Structure and function of aged skin

The most obvious outward signs of 'getting old' reside in the skin. However, the majority of these stigmata are the result of cumulated environmental damage and not due to intrinsic aging. Alterations that take place in non sun-exposed skin with increasing chronological age are more subtle than those due to climatic exposure but do result in detectable changes in appearance and function.

The skin surface and the stratum corneum

Poets talk of the 'bloom of youth' and difficult though it is to define, it does seem to exist. Even non sun-exposed skin looks and feels different in old age. It seems that the changes in appearance are primarily the result of altered optical properties of the stratum corneum and the skin surface. Although wrinkle lines increase in numbers, depth and prominence, the normal skin fine markings decrease with age. This change is more prominent in sun-exposed sites but is also seen in covered parts. The furrows are narrower and the lines intersect at less acute angles. The stratum corneum itself changes little if at all in thickness but its component cells - the keratinocytes -increase in surface area. Whether this increase in area is accompanied by a change in keratinocyte thickness is uncertain, though it seems likely that the cells do become thinner.

The change in mean keratinocyte area may have implications for stratum corneum function because of the decreased volume of interkeratinocyte space per unit volume stratum corneum compared with a horny layer containing smaller keratinocyte.If, as is believed, the interkeratinocyte space is important in percutaneous penetration, the movement of water vapour (transepidermal water loss) and in cell to cell cohesion, decrease in this structure owing to aging may be expected to result in changes in these functions. Observations suggest that there is indeed a drop in transepidermal water loss and cell to cell binding forces but the changes recorded are small and at the limit of sensitivities of the monitoring techniques. The same may apply to the rate of percutaneous penetration of topically applied substances, although there is very little published evidence to support this contention. Indirect supporting evidence is found in the increased time taken for the skin of the elderly to blister after application of

ammonium hydroxide and in the decreased reaction noted in aged skin after application of a variety of irritating substances.

The rate of renewal of the stratum corneum is undeniably altered in the elderly. Measurements taken with the fluorescent dyes tetrachlorsalicylanide and dansyl chloride indicate that the rate of loss of keratinocytes at the surface progressively decreases with age. In these tests the marker substances are placed on the skin surface occlusively and penetrate the stratum corneum. The time to disappearance of the fluorescence (extinction time) is the time taken for renewal of the stratum corneum and parallels the rate of epidermal cell production. The decreased rate of desquamation may give rise to an altered pattern of cell-loss and could in part account for the changed appearance of the skin surface.

There appears to have been relatively little investigation of any change in the mechanical properties of the stratum corneum that occur as a result of age. Observation would suggest that there is decreased elasticity and breaking strength resulting in an increase in fragility. This would explain the ease with which superficial fissuring occurs in the skin of the elderly when it is inflamed. It is often suggested that these altered physical properties are a result of a decreased stratum corneum water content in old age, but there is sparse evidence to support this suggestion.

Epidermal changes

The epidermis becomes thinner and loses its undulating Rete pattern with increasing age. The degree of epidermal thinning that occurs is extremely variable, as are most age related structural changes if examined in cohorts rather than sequentially in the same population. In the young adult the mean epidermal thickness of limb and trunk skin is 35 to 50 μm. At the age of seventy years the mean thickness is 25 to 40 μm. Of greater interest is the shrinkage of the epidermal cells themselves. The decrease in size seems to be linearly related to age and observed equally at all sites (non sunexposed) examined. It is seen equally in both sexes. The shrinkage appears to take place at all stages of epidermal differentiation and in all dimensions, ie, there is a volume decrease.

The decrease in epidermal cell size dies not seem to fit with the increase in keratinocyte area mentioned above. Several explanations are possible. The simplest is that although there is an increase in mean keratinocyte area, there is actually a decrease in keratinocyte volume. The decrease in keratinocyte thickness needed to 'match up' keratinocyte volume with the decrease in epidermal cell volume, despite an increase in keratinocyte area of the magnitude seen, seems more than possible. Unfortunately sufficiently accurate measurements of keratinocyte thickness cannot yet be made to test this hypothesis.

The increase in stratum corneum renewal time discussed above might be expected to be the result of a decrease in the rate of epidermal cell production. Although it has been disputed, the limited evidence available does indeed favour an age related decrease in this activity. Regrettably the available techniques are not sufficiently precise to determine at which stage or stages the process is slowed. Studies in which the number of cells in DNA synthesis are counted after exposing the tissue to the tritiated DNA precursor compound thymidine, and then preparing the tissue autoradiographically, only provide limited information. Such studies cannot reveal alterations in the number of cells capable of cell division (germinative pool) or the proportion of these cells that are in the growth cycle (growth fraction) or any change in the rate of DNA synthesis.

