MEDICAL PRACTICE

Today's Treatment

Diseases of the Skin

Structure and Function of Skin in Relation to Therapy

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Traditionally dermatological therapy has been associated with a degree of mystery and an unenviable number of well-worn clichés. This series aims to outline an up-to-date and rational approach to the treatment of common skin disorders. The first article will describe the structure and function of normal skin, as a knowledge of these is needed to understand the mechanisms of disease and the effects of drug action. The second introductory article will deal with more practical problems of prescribing.

Anatomy

The diagram opposite represents normal skin. It varies in thickness from about 3 to 5 mm and consists of three main layers: a stratified squamous epithelium called the epidermis, a connective-tissue dermis, and an underlying fatty layer. The normal function of each depends on the integrity of the others.

EPIDERMIS

The prickle cell layer consists of keratinocytes produced by cells dividing in the basal and suprabasal layers.

Keratinocytes contain bundles of fibrous protein (tonofibrils) and are connected with one another by numerous disc-shaped structures in the cell wall called desmosomes. With the electron microscope the "prickles" seen on light microscopy are shown to be cytoplasmic bridges and desmosomes (inset 2). As the keratinocytes approach the surface they change from living spherical cells, with prominent nuclei, to flattened, dead, thick-walled, and anucleate cells containing the fibrous protein keratin.

The most superficial layer of the epidermis, the horny layer (inset 1), is composed of many layers of these tightly packed cells. It can be removed experimentally and is a tough resilient membrane looking rather like tracing paper. The maturation of keratinocytes into horny cells is well synchronized in normal skin and is reflected by an orderly granular cell layer just deep to the horny layer.

Cells in the granular cell layer are distinguished by dense keratohyalin granules, which seem to form in or about the tonofibrils, extending along their lengths (inset 1). Histochemical methods show that the granular cells also possess many hydrolytic enzymes, which probably play a part in the death of the keratinocyte at this level.

Scattered mainly throughout the basal cell layer are cells whose dendritic processes pass between neighbouring keratinocytes. Routine light microscopic preparations tend to cause shrinkage of their

LEGEND TO FIGURE

Diagram of structure of normal skin. E1, Basal cell layer; E2, prickle cell layer; E3, granular cell layer; E4, horny cell layer; L, Langerhans cell; M, melanocyte; S, sebaceous gland; H1, hair shaft; H2, inner and outer hair root sheaths; H3, hair matrix; H4, dermal papillae; A1, subcutaneous vessel; A2, deep vascular plexus; A3, superficial vascular plexus; A4, papillary capillary; G1, eccrine sweat gland; G2, eccrine sweat duct.

Inset 1.—Junction of horny layer (top) and granular cell layer. Arrow: keratohyalin granule. (× 8,900). *Inset 2*—Keratinocyte in prickle cell layer. Broken arrow: tonofibril. Solid arrow: desmosome. (× 26,500). *Inset 3*—Part of a melanocyte containing numerous melanosomes (arrow). (× 17,600). *Inset 4*—Part of a Langerhans cell with distinctive rod-shaped and racket-shaped granules (arrow). (× 39,500).

