Dermatology in Internal Medicine

Sam Shuster

Dermatology in internal medicine

SAM SHUSTER

Professor of Dermatology,
University of Newcastle upon Tyne

OXFORD
OXFORD UNIVERSITY PRESS
NEW YORK TORONTO
1978

Oxford University Press, Walton Street, Oxford OX2 6DP

OXFORD LONDON GLASGOW
NEW YORK TORONTO MELBOURNE WELLINGTON
KUALA LUMPUR SINGAPORE JAKARTA HONG KONG TOKYO
DELHI BOMBAY CALCUTTA MADRAS KARACHI
IBADAN NAIROBI DAR ES SALAAM CAPE TOWN

British Library Cataloguing in Publication Data

Shuster, Sam
Dermatology in internal medicine. – (Oxford medical publications).
1. Skin – Diseases.
I. Title II. Series
616.5 RL71 78–40436
ISBN 0–19–261142–9

Phototypeset by Western Printing Services Ltd, Bristol
Printed in Great Britain
by J. W. Arrowsmith Ltd., Bristol

Preface

The problem with dermatological texts is size and sense. 'Size' because they are either too big or too small and the small ones are left behind with graduation and the big ones are for the professionals, leaving only a few texts for the interested majority in the middle. 'Sense' is a problem because dermatology is so easily practised at a visual descriptive level that mechanisms have not been its strongest point. That means that there is little you can deduce for yourself (as you can for the causes and consequences of hypokalaemia for example). So, for the physician, learning from skin books is a heavy, memory job.

My lead into these two problems happened by chance in writing a new Dermatology section for *Price's Textbook of the practice of medicine*. This meant covering dermatological medicine as well as some purely cutaneous diseases which were important because of their diagnostic or conceptual relevance; yet the section had to be kept in the confines of a not-too-large general textbook. That sorted out my problem of size. But boiling down the words also helped in the distillation of some of the sense. What I soon found was that a purely clinical approach led me to treat many of the diseases like old friends, and like old friends I could no longer recognize them for what they really were and how they actually appeared to others to whom they were less familiar. So rather than an avuncular descriptive account I set about trying to find the ground rules for a more analytical approach. From this I tried to simplify, not to cut corners, but to make more intelligible. In this way it was possible in many instances to build a framework of cause and effect in which the reader's thought and intuition would have a chance to find its own way without the lead weight of memory. This approach is not yet universally applicable to skin diseases, many of which mirror social life where 'what' happens is the fact, 'why' is the fable, and the mechanism 'how' is the bridge between. In this situation I have produced plans for bridges but clearly indicated they are not yet on the map. Complete cover of the subject

has not been my aim, that would have meant yet another large book with lots of very small print; instead I have given references (and a list of books and journals). But I have ensured that the text was adequate for the reader for whom I was writing. So for whom other than myself was I writing? Mostly for the postgraduate with an interest; either enforced by the M.R.C.P. examination, for which this should do the trick, or spontaneous, when the cure might take longer. But I am also much concerned with the new trainee in dermatology, the registrar and resident, because it is essential for him to take a synoptic and analytical view at the very beginning to be certain that he can build the facts from the big books into a firm, integrated conceptual framework rather than adding them like another coloured petal to his dermatological flowering.

I should like to thank my colleagues for not minding my having ignored their advice and Dr. Phil Harrison in particular who gave me the correct version of all the references I have misquoted.

February 1978 S. S.

Contents

1. Skin structure and function

STRUCTURE OF SKIN

The basic structural elements of skin are simple: the complexity of skin owes itself to the great variety with which these structures are arranged. Diagrams of skin structure must therefore be taken only as an outline of these basic elements. The skin has an epidermis concerned with producing protective keratin and pigment (melanin) and a dermis which provides the strength of the skin and houses the appendages.