Pigmentation

Persistently and heavily sun-exposed skin may become hyperpigmented. The colour change may be permanent and is more of a mahogany colour than the sun-tanned skin of younger individuals. The non-exposed sites are by contrast often less pigmented than in younger subjects.

Skin colour is a complex amalgam of the number and synthetic activity of melanocytes, the number and size of melanosomes, the number, depth and dilatation of the blood vessels, the state of oxygenation of the blood in the vessels, the presence of abnormal pigments and the optical properties of all the skin structures. Aging may involve changes in several of these and partially account for the 'loss of bloom' and altered pigmentation of old skin. Melanocytes participate in the aging process. Studies in which DOPA positive dendritic cells have been counted in whole epidermal mounts

(after splitting the dermis from the epidermis) have demonstrated a linear reduction of the numbers of melanocytes per mm with age. The decrease found has amounted to 10 to 20 per cent per decade in nonexposed aging skin, but there is an increase in sun-damaged areas.

Langerhans cells

These intra-epidermal dendritic cells are now recognized as of prime importance to the immune defences as 'antigen presenting cells'. In reality they belong to the reticuloendothelial system and originate in the bone marrow. After topical application of an antigen-containing substance the antigen is found on the surface of the Langerhans cells. The antigen-bearing Langerhans cells then 'process the antigen' and 'transmit' their message to T-lymphocytes, setting in motion the cell-mediated hypersensitivity response.

There is a reduction in the Langerhans cell population in elderly subjects. The functional consequence of the reduction in this vitally important cellular link in the immune defence chain has not been confirmed, but has led to some interesting speculation. In particular the relationship of the reduction in number to the development of neoplastic disease has been mooted. The reduction in the sensitizing capacity of potent antigens such as DNCB in the elderly also may in part be due to the reduced number of Langerhans cells.

Age changes in dermal connective tissue

Many of the clinical changes in the skin of the elderly are the result of the cumulative damage from environmental traumata. The wrinkling and leathery appearance of the skin of the face is due to solar metastatic degenerative change as are the odd angulated scars and ecchymotic spots on the backs of the hands and forearms. However, changes do take place in dermal connective tissue as a result of intrinsic aging. They are seen in their purest form in the covered skin of elderly black individuals but are also in the covered areas of Caucasians. The clinical sequelae of pure dermal aging are less obvious than the changes of chronic actinic damage. They consist of loss of elasticity and palpable thinning. There is also a loss of resistance to the indenting finger and loss of rebound of a pinched fold of skin, which are crude

tests of many mechanical features of skin but in part monitor dermal hydration and in part reflect alterations in the fibrous structure of the connective tissue framework.

The dermis becomes thinner in old age. This was first detected using a radiological method and later confirmed and the data extended using a special ultrasound device. The latter study showed that skin thickness gradually increased up to the age of twenty years, remained constant between twenty and forty, and then gradually declined in an age-related manner. As so often appears to be the case, men fare worse than women in the attrition of aging, and the rate of decline of total skin thickness (of which dermis accounts for the major part) is greater in men than in women. The normal total skin thickness in maturity in men is 1.0 to 1.2 mm and in women is 0.8 to 1.0 mm. At the age of seventy the measurements are similar in both sexes, from 0.7 to 0.9 mm. As with all biological measures of aging in populations there is marked variability in the observations but the tendency to thinning is undeniable. The loss of dermal substance seems to be from all parts of the dermis but may be particularly marked from the papillary dermis. Not only does the dermis feel thinner, but it also looks less substantial and may be optically more transparent, allowing veins, tendons and muscles to be more easily seen. If the individual has senile or postmenopausal osteoporosis, the tendency to dermal thinning is even more marked. Interestingly, the depressed collagen content can be restored in postmenopausal women by hormone replacement treatment.

The dermal thinning accompanying senescence seems to be mainly the result of loss of proteoglycan, although there is also a decreased amount of total collagen when the results are expressed per unit surface area. Strangely, the water content of the skin seems greater with increasing age when expressed per unit weight. The number of stable intermolecular cross links increases with age and the proportion of insoluble collagen increases while that of soluble collagen decreases. Recent studies suggest that elastic fibres are not immune from the aging process (independent of any additional solar effect). Ultrastructurally the elastic fibres appear broader and more 'ragged' at the margins in skin from elderly subjects. They are also irregularly distributed, looser in texture and more easily dissociated by enzymes. These biochemical and structural changes are almost certainly responsible for the biomechanical profile of aged skin.

