11 Skin Morphology and Its Mechanical Properties Associated with Loading

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Introduction

It is recognized that pressure ulcers develop as a consequence of soft tissue reaction to mechanical loading of localized areas for a prolonged period of time, resulting in ischaemia followed by tissue necrosis. Therefore, in order to prevent the development of pressure ulcers it is essential to reduce the amount and duration of pressure and/or to enhance the tissue tolerance to ischaemia. In this regard, numerous studies have been undertaken in recent decades in the attempt to reduce the amount and duration of interface pressure applied to the skin surface, especially with regard to supporting surfaces. However, not much work has been carried out regarding tissue tolerance in terms of pressure ulcer development and how the structural characteristics of the tissue affect tissue tolerance.

In this chapter, we set out to demonstrate the morphological characteristics of human tissue, especially the skin, to discuss how morphology affects mechanical properties and to highlight the deficiencies in this field of pressure ulcer research.

What Is "Tissue Tolerance"?

What does "tissue tolerance" represent? How can we evaluate "tissue tolerance"? Without answering these questions, how can we verify that all pressure ulcers are preventable?

The tissue tolerance in pressure ulcer development will be defined as a tissue resistance to mechanical stress representing a tissue integrity, where the function and structure are inter-relatively well maintained without adverse sequence. The intensity of tissue resistance is affected by various intrinsic factors (Fig. 11.1). These can be divided into two groups, systemic and local factors, where systemic factors include nutrition [1, 2], mobility/activity [3], oxygen intake and delivery [4], and existing disease/disability, which affect the local tissues' integrity indirectly.

Local factors include nerve control, immunity, metabolism, circulation and tissue structure/composition, all of which affect underlying tissue viability/integrity directly. Ageing [5] and psychological stress [6, 7] may also influence the systemic and local intrinsic factors. Many studies have been

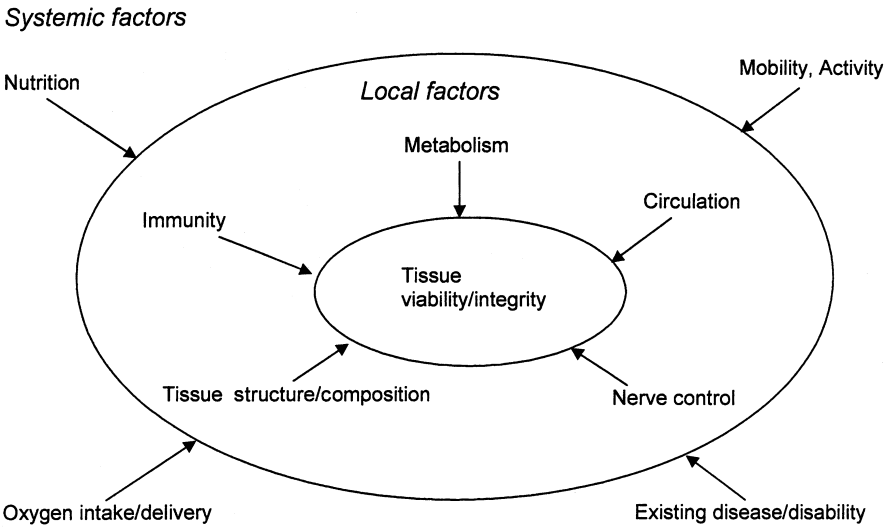

Fig. 11.1. Systemic and local intrinsic factors associated with pressure ulcer development

undertaken to evaluate the tissue viability following ischaemia by measuring skin blood flow [8, 9] and transcutaneous PO_2 ($TcPO_2$) [10, 11], both of which are parameters of function. The circulation is also closely related to metabolism and immunity, participating in tissue tolerance at cellular level. Little work has been undertaken to determine how the tissues react to mechanical forces to protect themselves locally. The cellular enzymes and/or metabolites may be more sensitive indicators of cellular dysfunction and death [12]. Only tentative attempts have been made to seek the potential indicators of pressure ulcer onset through biochemical analysis of sweat during ischaemia [13, 14]. In general, the local tissue metabolism changes in association with the local blood flow under normal conditions; however, it is not certain how this relationship is altered under pathological conditions [15], e.g. multi-organ failure or paralysis. If the relationship is altered, the recovery of blood flow following ischaemia may not be a sign of tissue recovery, as indicated below.