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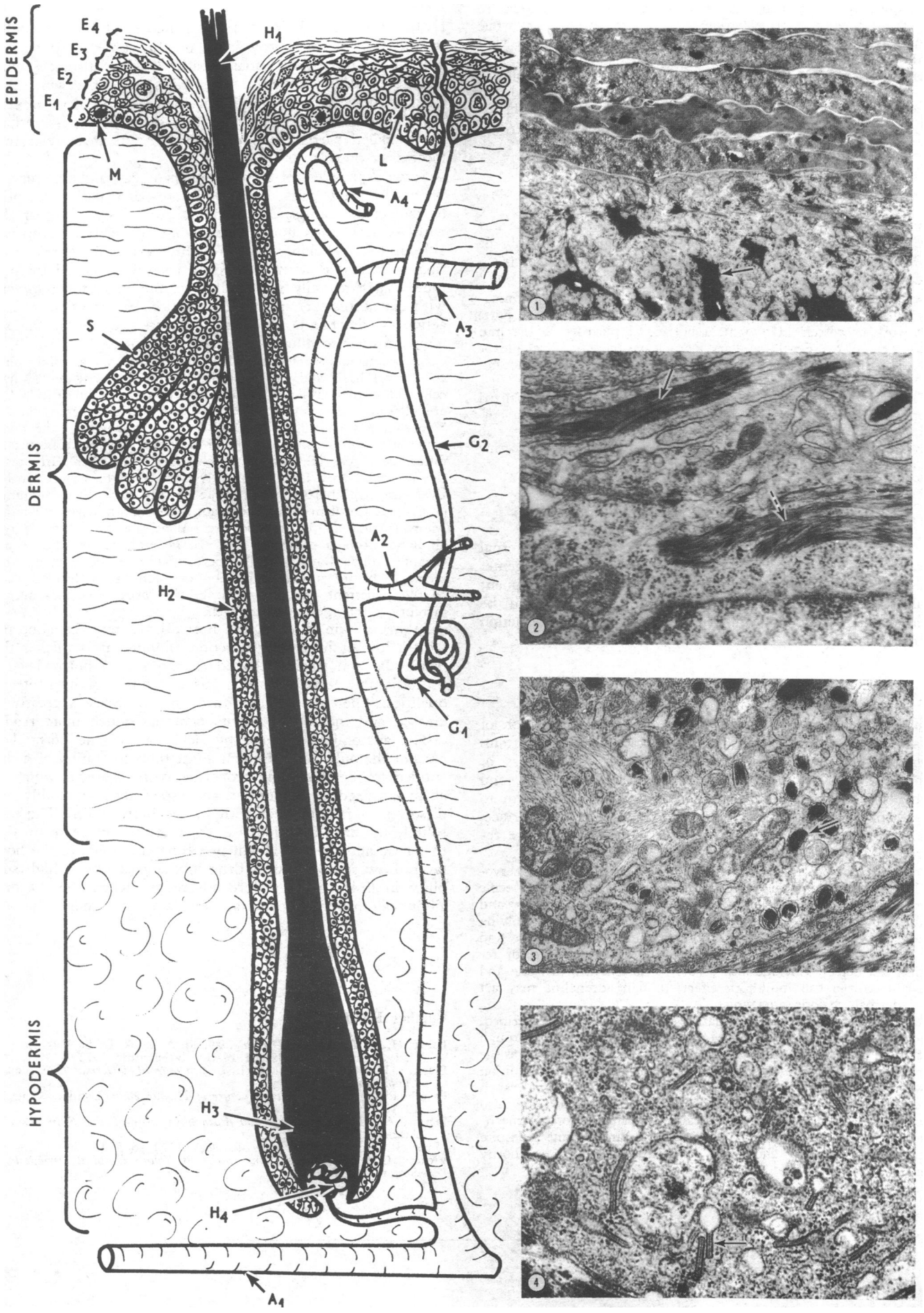
EPIDERMIS
DERMIS
HYPODERMIS
E4
E3
E2
E1
M
S
H1
H2
H3
H4
L
A4
A3
G2
A2
G1
A1
1
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4

cytoplasm, giving them the appearance of a clear cell. These are the pigment-forming melanocytes; they contain melanin granules and their precursors (melanosomes and premelanosomes while tonofibrils are absent (inset 3). They have no connexions with neighbouring cells.

The Langerhans cell is another dendritic cell found usually in the mid epidermis. It also does not contain tonofibrils and can be identified only by the presence of characteristic racket-shaped and disc-shaped granules which are not visible with the light microscope (inset 4).

DERMIS

The connective-tissue dermis supports the epidermis and separates it from the fatty layer below. It consists mainly of the fibrous proteins collagen and elastin embedded in a mucopolysaccharide ground substance.

Scattered throughout are fibroblasts, the odd chronic inflammatory cell, and mast cells. The connective-tissue framework supports a network of vessels in two main horizontal plexuses in the mid and upper dermis. Small capillary loops leave the superficial plexus and, though their apices reach the dermal papillae, they do not penetrate the epidermis.

The dermis also contains a fine nervous network, with specialized receptors in some areas. Again, this does not penetrate the epidermis. Neurovascular bundles supply the various appendages also found in the dermis (hair follicles, sabaceous glands, and eccrine and apocrine sweat glands—see diagram).