Fibroblasts appear to decrease in number and size with age. The replicative ability of fibroblasts in vitro appears to be finite and not unlimited. The fact that the cells are capable of only a certain number of cell divisions suggests that there is programmed senescence in tissues and has led to considerable speculation as to the nature of the aging process.

Age related changes in hair

Changes in hair are among the most obvious effects of growing old. Androgenic alopecia has been extensively investigated. As the term implies, androgenic alopecia is not purely age related. It is dependent on two other variables – a dominantly inherited tendency to develop the condition, and on the influence of male sex hormone. Thus the condition is not seen in some families unless the gene responsible is introduced, and it does not develop in eunuchs even if they possess the gene unless they receive supplements of testosterone. However, once started, the process is progressive and worsens with the passing of the years. Although the process is often called male pattern baldness or androgenic alopecia, it occurs in some women as well and is a cosmetic problem for these individuals.

Clinically the condition starts in the temporal regions as a recession of the hair line (the so-called bi-temporal recession or 'widow's peak'). A little later, thinning over the vertex occurs, and later the process spreads to include, in the most severe cases, most of the crown, giving the typical billiard ball appearance. In women there may be a different pattern; it is true that bi-temporal loss and thinning of the hair of the vertex are quite often seen but in a proportion of affected women there is also a marked diffuse loss of hair. As close inspection will confirm, the pigmented terminal hair gives way to a sparser 'fuzz' of vellus hair. After many years even this is lost and the skin becomes perfectly smooth and atrophic.

Androgenic alopecia aside, there is a gradual loss of hair as part of the aging process. The loss is not confined to the scalp but includes all body hair. The hair shaft diameter decreases and the anagen phase shortens, so that hair density decreases. In addition the rate of hair growth decreases.

The greying of hair is among the popularly recognized signs of growing old. The time of its onset is variable and 'premature' greyness is not at all uncommon. However, advancing age does produce more grey hairs. This is due to the decreasing melanin synthetic activity of the melanocytes of the hair bulb.

Sebaceous glands

Sebaceous glands do not appear to diminish noticeably with age. Indeed, in some individuals, particularly elderly men, the sebaceous glands on the face and upper back are paradoxically hypertrophied. Clinically the hypertrophied glands are obvious as small yellow nodules. The condition has been extensively studied.` The sebaceous gland cells appear to mature and migrate more slowly than in normal glands but the cause of sebaceous gland hyperplasia remains mysterious. The rate of sebum secretion does not decrease in elderly men until the age of eighty but does decrease in women after the menopause. In Parkinsonism there is an increased rate of sebum secretion. It is of considerable interest that despite the maintenance of sebum secretion in old age, acne is uncommon.

The nails

As may be expected, the nail plates grow less rapidly in the elderly. The nails also become thinner, less flexible and more brittle.

Sweat glands

The eccrine sweat glands seem to diminish in size in old age and secrete less sweat than in younger individuals in response to stimuli. Occasionally yellowish granules of lipofuscin are found within the glandular epithelium. Their significance is unknown. The apocrine glands also become smaller and their ability to secrete is also reduced.

The dermal vasculature

There are no capillary vessels in the epidermis, and this part of the skin is supplied with oxygen and nutrients by capillary vessels in the dermal papillae. These arise from vascular plexuses arranged horizontally in the dermis. There are also rich plexuses of blood vessels that ramify around the hair follicles and to a lesser extent the sweat glands. The arterial vessels tend to thicken in older individuals and there is a

reduction in the number of capillaries. The capillaries of non-exposed skin become thinner, probably owing to decreased synthetic activity and the number of investing fibroblasts (Veil cells).Vascular response to all types of stimuli also tend to be muted in old age and this is one explanation for the apparent decreased response to chemical and mechanical trauma. Materials injected intracutaneously, such as saline or fluorescein solutions, take longer to clear from the injected site in the elderly.

Neural structure and function

Neural structures are embryonically derived from the embryonic neural crest and include the nerves, nerve fibres and end organs. Discriminative tactile ability is decreased in the elderly but little in the way of structural alteration has been recorded.