Epidermis and stratum corneum

This layer is 50–100 μm thick. The living epidermis consists of keratinocytes, melanocytes, Langerhans cells, and some undefined cells. Sensory nerve endings mostly terminate at the dermo-epidermal junction and there is continued debate about the fibres which do penetrate into the epidermis. The epidermis is maintained by division of the germinative cells which are in the basal layer and the turnover time of epidermis is about 50 days for forearm skin. In many mammals a germinative cell and its daughter cells constitute a structural unit which is repeated over the skin surface. Although cell division is random the geometry of the cells itself dictates an ordered movement, the cells moving out in regular columns when division is slow. The way in which germinative cell division is controlled in the epidermis is unknown.[5] The predominant response to local need (e.g. the response to injury and friction) and the close matching of cell production and loss implies a local mechanism.[9] Chemical regulators have been postulated, e.g. 'chalone', a locally produced inhibitor, but the evidence for this is poor. The effect of Epidermal Growth Factor (recently found in human blood and urine and shown to be similar to urogastrone) is unknown in man although it speeds both epidermal cell division and keratinization in the new-born mouse.

After dividing, some of the cells leave the germinative com-

partment and become differentiating keratinocytes. These cells synthesize the fibrillar protein keratin which is laid down as tonofilaments and gives the stratum corneum its toughness. Keratin is made up of units of prekeratin each consisting of two subunits each with a primary structure of 3 peptide chains cross-linked as a α-helical structure; as with collagen [p. 229] this confers strength. The skin is under constant mechanical stress: the epidermis maintains a flexible resistance to these forces in part by the keratin and in part by specialized areas of contact between epidermal cells, the desmosomes. In formalin fixed sections these produce the artefacts of 'prickles' which give the name to this cell layer. As the keratinocytes move upwards they reach the granular layer. Here quite rapidly the cells die, the nucleus disappears, and the cells assume the flattened shape of horny cells of the skin surface. The cell membranes and associated keratin tonofilaments make a tough waterproof layer. This is partly due to associated lipid and scaly skin and abnormal epidermal lipogenesis are usually found together [p. 48]. The thickness and appearance of these cell layers varies in different parts of the body. In palmar and plantar skin there is a much thicker stratum corneum than elsewhere and the epidermal ridges are deeper; the latter serves to increase the number of dividing cells and the area of contact between epidermis and dermis in areas particularly subject to friction.

The melanocytes are derived from the neural crest cells. They are dendritic and lie on the basement membrane. They synthesize the complex polymer melanin from phenylalanine via tyrosine by a series of reactions catalysed initially by tyrosinase. The melanin is formed in specialized organelles, melanosomes, and remains as a granular insoluble material. It passes from the melanocyte into the keratinocyte both by a process of 'injection' and phagocytosis and passes out through the skin with the shedding scales. Pigmentation is related more to melanin synthesis than to number of melanocytes in that there is no difference in number of melanocytes in Negro and Caucasian skin [see p. 82].

The function of the Langerhans cell is not clear. It has distinctive features, notably 'tennis racquet' shaped organelles and staining with ATPase. Rôles in both phagocytosis and control of epidermopoiesis are claimed but unproved. Another interesting possibility is they may be related to the initiation of immune

reactions. Despite its similar dendritic appearance to the melanocyte and its increase in number when melanocytes disappear, the two cell types are unrelated.

The dermo-epidermal junction

This zone is vital for maintaining adherence of epidermis to dermis. Evidence from enzymic attack, electron-microscopy, and disease suggest that it is constituted by a mucoprotein 'glue' containing fine collagen anchoring, fibres.

