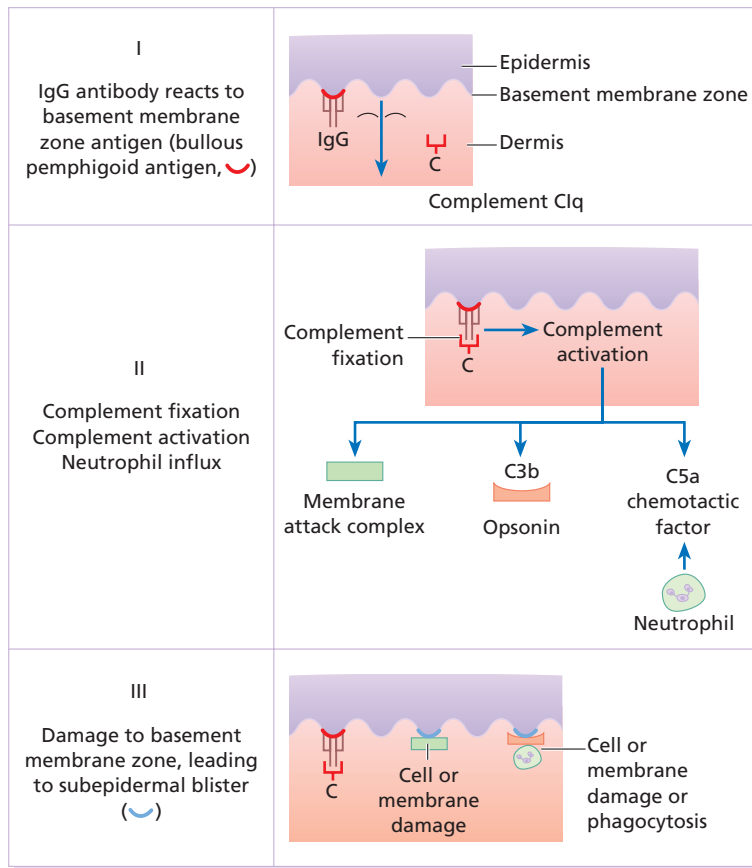
Fig. 2.15 Bullous pemphigoid: a humoral cytotoxic (type II) reaction against a basement membrane zone antigen.

(properdin). Aggregated IgA can also activate the alternative pathway.

Activation of either pathway produces C3b, the pivotal component of the complement system. Through the amplification loop, a single reaction can flood the area with C3b, C5a and other amplification loop and terminal pathway components. Complement is the mediator of humoral reactions.

Humoral cytotoxic reactions are typical of defence against infectious agents such as bacteria. However, they are also involved in certain autoimmune diseases such as pemphigoid (Chapter 9).

Occasionally, antibodies bind to the surface of a cell and activate it without causing its death or activating complement. Instead, the cell is stimulated to produce a hormone-like substance that may mediate disease. Pemphigus (Chapter 9) is a blistering disease of skin in which this type of reaction may be important.

Type III: immune complex-mediated reactions

Antigen may combine with antibodies near vital tissues so that the ensuing inflammatory response damages them. When an antigen arrives in the dermis (e.g. after a bite or an injection) it may combine with appropriate antibodies on the walls of blood vessels. Complement is activated, and polymorphonuclear leucocytes are brought to the area (an Arthus reaction). Degranulation of polymorphs liberates lysosomal enzymes that damage the vessel walls.