Recently a concept of reperfusion injury has been introduced to explore the mechanism of pressure ulcer development. The reperfusion injury has already been demonstrated in other organs, e.g. brain, liver and heart, in which much of the injury occurs not during the period of hypoxia but rather during the period of reperfusion [16]. During reperfusion, formation of reactive oxygen metabolites, which generate superoxide and hydrogen peroxide, contributes to granulocyte infiltration, microvascular barrier disruption and oedema formation [17, 18]. These products are powerful mediators of endothelial injury and tissue damage and amplify the effects of the initial inflammatory stimulus. The concept that free radicals have a role in ischaemic injury is supported by studies demonstrating that the administration of free radical scavengers inhibits the damage caused by post-

ischaemic reperfusion. Sundin et al. [19] and Houwing et al. [20] investigated the role of reperfusion injury and the effect of free radical scavengers in pigs with regard to pressure ulcer development. They concluded that an inflammatory process is the key mechanism in the development of necrosis in the deeper subcutis and muscle. More basic study is needed to determine how the immune, metabolic and circulatory systems inter-relating in the process of tissue damage-recovery with regard to human pressure ulcer development.

Limitation of Previous Animal Studies on Pressure Ulcers

A number of animal experiments have been undertaken to clarify the development of pressure ulcers histologically, using various animal models. Husain [21], Kosiak [22], Wilms-Kretchmer and Majno [23], and Nola and Vistnes [24] used rats, Groth [25] used rabbits, Kosiak [26] used dogs, and Dinsdale [27] and Daniel et al. [28] used pigs. The results from these studies demonstrate that there is an inverse relationship between the amount of pressure and the duration of time to development of pressure ulcers. Reswick and Rogers [29] demonstrated a similar relationship in human subjects.

However, there are limitations to the extrapolation of results from animal studies to pressure ulcer development in humans. The results with regard to magnitude and duration of pressure before tissue damage occurred are inconsistent and difficult to compare because of the different animal models, different protocols and different parameters measured. In addition, the investigators used mostly healthy, young animals, whereas the susceptible humans are mostly aged and debilitated. In addition, the soft tissue composition of the animal models used (except pigs) differs from that in humans (Table 11.1). The usual laboratory animals with loose skin, e.g. rats and dogs, lack a substantial attachment to the deep fascia, whereas in the pig skin the panniculus carnosus is more intimately connected through a hypodermal fibre network to the deep muscular fascia as well as to the reticular layer of the dermis [30]. Thus, the soft tissue behaviour in animals with loose skin is different from those with fixed skin when the force is applied to the skin. Little work has been done on human tissues with respect to pressure ulcer formation. In addition, human pressure ulcers develop due to localized tissue ischaemia caused by repeatedly applied forces, mostly a combination of compression and shear stress.

One of the difficulties in undertaking the research on pressure ulcer development in human is the issue of ethics; another is that the soft tissue loses its characteristics when it is separated from the living body for the examination. Therefore, it is difficult to create a human pressure ulcer model, especially with regard to loading conditions and clinical status. Thus, the precise mechanisms of pressure ulcer development in humans remain uncertain.

Table 11.1. Differences in characteristics between experimentally generated pressure ulcers in animal models and human pressure ulcers developed

	Animal models of pressure ulcers	Human pressure ulcers
Health condition	Mostly healthy, young adult animals	Mostly elderly, debilitated, or disabled individuals
Pressure application	Mostly wide range of pressure, continuously (recently: determined pressure, repeatedly	Relatively low pressure, repeatedly
Direction of force application	Mostly compression only	Probably compression + shear
Tissue characteristics	Loose-skin (except pig)	Fixed skin

How Does the Skin Respond to Mechanical Loading?

Morphological Architecture in Human Skin

Human tissues function depending on the local tissue need and are controlled in a sophisticated manner with changes in physiology and morphology. Therefore, when discussing morphological changes in relation to pressure ulcer development, we should keep in mind that physiological changes are always present too.

Before discussing the morphological characteristics of skin, we would like to describe how the force is transmitted to the underlying tissues when it is applied to the skin surface.

The underlying soft tissues consist mainly of skin, adiposa tissue and muscle. Because these tissues have different characteristics in respect of linearity, anisotropy and visco-elasticity, it is not easy to identify how differently the individual layers of soft tissues behave when the force is applied to the skin surface and how it is transferred through the soft tissues. In this regard, Le et al. [31] measured pressures at different depths of the tissues overlying the pig trochanter using silicon pressure sensors. They reported that the internal pressure on the weight-bearing bony prominence was several times greater than the surface pressure. However, the sensor they used is somewhat unreliable because of hysteresis and the effect of infusion fluid on local tissue pressure.

Dodd and Gross [32] measured the interface pressure between the skin and an external load, and interstitial fluid pressure over the wing of the ilium of a pig using a wick-in-needle catheter attached to the pressure transducer. They reported that only about 28% of the interface pressure is

transferred to the interstitial fluid directly because of the complex geometry of the underlying bone; the load is not purely compressive, as tissues move away from the load and the forces are dissipated to some degree.

The structure of underlying soft tissues also influences the capability of pressure distribution. Sangeorzan et al. [33] investigated the tolerance of skin to mechanical loading over the tibia and over the tibialis anterior muscle in normal volunteers. The results indicated that the applied pressure at which $TcPO_2$ reached 0 was significantly greater for skin over muscle (71±16 mmHg) than for skin over bone (42±8 mmHg). This suggests that a higher pressure is required to interrupt blood supply in skin over muscle than in skin over bone.