The dermis

The bulk of the dermis is collagen. Its thickness varies greatly with age and sex and site [see p. 25]. It is thick on the skin of the back and thin on the eyelids: it is thicker in males than females and thins with age. On the extensor surface of the forearm, a site at which it is often measured clinically, it is about 1 mm in young adult females and 1·4 mm in young adult males. The collagen layer is organized in two main parts: superficially under the epidermis at the level of the papillae, and the more deeply placed fibres. The superficial fibres are finer and this probably represents the need to remodel with changes in epidermal configuration: this part of the dermis is rich in collagenase which is no doubt involved in the process. The deeper fibres are coarse. They are arranged in a three-dimensional irregular lattice. The specific organization of these fibres varies with site so as to cope with the stresses to which the particular region is exposed. Thus in some parts (e.g. the finger pulps) the fibres are tethered deeply; elsewhere (e.g. over a joint) they are arranged to permit mobility. Associated with the collagen are the elastic fibres which can easily be distinguished by both light and electron microscopy. Although it is suggested that they pull the collagen lattice back to shape after stretch deformation their precise rôle is not clear and the toughness and elasticity of the skin is mainly due to the collagen fibres.

The collagen is synthesized and secreted by fibroblasts. These processes are described in greater detail on p. 229. The immature collagen has few intermolecular links and so is very soluble; with time more cross-links are formed and the fibril eventually becomes tougher and less soluble. Thus the passage from saline to neutral salt solubility to insolubility is an index of collagen age.

In various disease states there are alterations in collagen solubility and physical properties due to fundamental defects in fibril synthesis and maturation. Thus the more cross-linked the fibrils the more resistant they are to stretch and the more 'inelastic'. The metabolic turnover of collagen varies with its age and molecular type. The half-life of insoluble collagen is not certainly known in man but may be of the order of two years. This may however be altered by disease and drugs.

The collagen and elastic fibres are surrounded by a gel of glycosaminoglycans (mucopolysaccharides). Mast cells secrete dermal mucopolysaccharides but their total source of origin is not known for certain. The function of these glycosaminoglycans is unknown but some appears to be important for the structure and function of the collagen fibrils. The dermis contains the usual array of tissue components as well as the specialized features of sensory nerve endings and skin appendages.

Sensory nerves

The classification of cutaneous sensory nerves is still evolving. The present view is that free nerve endings are the most frequent and occur in both hairy and glabrous skin. The specialized 'organized' nerve endings, the Paccinian and Meissner's corpuscles and Merkel's discs, occur only in glabrous skin and mucocutaneous junctions. With the exception of Merkel cells, which have been found in the epidermis and the sensory status of which is unknown, all sensory endings are in the dermis. The free nerve endings surround the hairs providing some sort of sensory apparatus. Temperature, touch, and pain are transmitted by free nerve endings and stimulus-specific receptors have not been identified. Of the specialized endings only the function of the Paccinian corpuscle (pressure-deformation) has been certainly elucidated. A feature of cutaneous sensory organization is the overlap of the various nerve endings so that each area has a multiple innervation. The rôle of purinergic fibres and Substance P is not yet known. There is some evidence that the former may be concerned with the axon-reflex flare.

Hairs

There are about 5 million hairs in the adult, 0.1 million of which are on the scalp. The number of hair follicles does not increase

after birth though the number and appearance of the hairs is modified continuously throughout life with a decrease in number in middle and old age. The hair grows from a root which consists of specialized epidermal cells surrounding a core of connective tissue. The hair follicle also contains melanocytes which provide hair colour. Hairs are usually divided into vellous (short, pale, and fine) and terminal (coarse, dark, and large). Hair is a specialized keratin formed as is the horny layer from dead keratinocytes. Most of the features of the hair are genetically controlled—rate of growth, duration of cycle, diameter, crimp, and colour—and these features are maintained with transplantation. The most important determinant of length of hair is the duration of the follicular growth phase. Thus the growth rate for both the long hairs on the scalp and the short hairs on the chest is 0·4 mm per day; on the scalp the hairs grow for three years or so and on the chest for three or four months. Hair follicles have a repetitive sequential growth pattern (confusingly known as the 'hair cycle') with a growing phase (anagen), a short phase of involution (catagen), and a resting phase (telogen) of varying length ending with shedding of the effete follicle—known as a club hair because of the shape of its spent root. The telogen club hair is usually shed as the new hair grows. Growth of the new hair is induced by the matrix of connective tissue left behind in the dermis as the hair involutes from catagen to telogen. The new hair repeats the same sequence. Shortly after birth the growth phases of adjacent scalp follicles are synchronous so that hair loss and regrowth occurs in waves. Throughout subsequent life adjacent scalp follicles are asynchronous, with over 80 per cent in the growing phase. In certain acute diseases (e.g. pneumonia) and physiological states (e.g. parturition) the hairs are synchronized through catagen into the resting phase and this leads to a diffuse hair loss known as telogen effluvium [p. 94].