Antigen–antibody complexes can also be formed in the circulation, move to the small vessels in the skin and lodge there (Fig. 2.16). Complement will then be activated and inflammatory cells will injure the vessels as in the Arthus reaction. This causes oedema and the extravasation of red blood cells (e.g. the palpable purpura that characterizes vasculitis; Chapter 8).
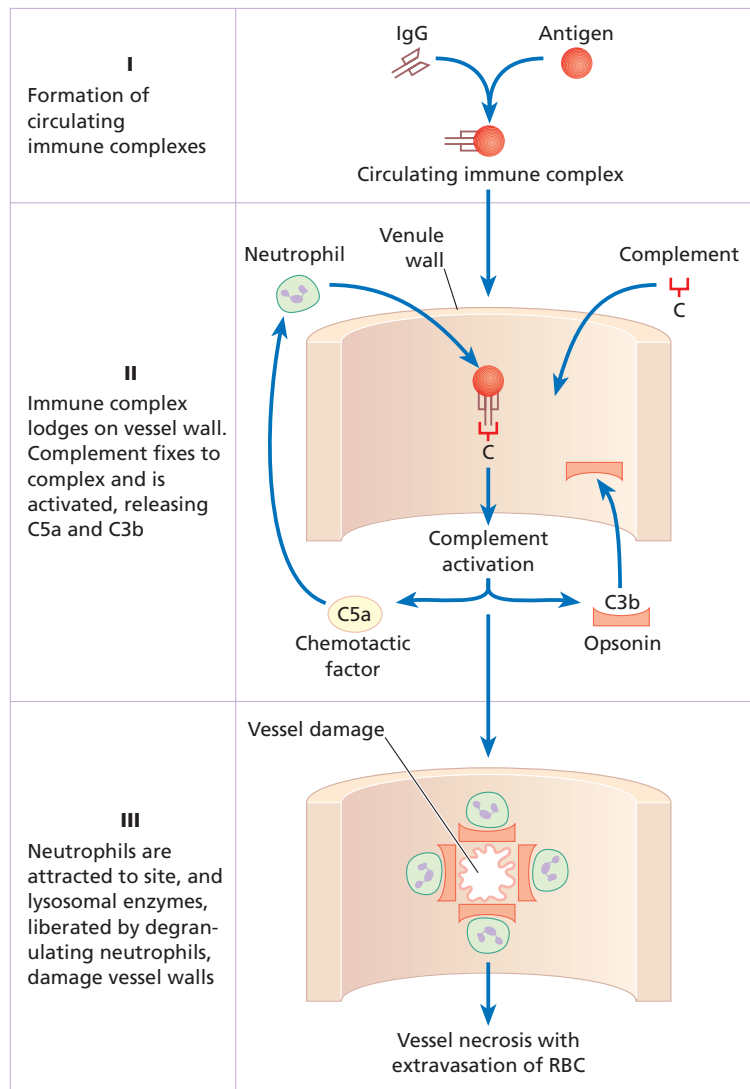
Fig. 2.16 Immune complex-mediated vasculitis (type III reaction). RBC, red blood cell.

Type IV: cell-mediated immune reactions

As the name implies, these are mediated by lymphocytes rather than by antibodies. Cell-mediated immune reactions are important in granulomas, delayed hypersensitivity reactions and allergic contact dermatitis. They probably also play a part in some photosensitive disorders, in protecting against cancer and in mediating delayed reactions to insect bites.

During the elicitation phase, most protein and chemical antigens entering the skin are processed by antigen-presenting cells such as macrophages and Langerhans cells (Fig. 2.17) and then interact with sensitized lymphocytes. The lymphocytes are stimulated to enlarge, divide and to secrete cytokines that can injure tissues directly and kill cells or microbes.

Allergic contact dermatitis

Induction (sensitization) phase (Fig. 2.17)