In this regard, Todd and Thacker [34] verified a computational three-dimensional model of the human buttock in vivo with magnetic resonance imaging experimentally. The development of a precise model of human soft tissue is needed to examine how the force is transferred to individual tissues and how the individual tissue responds when the force is applied to the surface of the skin.

In this chapter, the mechanical properties of soft tissue are discussed. The focus is on skin as a typical example.

Skin Structure/Physiology

The skin has been called the largest organ of the human body and has many functions; protection from outside injury and invasion, prevention from drying out, regulation of body temperature and release of some body wastes while absorbing nutrients. The structure of the skin is shown in Fig. 11.2.

Morphologically, skin is composed of two layers; a thinner, outer layer known as the epidermis and an inner layer known as the dermis. Because

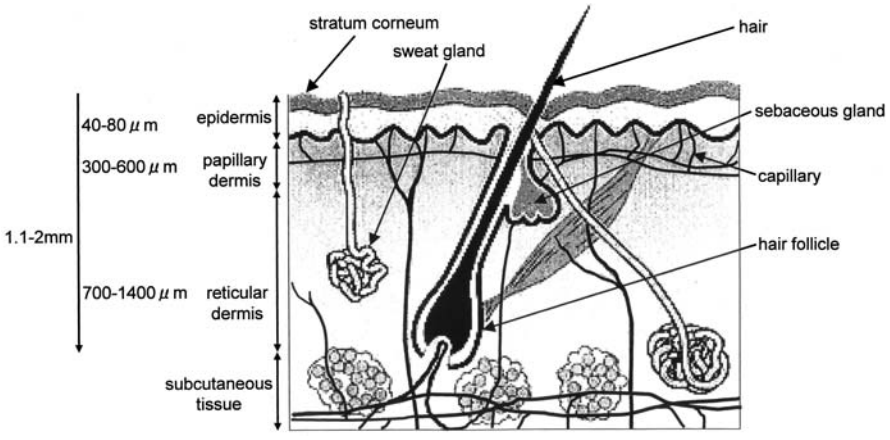

Fig. 11.2. Schematic diagram of skin structure

the epidermis contains keratin, a tough, fibrous protein, and has no blood supply, its nutrition is provided via the papillary layer of the dermis. The exposed surface of the epidermis is illustrated in Fig. 11.3.

The dermis is the connective tissue matrix of the skin, providing structural strength, storing water, and interacting with the epidermis. It consists of papillary and reticular layers containing collagen and elastic fibres, blood vessels, sweat glands, hair follicles and nerves.

The papillary layer, which provides oxygen and nutrition to the epidermis, and the reticular layer are of great importance in maintaining the integrity of the skin and protecting the body from external stimuli. The thickness of the papillary layer varies from site to site (Fig. 11.4); it is thinner in the sacral skin than in the ischial skin of aged individuals post mortem [35]. This suggests that the blood supply and nutritional transport in the sacral skin may be impaired when force sufficient to induce collapse is applied.

The epidermal–dermal junction is an interface between the epidermis and the dermis composed of the basement membrane, which is wavy in shape with finger-like projections into the dermis (Fig. 11.3). It has three major functions: it provides a permeable barrier between the vascular dermis and avascular epidermis; it is thought to influence the epidermal cells during their differentiation, growth, and repair; and it provides adherence of the epidermis to the underlying tissues [36]. In addition, the structure

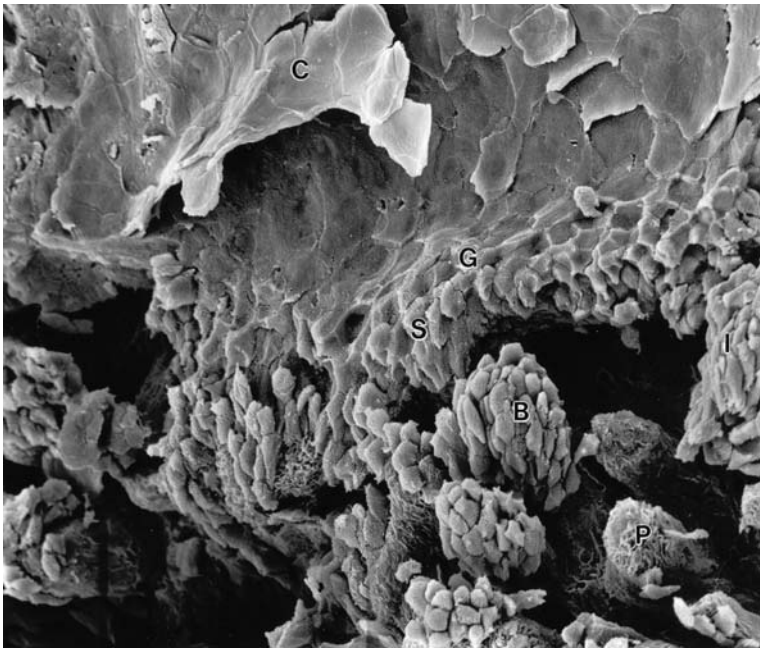

Fig. 11.3. Scanning electron micrograph showing free and lateral surfaces of the human epidermis. Age 73 years, female, sacrum (×560). *B* stratum basale, *C* stratum corneum, *G* stratum granulosum, *P* dermal papillae, *S* stratum spinosum