Sebaceous glands

These lobulated holocrine glands are associated with hair follicles, into the upper part of which they empty. Their density and size is greatest on the scalp, face, and front and back of the upper chest. Sebum is a mixture of triglyceride, fatty acid, wax ester, squalene, and cholesterol. By waterproofing hair, sebum performs a thermoregulatory function in hairy mammals but the

function of sebum is unknown in man. Although many consider the glands to be vestigial, the author considers this unlikely (i) because they have a close and complex endocrine control; (ii) because they are, relative to the hairs, enlarged rather than atrophied in areas such as the face and upper back; and (iii) because of the ubiquity of their main disease, acne. Both sebum and acne may serve a biological purpose [p. 42]. The activity of the sebaceous glands is totally under endocrine control in man. The precise nature of this control is still uncertain but the pituitary, thyroid, adrenals, and gonads all play a part. The major influences are androgens and a pituitary factor which has been identified as an MSH peptide in rodents but not in man. Sebum secretion occurs *in utero* then declines in early life beginning again at the time of puberty; it decreases again from middle age in females and to a much lesser extent in males. A number of endocrine, metabolic, and neurological disorders are associated with a change in sebum secretion.

Sweat glands

Apocrine sweat glands. These are found mainly in the axillae and anogenital skin where they open into hair follicles. They are merocrine glands and the 'decapitation secretion' of light microscopy is an artefact, secretion being analagous to reversed pinocytosis with cell membrane formation. The general form of the glands resembles an eccrine gland. They respond sluggishly to both adrenergic and cholinergenic stimuli with excretion of a whiteish viscous fluid, but it is not certain that this reflects a physiological secretory control. In the author's view, the merocrine nature of the secretion makes it more likely that the effect of neurotransmitters is on ductal expulsion. They also appear to be androgen primed. Freshly secreted aprocrine sweat is odourless and its bacterial decomposition produces the characteristic axillary odour. The function of apocrine sweat is unknown but may once have been pheromonal.

Eccrine sweat glands. These cover most of the body surface with a ratio to hair follicles of 3 to 1 (0·3:1 on the face). New sweat glands probably do not develop after birth. The glands consist of a secretory coil (shaped like a sandworm cast) in the lower dermis passing up to the epidermis by an almost straight duct.

The duct begins to coil in the epidermis and continues to spiral out through the stratum corneum [see p. 10]. There are two cell types in the duct, one rich in glycogen and thought to be concerned with electrolyte transport and the other which contains mucopolysaccharide. The gland is sympathetically innervated but has a cholinergic transmitter. Thus sweating can be blocked by sympathectomy or an anticholinergic drug. The gland is also exceptional in that following post-ganglionic denervation it is hyposensitive to pharmacological stimulation. The sweat is secreted in the coil as an isotonic fluid and it is elaborated into a hypotonic fluid in the duct by disproportionate absorption of water and salts. Thus the concentration of sodium increases the faster the rate of sweating; this is important in the diagnosis of fibrocystic disease. Although sweat sodium is generally thought to be wasted it seems likely to the author that it is in fact part of a mechanism to maintain patency of the duct as it passes through the keratin since maceration occlusion of the duct [see pp. 10 and 109] is less rapid with salt solutions than with water. The spiral nature of the duct also seems to be a device to minimize occlusion by external pressure.