When the epidermal barrier is breached, the immune system provides the second line of defence. Among the keratinocytes are Langerhans cells, highly specialized intra-epidermal macrophages with tentacles that intertwine amongst the keratinocytes, providing
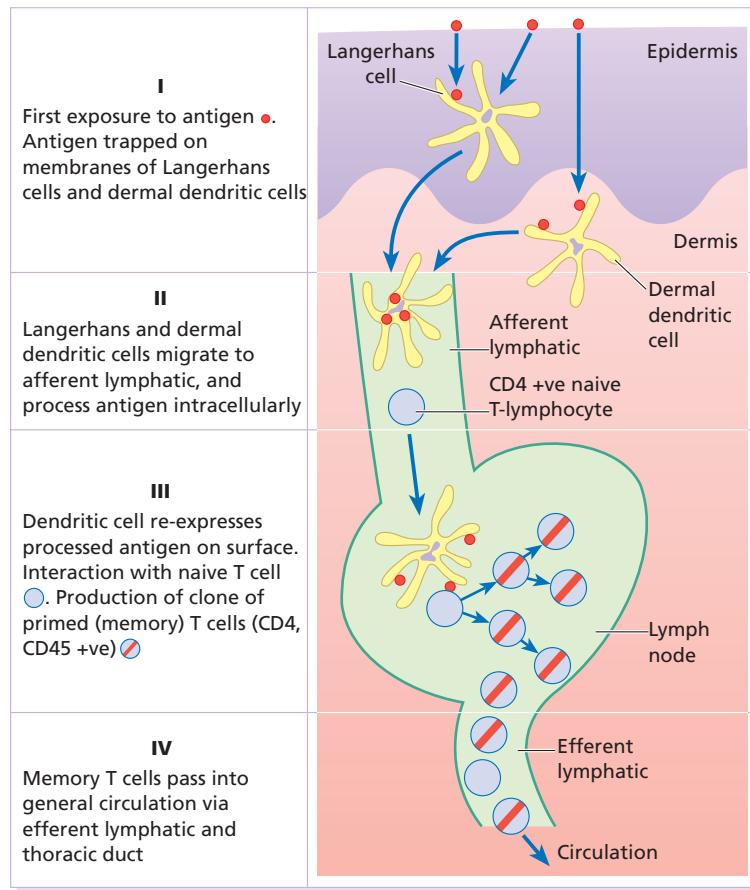
I

First exposure to antigen ●. Antigen trapped on membranes of Langerhans cells and dermal dendritic cells

II

Langerhans and dermal dendritic cells migrate to afferent lymphatic, and process antigen intracellularly

III

Dendritic cell re-expresses processed antigen on surface. Interaction with naive T cell ○. Production of clone of primed (memory) T cells (CD4, CD45 +ve) ◭

IV

Memory T cells pass into general circulation via efferent lymphatic and thoracic duct

Langerhans cell — Epidermis

Dermis

Dermal dendritic cell

Afferent lymphatic

CD4 +ve naive T-lymphocyte

Lymph node

Efferent lymphatic

Circulation

Fig. 2.17 Induction phase of allergic contact dermatitis (type IV) reaction.

a net (Fig. 2.7) to 'catch' antigens falling down on them from the surface, such as chemicals or the antigens of microbes or tumours. During the initial induction phase, the antigen is trapped by a Langerhans cell which then leaves the epidermis and migrates to the regional lymph node. To do this, it must retract its dendrites and 'swim upstream' from the prickle cell layer of the epidermis towards the basement membrane, against the 'flow' of keratinocytes generated by the epidermal basal cells. Once in the dermis, the Langerhans cell enters the lymphatic system, and by the time it reaches the regional lymph node it will have processed the antigen, which is re-expressed on its surface in conjunction with MHC class II molecules. In the node, the Langerhans cell mingles with crowds of lymphocytes, where it is quite likely to find a T cell with just the right TCR to bind its now processed antigen. Helper (CD4$^+$) T lymphocytes recognize antigen only in the presence

of cells bearing MHC class II antigens, such as the Langerhans cell. The interactions between surface molecules on a CD4$^+$ T cell and a Langerhans cell are shown in Fig. 2.12. To become activated the T lymphocyte must also bind itself tightly to certain 'accessory molecules', also called co-stimulatory molecules. If these are not engaged, then the immune response does not occur.

When a T cell interacts with an antigen-presenting cell carrying an antigen to which it can react, the T lymphocyte divides many times. This continuing division depends upon the persistence of antigen (and the antigen-presenting cells that contain it) and the T-cell growth factor IL-2. Eventually, a whole cadre of memory T cells is available to return to the skin to attack the antigen that stimulated their proliferation.