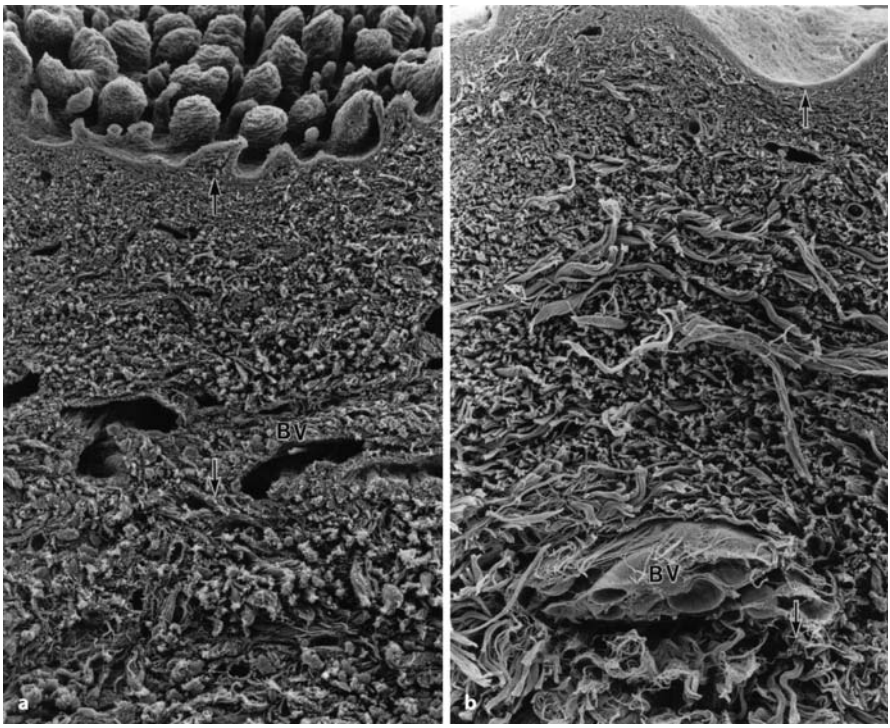

Fig. 11.4 a, b. The papillary layer of the dermis in different body sites. The thickness of the papillary layer allowing tissue fluid transportation is less in the sacrum. *Arrows* show the thickness of the papillary layer. Age 73 years, female (×130). **a** sacrum; **b** gluteus. *BV* Blood vessels

of the epidermal–dermal junction may greatly affect the tissue integrity. The skin capillaries are situated just under the reticulin sheet of the papillary layer of the dermis, providing the oxygen and nutrients to the epidermis. Thus, if the junction becomes flattened, capillary density becomes less and consequently compromises the tissue viability.

The distribution of blood capillaries in the papillary dermis depends upon the local tissue metabolic requirements and thus differs according to site on the body [37], age, and usage [38]. They are densely distributed in the head and neck region in children's skin compared with all other regions except the palm and sole, while they are less dense in the lower limb [39]. This phenomenon is also seen in the adult skin, as confirmed by Xe clearance [40]. A typical example of regional difference is seen in the fingers, where the blood capillaries are densely distributed due to the frequent use.

Capillary distribution in areas susceptible to pressure ulcers in aged post-mortem skin was found to be higher in the sacrum than in the ischial tuberosity (Fig. 11.5) [35].

The lymph vessels are primarily involved with removing proteins, large waste particles, and excess fluids. Most studies on pressure ulcers are inter-