Physiology

The skin has many functions. It helps to preserve the internal mileu of the body; protects against external injurious agents; takes part in sensation, temperature regulation, and pigment production; and synthesizes vitamins. Only protection will be discussed here as this is important in considering the action of drugs on the skin.

KERATINIZATION

Though all layers of the skin help to prevent penetration of a locally applied drug, the horny layer is the most important. Its formation depends on the highly organized process of keratinization. Keratinocytes have a relatively short life, and probably in normal skin it takes about 28 days for them to pass from their origin in the basal layer to the skin surface, where they are shed as horny squames. The cells lost are replaced by the mitotic activity in the deeper layers.

Probably epidermal mitosis is influenced by a delicate servomechanism using a negative feed-back principle. A tissue-specific glycoprotein (chalone) has been isolated from the epidermis, and inhibits mitotic activity, possibly through processes involving adenyl cyclase and cyclic AMP. Trauma inhibits this chalone and the resulting increased rate of mitosis is partly responsible for repairing the defect. Chalone also seems to need hydrocortisone and adrenaline for a full inhibitory effect, though adrenaline may act via a dermal chalone antagonist.

Other epidermal growth-stimulating factors have been described, and there dermis may influence epidermal differentiation through substances produced by fibroblasts. Further local factors such as the Langerhans cell in influencing keratinization, and contact inhibition between epidermal cells may have roles, while other stimuli such as temperature and circulating thyroid and sex hormones may also be concerned. This interplay of local and systemic control mechanisms keeps normal skin at a relatively constant thickness despite repeated trauma, and allows it to produce an effective horny layer.

BARRIER FUNCTION AND PERCUTANEOUS ABSORPTION

Drugs applied to the skin might penetrate it by two routes: directly across the horny layer or through the appendages. The horny layer is the major pathway for substances which penetrate rapidly, while the appendages play a part when there is slow penetration. The horny layer behaves as a semi-permeable membrane but it is its resistance to penetration—the so-called barrier function—which is the most relevant to local drug therapy.

Some skin is less of a barrier than others, and this may explain why some parts of the body are particularly susceptible to contact dermatitis. Two extreme examples are palmar skin, with its very thick horny layer, which is relatively impermeable, and scrotal skin, which is highly permeable. Barrier function is decreased when the horny layer is removed by stripping (experimentally with Sellotape, but in common practice with elastic plaster) and with hydration, dehydration, and the action of detergents and lipid solvents. A rise in the skin temperature also allows increased penetration.

Several factors suggest that barrier function has a purely physicochemical basis and does not depend on the activities of living cells. Thus the physiocochemical laws of penetration (Fick's Law) are obeyed and the horny layer acts as a resistance to diffusion. Hence at low concentrations and a fixed temperature, the rate of penetration of a substance is proportional to the concentration difference across the barrier membrane (horny layer). In practice the normal horny layer is slightly permeable to water but relatively impermeable to ions in aqueous solution such as sodium or potassium. Covalent substance in aqueous solution behave differently. Many (including glucose and urea) penetrate poorly, while some aliphatic alcohols penetrate well. In general, solutes dissolved in organic liquids show a similar permeability to the solvent. There seems to be no simple correlation between the molecular weight of the penetrant and its permeability: large molecules such as mercuric perchloride penetrate well.

In many skin diseases the horny layer may be abnormal, with a loss of its barrier function. Though it is thicker than usual, the abnormal nucleated (parakeratotic) horny layer of psoriasis and chronic eczema has lost much of its protective qualities. The loss of water through the scales is greatly increased and therapeutic agents penetrate much more readily.

The anatomical site and physical state of the horny layer are not the only factors which affect the penetration of a drug applied to the skin. The properties of the base in which the agent is mixed are important, and especially how readily drug dissolves in it compared with in the horny layer. The more soluble the drug is in its base, the more it will be retained by that base and the less it will penetrate the lipids of the horny layer. Low solubility of a drug in the base and a high solubility in lipids are therefore advantages when the doctor is aiming at maximum penetration of a drug through the skin.

Further Reading

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