CD4$^+$, CD45$^+$ memory T lymphocytes then leave the node and circulate via lymphatic vessels, the

thoracic duct and blood. They return to the skin aided by 'homing molecules' (cutaneous lymphocyte antigen; CLA) on their surfaces that guide their trip so that they preferentially enter the dermis. In the absence of antigen, they merely pass through it, and again enter the lymphatic vessels to return and recirculate. These cells are sentinel cells (Fig. 2.18), alert for their own special antigens. They accumulate in the skin if the host again encounters the antigen that initially stimulated their production. This preferential circulation of lymphocytes into the skin is a special part of the 'skin immune system' and reflects a selective advantage for the body to circulate lymphocytes that react to skin and skin surface-derived antigens.

Elicitation (challenge) phase (Fig. 2.18)

When a T lymphocyte again encounters the antigen to which it is sensitized, it is ready to react. If the antigen is extracellular, as on an invading bacterium, toxin or chemical allergen, the CD4$^+$ T-helper cells do the work. The sequence of antigen processing by the Langerhans cell in the elicitation reaction is similar to the sequence of antigen processing during the induction phase, described above, that leads to the induction of immunity. The antigens get trapped by epidermal Langerhans cells or dermal dendritic cells, which process them intracellularly before re-expressing the modified antigenic determinant on their surfaces. In the elicitation reaction,
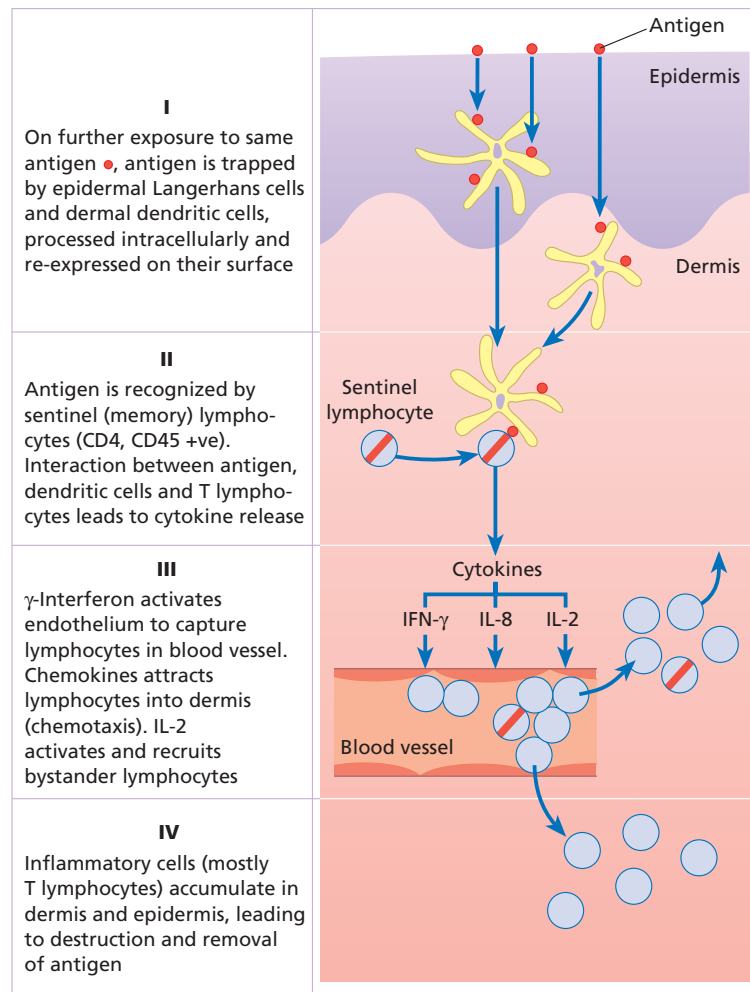

I On further exposure to same antigen ●, antigen is trapped by epidermal Langerhans cells and dermal dendritic cells, processed intracellularly and re-expressed on their surface	Antigen / Epidermis / Dermis
II Antigen is recognized by sentinel (memory) lymphocytes (CD4, CD45 +ve). Interaction between antigen, dendritic cells and T lymphocytes leads to cytokine release	Sentinel lymphocyte
III γ-Interferon activates endothelium to capture lymphocytes in blood vessel. Chemokines attracts lymphocytes into dermis (chemotaxis). IL-2 activates and recruits bystander lymphocytes	Cytokines / IFN-γ IL-8 IL-2 / Blood vessel
IV Inflammatory cells (mostly T lymphocytes) accumulate in dermis and epidermis, leading to destruction and removal of antigen	