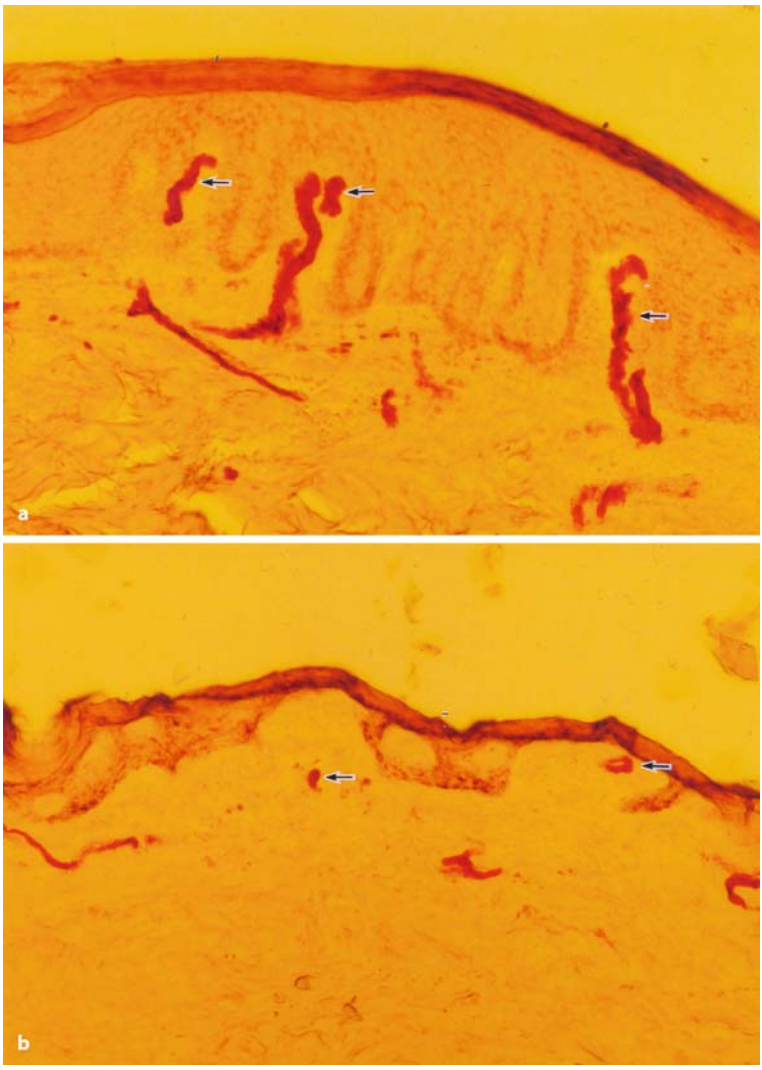

Fig. 11.5 a, b. Blood capillary (*arrows*) distribution in different body sites corresponding to papillae distribution. Age 73 years, female (×100). **a** sacrum; **b** gluteus

ested in blood flow (inflow), but in order to maintain the normal circulation, both inflow and outflow (lymphatic flow), should be well maintained.

The terminal lymphatics, made up of a single layer of endothelial cells, are distributed in the dermis. Several lymphatics join to form collecting lymphatics under the dermis. These join to form larger transporting lymphatics. There are some open junctions and rare intercellular channels in the terminal lymphatics. The surrounding connective perivascular matrix is characterized by regular bundles of collagen and elastic fibres [41]. The terminal lymphatics do not have smooth muscle in the wall. Some of them are collapsed in normal

condition and are connected to tissue fibres via anchoring filaments [42, 43]. In contrast, the transporting lymph vessels have smooth muscle, controlling fluid transportation by its contraction. Reddy and Patel [44] attempted to formulate a mathematical model and simulate lymph flow through terminal lymphatics under various physiological conditions.

Lymph flow increases whenever the interstitial fluid pressure rises above its normal level. Miller and Seale [45] investigated lymph clearance during compressive loading on the hind limb of mongrel dogs and reported that a pressure of 60 mmHg can initiate lymph vessel closure. They also suggested that it is more likely that the terminal lymph vessels would collapse before the collecting lymph vessels as they are smaller and closer to the site of pressure application. Krouskop [7] reported that the lymphatic propulsion is dependent on lymphatic smooth muscle sensitive to hypoxia. However, not much attention has been paid to how the lymph flow affects the viability in the impending tissues with respect to pressure ulcer development.

The defence system of the body against external stimuli – Langerhans' cells in the epidermis and the immune system participating in the body's immune response – is related to tissue integrity. If the barrier is disrupted, both a cytokine response and an increase in Langerhans' cell density are induced [46].

Little attention has been paid to how this defence system is associated with pressure ulcer formation. Recently Sundin et al. [19] investigated the role of allopurinol and deferoxamine, both acting to prevent free radical formation or to scavenge free radicals. They attempted to explore pressure ulcer pathogenesis using pigs, in which 150 mmHg of pressure was applied to the scapulae repeatedly. As a conclusion, it was demonstrated that deferoxamine could significantly reduce cutaneous and skeletal muscle necrosis compared with allopurinol. Similarly, research was undertaken by Houwing et al. [20] to test the hypothesis that pressure ulcers are the results of inflammation caused by ischaemia and reperfusion, and that the pressure damage can be reduced by prophylactic administration of vitamin E as a free radical scavenger. A constant force (100 N) was applied to the trochanteric region of the pig for 2 h. Immediately after release of pressure, no pressure damage in the muscle was visible microscopically, whereas 2 h after, there was severe influx of granulocytes and the myocytes had completely disappeared, showing muscle necrosis. There was a significant increase in hydrogen peroxide after pressure release. After pre-treatment with vitamin E, however, there was no increase in hydrogen peroxide and the tissue damage was significantly less.