The dermo-epidermal junction

This is an extremely complex zone that is important for skin function and is frequently involved in disease. It can be adequately visualized only through ultrastructural techniques. It consists of a basal lamina on which rest the epidermal cells and which itself consists of an upper lamina lucida and a lower lamina densa. Dermal microfibril bundles and anchoring fibrils link the dermal elastic fibre network to the lamina densa. Anchoring filaments join the lamina densa to the epidermal cells at the sites of hemidesmosomes. Numerous proteins are associated with the region and seem vital to the integrity of the structure. Detailed ultrastructural studies have shown that at least up to the age of sixty there is no alteration in width of the basal lamina but that there is a decrease in the number of dermal microfibril bundles.

Wound healing in the elderly

The sequence of events following wounding is complex but similar in outline whether the wound is caused by something sharp, by a burn or by a destructive disease process. Haemostasis and vasoconstriction are the initial 'emergency measures' in an incisional wound. Within the first few hours the wound cavity becomes filled with blood clot, inflammatory cells and tissue debris. Re-epithelialization begins some time between twelve and twenty-four hours later and continues until the breach in the skin surface is repaired. The new epidermis burrows between the slough and the viable dermal tissue beneath, using its own fibrinolytic and collagenolytic activities. The

migrating epidermal cells are actively motile and bursts of mitotic activity are not seen until some seventy-two hours after wounding.

Whilst re-epithelialization proceeds, damaged dermal elements are removed by macrophages and new collagen is laid down from the third or fourth day after wounding. The new collagen takes up the orientation of the surrounding dermis and becomes functionally protective only some weeks later. In addition to these processes, wound contracture occurs from the third or fourth day after wounding. Fibroblasts develop an ability to contract (myofibroblasts) and draw the edges of the wound together.

Many who have studied the subject of wound healing in the elderly agree that the process appears slower and less efficient in old age. These opinions are, however, based mainly on clinical evidence, there being a deficiency of studies on the effects of aging on the wounding process in man. Early studies on the healing of war wounds demonstrated that wounds decreased in area as a consequence of age but that there was considerable variability-leading to the concept of biological aging. More recently blister bases were found to re-epithelialize at a slower rate in the aged.

This aspect of the skin in old age must be appreciated for its influence both on the clinical features and on the response to treatment of all skin disorders in the elderly patient.

Premature aging

A look around a peer group will confirm that the rate at which the signs of aging are developed is remarkably variable. This variability appears to be independent of the differing experience of environmental injury and as with other aspects of true aging, is unexplained. Apart from the inherent differing rates of senescence, whether the process of aging can be accelerated or not is a moot point. It is clear that some of the skin signs of aging can be simulated. Radiation and corticosteroids thin the epidermis, slow its rate of growth, decrease the size of epidermal cells and thin the dermis - all changes observed in the aging process. However, it seems likely that this similarity is merely the result of the limited range or response of the skin to 'suppressive' stimuli.

Premature aging syndromes are those disorders in which the signs of aging appear very early in life. Progeria is the archetypal example of this group of diseases and the results of its investigation highlight the discussion concerning the possibility of there being a true acceleration of the process of aging. It is an extremely rare disorder characterized by loss of hair, thinning of the skin and loss of subcutaneous fat. The skin becomes brownish in colour, bound down and scleroderma-like. These signs develop in the first years of life, or even the first few months, and are accompanied by skeletal hypoplasia and cataracts. A rare condition in which the changes of aging are confined to the extremities has been described and is termed acrogeria.

Werner's syndrome (adult progeria) is less rare but still very uncommon. The disorder is characterized by sclerodermatous and poikilodermatous changes developing in the skin, as well as loss of hair, and cataracts. The skin atrophy results in intractable ulcerations. Many other abnormalities are present, including short stature, hypogonadism and predisposition to diabetes, atherosclerotic disease and malignancies. A further similar disease, termed metageria, has also been described.

There is considerable confusion in the literature concerning the identities and similarities within this odd group of tragic diseases, and there is virtually no information available as to whether or not they represent the same underlying metabolic (or immunological) abnormality. To add to the confusion there are several syndromes in which there are some of the signs of premature aging but which for other reasons can be differentiated. One such disorder is the Rothmund-Thomson syndrome (poikiloderma congenitale) which is characterized by the presence of mottled pigmentation, telangiectasia and atrophy, as well as hyperkeratotic lesions and a predisposition to cutaneous malignancies.