Fig. 2.18 Elicitation phase of allergic contact dermatitis (type IV) reaction.

the Langerhans cells find appropriate T lymphocytes trafficking through the dermis. In the elicitiation phase, most antigen presentation occurs here. The antigen is presented to CD4$^+$ T cells, which are activated and produce cytokines that cause lymphocytes, polymorphonuclear leucocytes and monocytes in blood vessels to slow as they pass through the dermal blood vessels, then to stop and emigrate into the dermis causing inflammation (Fig. 2.18). Helper or cytotoxic lymphocytes help to stem the infection or eliminate antigen, and polymorphonuclear leucocytes engulf antigens and destroy them. The traffic of inflammatory cells in the epidermis and dermis is determined not only by cytokines produced by lymphocytes, but also by cytokines produced by injured keratinocytes (Fig. 2.11). For example, keratinocyte-derived chemokines bring lymphocytes into the epidermis, and IL-8, also produced by keratinocytes, bring in polymorphonuclear leukocytes, is a potent chemotactic factor for lymphocytes and polymorphs, and brings these up into the epidermis.

Response to intracellular antigens

Antigens coming from inside a cell, such as intracellular fungi or viruses and tumour antigens, are presented to cytotoxic T cells (CD8$^+$) by the MHC class I molecule. Presentation in this manner makes the infected cell liable to destruction by cytotoxic T lymphocytes or K cells. NK cells can also kill such cells, even though they have not been sensitized with antibody.

Granulomas

Granulomas form when cell-mediated immunity fails to eliminate antigen. Foreign body granulomas occur because material remains undigested. Immunological granulomas require the persistence of antigen, but the response is augmented by a cell-mediated immune reaction. Lymphokines, released by lymphocytes sensitized to the antigen, cause macrophages to differentiate into epithelioid cells and giant cells. These secrete other cytokines, which influence inflammatory events. Immunological granulomas

of the skin are characterized by Langhans giant cells (not to be confused with Langerhans cells; p. 16), epithelioid cells, and a surrounding mantle of lymphocytes.

Granulomatous reactions also occur when organisms cannot be destroyed (e.g. in tuberculosis, leprosy, leishmaniasis), or when a chemical cannot be eliminated (e.g. zirconium or beryllium). Similar reactions are seen in some persisting inflammations of undetermined cause (e.g. rosacea, granuloma annulare, sarcoidosis and certain forms of panniculitis).

> **Learning points**
>
> 1 Many skin disorders are good examples of an immune reaction at work. The more you know about the mechanisms, the more interesting the rashes become.
> 2 However, the immune system may not be the only culprit. If *Treponema pallidum* had not been discovered, syphilis might still be listed as an autoimmune disorder.
> 3 Because skin protects against infections, it has its own unique immune system to cope quickly with infectious agents breaching its barrier.

Further reading

Asadullah K, Sterry W & Volk HD. (2002) Analysis of cytokine expression in dermatology. *Archives of Dermatology* **138**, 1189–1196.

Boehncke WH. (2005) *Lymphocyte Homing to Skin: Immunology, Immunopathology, and Therapeutic Perspectives*. CRC Press, Boca Raton.

Bos JD. (2005) *Skin Immune System: Cutaneous Immunology and Clinical Immunodermatology*. CRC Press, Boca Raton.

Chaplin DD. (2006) Overview of the human immune response. *Journal of Allergy and Clinical Immunology* **117**, S430–S435.

Freinkel RK & Woodley DT. (2001) *The Biology of the Skin*. Parthenon, London.

Kang SSW, Sauls LS & Gaspari AA. (2006) Toll-like receptors: applications to dermatologic disease. *Journal of the American Academy of Dermatology* **54**, 951–983.

Yokoyama WM. (2005) Natural killer cell immune responses. *Immunology Reviews* **32**, 317–326.