Mechanical Properties of the Skin

The skin is a visco-elastic material showing unique mechanical properties primarily reflecting the characteristics of the network of collagen and elastic fibres that support tensile loads (Fig. 11.6).

Therefore, if the structure/composition of the skin has been changed, it is assumed that the mechanical properties of the skin are also altered.

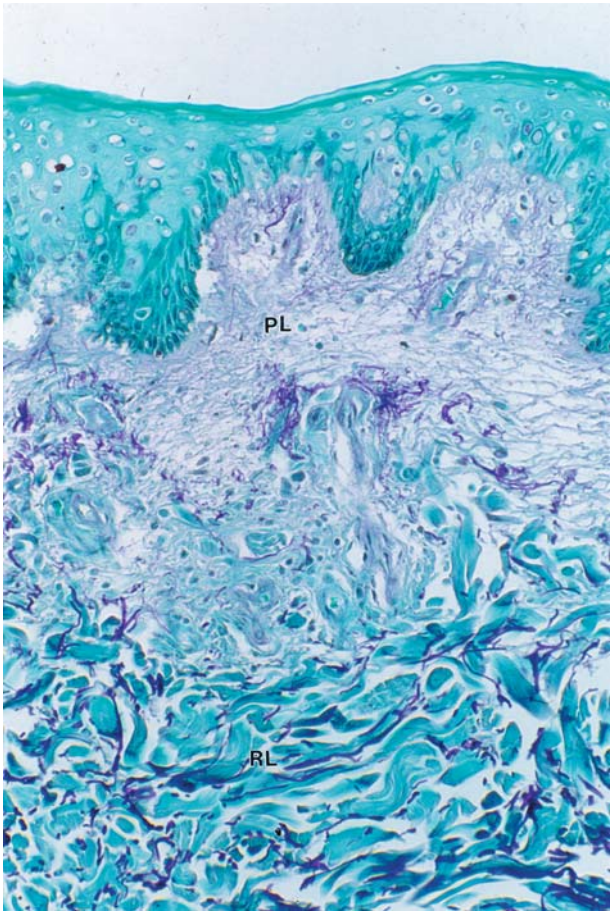

Fig. 11.6. Light micrograph of the human sacral skin stained with both aldehyde-fuchsin and light green. In the dermis, elastic fibres (*purple*) are in close proximity to collagen fibres (*green*). Both types of fibres are much denser and much larger in the reticular layer (*RL*) than in the papillary layer (*PL*). Age 79 years, male (×280)

In the relaxed state, the collagen fibres are unoriented, convoluted structures separated from each other by tissue fluid and ground substance [47]. As skin is stretched along one or both of the axes within its plane, collagen fibres become straightened and then begin to align with the applied force. When the skin is fully stretched, tissue fluid and ground substance between the collagen fibres is displaced. A stress–strain curve for skin is characterized by three components – low modulus, linearity and yield – and by failure when the load is increased [47].

The behaviour of the soft tissues, and thus the nature of the recovery, will depend on the rate and time of loading as well as the magnitude. Short-term loading generally produces elastic deformation with minimum

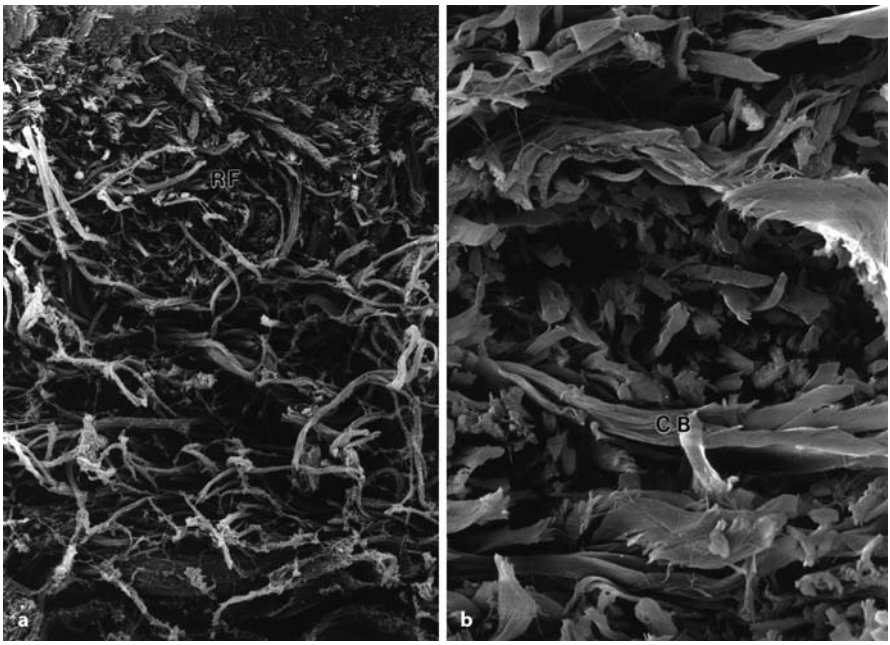

Fig. 11.7. Higher magnification views of the cut surface of the papillary (**a**) and the reticular (**b**) dermis. Delicate reticulin fibrils (*RF*) with small diameter are seen in the papillary layer. In the reticular layer, collagen bundles (*CB*) consisting of collagen fibrils form a feltwork. Age 79 years, male (×1,400)

creep and rapid elastic recovery, whereas long-term loading results in marked creep and requires significant time for complete tissue recovery.