In addition to sodium, potassium, urea, and calcium the sweat contains small quantities of protein, mucopolysaccharide, and amino acids. During acclimatization to heat, sweat rate increases and sweat sodium concentration declines. The former is a local effect of 'training'; the latter is partly due to aldosterone. In the hairy skin, the function of the sweat gland is thermoregulatory, sweating being stimulated by the balance between hypothalamic temperature and the 'setting' of the thermoregulatory centre. In the glabrous skin of the palms and soles (and to a lesser extent on the face, axillae, areolae, and anogenital regions) sweating is primarily neural or emotional; the palmar sweat response to stress or pain is extremely rapid, though variable from individual to individual. Although the biological purpose of 'emotional' sweating is unknown, the increased friction of wet keratin would offer advantages in both fight (hand grip) and flight (foot grip).

Nails

Like hair, nails are specialized types of keratin. The nail plate lies on the nail bed, it grows from the nail matrix which lies under the nail fold and extends into the lunula. It is believed that a small

contribution to the underside of the nail (ventral nail) is also made from the keratinizing cells of the nail bed distal to the lunula. The rate of growth of nails is about 0·1 mm per day. The rate of growth is different for the different fingers: it is fastest for the middle finger less for the fore and ring fingers and least for the thumb and little finger. Thus the shape of the graph joining these rates corresponds to the line joining the tips of the outstretched fingers. No doubt this represents a genetic recognition of the rate of wear and tear in man's recent and more physical past. This may also explain the greater rate of growth on the dominant hand.

Skin colour

The three major determinants of skin colour in health are melanin [see p. 81], haemoglobin, and carotenoids.

Melanin produces a brown colour in the epidermis; deep in the dermis it produces a blue colour because of the Tyndall light scattering effect. The colour of haemoglobin depends upon quantity and state of oxidation. Extravasated blood will always appear bright red if the corpuscles are lysed but may appear blue when the cells are intact. It is not clear whether this is due to oxygenation or the light scattering effect of the erythrocytes. The characteristic yellowish colour comes mostly from carotenoids in the stratum corneum and so it is particularly obvious in the palm where the keratin layer is thick.

The combination of these three colours and their modification by disease leads to the great variation to be seen.

Ridged skin

Ridged skin occurs on the volar aspects of the palms and soles in primates and certain other mammals. The probable function of the ridges is to increase friction and tactile discrimination. The ridge pattern is determined by the dermal architecture though precisely how is not known. The clinical interest in dermatoglyphics derives from the totally genetic basis of their control. Thus the total digital ridge count is transmitted precisely as would be predicted of Mendelian genetics. Although gross and easily detected abnormalities have been detected, e.g. the diagnostically useful wide 'atd' palmar triradiate in Down's syndrome, many other abnormalities have been found by statistical

analysis of pattern and ridge count. Because of the genetic specificity further analysis is likely to assist in the classification of disease much as has the HLA system.

FUNCTIONS OF SKIN

Classical lists of skin functions are unsatisfactory because they are isolated items of systemic functions and local attributes. Although the following account is a personal view the author feels obliged to put it forward in the absence of any recent account because it is impossible to understand the skin and its diseases without a functional understanding.

The functions of skin can be understood only in the light of its anatomical position and consequent functional evolution. The fundamental requirement of a cuticle is resistance to (and separation from) the environment. In the case of mammalian skin this entails resistance to injury and imperviousness (from within and without). The former immediately devolves into mechanical properties and wear and repair. These provide the primary requirements of skin, namely *mechanical appropriateness*, *wear and repair*, *imperviousness*. Resistance to ultraviolet injury is a later adaptive response. The evolutionary solution to these requirements has been to leave mechanical appropriateness to a relatively inert dermis and the remainder to a very active epidermis. A remarkable and unexpected feature of the apparently inert dermis is its capacity to initiate events in the epidermis. Transplantation – recombination of epidermis and dermis shows that dermis initiates the development of structural and functional characteristics of skin such as site specificity and appendages. Mechanical needs are predictable and in the course of evolution have become incorporated structurally. In this way the toughness and elasticity of the dermis have become nicely attuned to the needs of different areas, with dermal flexibility over joints; toughness of the back skin, which is unprotected in flight; and the essential delicacy of the periocular skin. These and many other local properties of the skin are now genetically imprinted.