When the force is applied, initially elastic fibres are thought to be stretched, while collagen fibres change their geometrical configuration before they play a part in load resistance. If the force applied is extensive, the collagen fibres will not return to their original alignment even after the force is removed [47].

Collagen, elastic fibres and proteoglycans play a key role in determining the mechanical properties acting to maintain tissue shape, transmit/absorb loads, and recover from deformation. Collagen is the major structural component existing in a variety of diameters and geometries (Fig. 11.7)

Collagen fibres are made up of fibrils. The molecules of the fibrils are arranged in a staggered array with quarter-length overlap between adjacent molecules via cross-links that provide stress-bearing networks. In the absence of cross-links, connective tissue would not be able to support tensile loads. The type and extent of cross-link may be a critical factor affecting mechanical properties. The collagen fibres consist of bundles of fibrils, 0.6–1.8 μm in diameter in the papillary layer, and 6–10 μm in the reticular layer, that are responsible for preventing tensile and shear failure.

The collagen fibrils in the skin are composed primarily of collagen types I and III. The diameter of collagen type I, 80–120 nm, is greater than that of

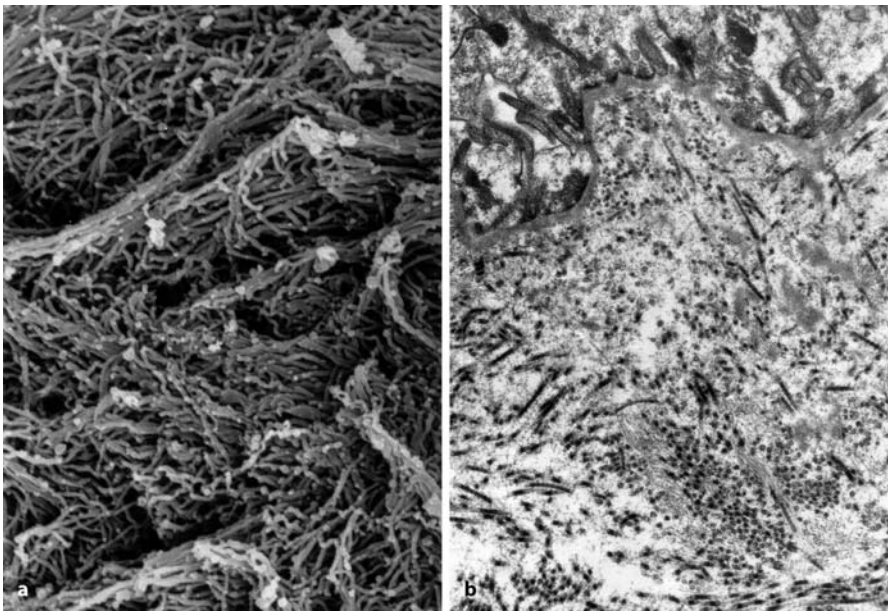

Fig. 11.8. Scanning (**a**) and transmission (**b**) micrographs showing the interstitial space between reticulin fibrils of the dermal papillae. It allows transportation of tissue fluid and metabolites. Age 84 years, female, sacrum (**a** ×20,600; **b** ×14,300)

type III, 40–60 nm. The most superficial surface of the papillary layer is made up of a continuous thin sheet of reticulin fibrils (type III), showing finger-like configuration, a delicate network and regular arrangement of the dermal papillae. The reticulin fibrils are interwoven in slightly loose networks with 30- to 60-nm spaces through which the tissue fluid and other substances pass [48]. This space plays an important role in maintaining viability of the tissues by enabling exchange nutrients and metabolites (Fig. 11.8).

Type I collagen fibrils are mainly found in the reticular layer of the dermis. This layer is composed of a dense meshwork of large-diameter collagen fibres showing a feltwork appearance, accompanied by elastic fibres (Fig. 11.7).

Collagen fibril diameter distribution is a function of both the applied load and its duration. The mechanical properties of a connective tissue are strongly correlated with the collagen fibril diameter distribution [49].

The mechanical properties of elastic fibres can be compared with a rubber-like state. The ultimate tensile stress of elastic fibres amounts to only several percent of that of collagen fibres [50]. Therefore, elastic fibres are weaker, softer, and more extensible than collagen fibres.