Wear and repair require a different approach since the magnitude of the one and need for the other are unpredictable. Thus the epidermis responds locally to wear, producing more keratin to cope with frictional needs, and it also responds locally to

wounding. Where prediction of need has been possible these responses have to some extent become inbuilt structurally—e.g. the thick keratin of the palms and soles and the epidermis that goes with it, or again the fast turnover of buccal epidermis and its rapid response to wounding. We can but be grateful that the solution to wear and repair was continuous replacement rather than the reptilian solution of periodic shedding. But having taken this solution it followed that the outer layer of friction shedding cells would also have to provide the essential imperviousness and this explains the curious structure and properties of the stratum corneum. A further consequence of this solution becomes apparent with the evolutionary replacement of the hair by sweat glands. Their ducts have to remain patent in a moving and potentially collapsible layer. This is beautifully solved by a non-compressible spiral and by maintaining sufficient sodium in the sweat to prevent maceration occlusion of its duct [see pp. 7 and 109].

A further consequence of the fundamental requirement of resistance to the environment in mammals and birds is the need for thermostasis. In many mammals metabolic production and thermal loss are mainly balanced by hair. The replacement of hair by sweat glands gave man a far greater range and speed of thermoregulatory control. He could survive the cold by fires and other animals' hair, and heat by sweating. Thus the skin evolved a thermoregulatory rather than a purely insulatory function. Subcutaneous fat is undoubtedly involved in this and the inverse relationship between the amount of subcutaneous fat and sweating in males and females may well have had a thermoregulatory basis in the past.

The evolution of the protective role of the skin is again apparent in the evolution of melanin pigmentation and its relationship to vitamin D synthesis. Melanization of the skin as distinct from the hair is likely to have evolved with the loss of hair which protected against ultraviolet irradiation. Melanin undoubtedly protects the skin from ultraviolet induced burning, atrophy, and cancer and it has also been suggested that it may protect the organism from excessive vitamin D synthesis. Perhaps more relevant is the balance which the degree of melanization strikes between skin cancer protection and vitamin D deficiency.

A further inevitable consequence of the skin's position is that

it houses neural sensors of the environment. In this respect the role of the skin is passive except that the density and structure of the receptors are modified by the skin's structure e.g. the organization of sensory fibres around hairs which inadvertently therefore constitute a tactile organ. The only truly cutaneous modality is itch (the tactile components of grooming and sexual behavior are possible exceptions) and its function was probably to warn of parasites and elicit the appropriate removal response of scratching.

With increasing evolutionary complexity one of the new and most important consequences of the skin's position is that it becomes an organ of communication and of social and sexual modulation. The sebaceous appendages appear to have been related to maintenance of the thermoregulatory function of hair in mammals and have been devolving with them in man. Acne is the consequence of this otherwise successful piece of biological planning, the follicles devolving more rapidly than the sebaceous glands. It may well be however that both the residual sebaceous glands and acne have functions not yet understood [p. 42]. In rodents and some primates they have evolved into pheromonal glands which have profound effects on social and sexual behaviour, thus the hormones which control the sebaceous glands, mainly androgens and melanocyte stimulating hormone (MSH), have taken on a new social role through these glands. In addition to the pheromonal smell mechanism, skin colour and appearance may indicate sexual state, fear, and anger: thus in the vervet monkey the blue scrotal colour (produced by melanin in dermal melanocytes) is the insignium of social and sexual rank. In other species the smell and appearance of the skin constitute a conversation without words. Although most attention has been given to the motor component of these social functions the sensory component is also important, as in the specialized tactile sensations of sexual and grooming behaviour: in particular it is not known how much is a discrete tactile sensation and how much is central organization.

The skin metabolizes hormones, but with one exception it is not yet known whether this contributes significantly to the systemic pool (although it is the author's belief that it will prove to do so for androgens: the origin of the hyperoestrogenism caused by certain skin diseases [p. 76] is not known). This exception is