Elastic fibre networks dominate the low-strain mechanical response in tissues where energy and shape recovery are critical parameters [50]. The diameter of elastic fibres is approximately 1–10 μm; each fibre is made up of microfibrils of 10-12 nm in diameter. The fibres are connected via cross-

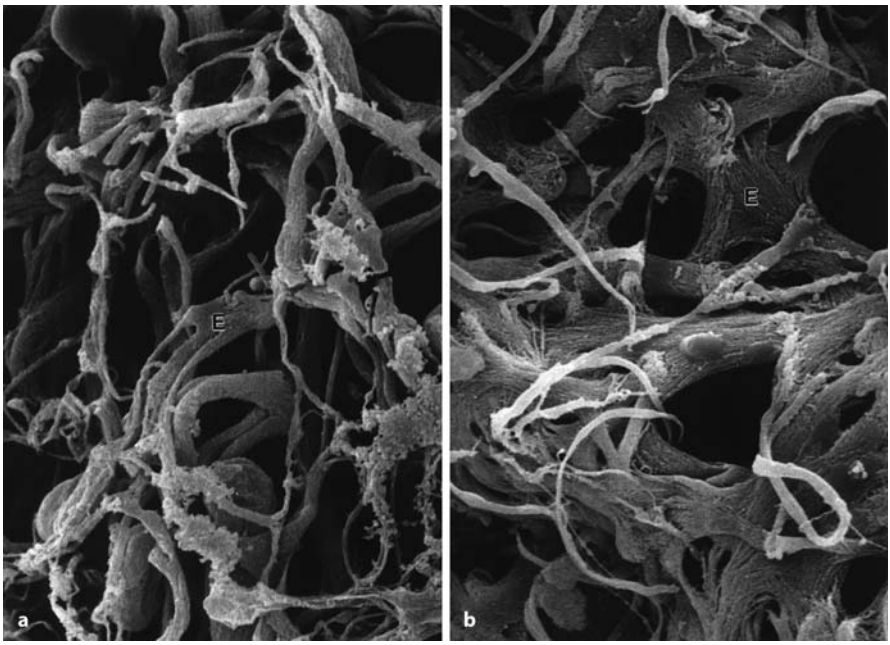

Fig. 11.9 a, b. Elastic bundles (*E*) distributed in the human papillary layer. Thick elastic bundles are densely distributed in the ischial skin. Elastic fibres were exposed with a treatment of 6N NaOH solution at 60 °C to enable three-dimensional visualization. Age 87 years, female (×6,500). **a** sacrum; **b** ischium

links, similar to collagen. The distribution of elastic fibres in the areas of the skin prone to pressure ulcers has been examined microscopically by Hagisawa et al. [35]. Thick elastic fibres (5–10 μm) are densely distributed in the ischial skin, where extension of the skin is needed associated with various body movements, in contrast with the sacral skin, where thinner, less dense elastic fibres (2–3 μm) are seen (Fig. 11.9). This difference may greatly contribute to tissue recovery from deformation in the ischial skin, in which the blood restoration may also be facilitated following ischaemia.

Proteoglycans consists of a protein core to which glycosaminoglycan side chains are attached, composing the bulk of the interfibrillar matrix, including hyaluronic acid, chondroitin sulphate and dermatan sulphate. Proteoglycans are involved in resisting compressive forces and facilitation of the response to stress at the fibrillar level [50].

Factors Affecting Tissue Integrity

When the structure/composition of the skin has been changed by various factors, the mechanical properties leading to tissue integrity may also be altered. However, little work has been undertaken to demonstrate how it is

altered. In this chapter, ageing, loss of autonomic nerve control and moisture are described as affecting factors.

Age-associated changes in skin are manifested in all regions of the body. Many of the structural alterations correlate with mechanical, biochemical, and physiological changes associated with advancing age. The epidermis becomes thinner and flatter, and the epidermal–dermal junction is flattened with loss of rete pegs, resulting in decreased attachment strength and interface communication. Age-associated changes also increase the chance of skin breakdown when force is applied tangentially, thus making blisters or tear-type injury more likely [51].

The quality of collagen fibres changes in aged skin, affecting the tensile strength. The collagen fibres may appear looser and fibre bundles may be disrupted by tangled fibrils, or the collagen may be densely packed in some areas with loss of ground substance [52], resulting in less potential for spaces between the fibres. The number of intramolecular cross-links become less soluble and the size of the collagen fibres increase with advancing age; thus, there is exaggerated tensile strength and decreased extensibility [53].

The elastin fibres are also altered with ageing. They become frayed, porous and matted together [54], leading to loss or delay of resiliency and recuperability after stretching. Daly and Odland [55] revealed an age-dependent decrease in elastic recovery, in which the recovery of the skin to its initial resting place after mechanical depression in young adults was complete within a few minutes while in the elderly a full recovery or reconstitution often required over 24 h.

There are decreased numbers of capillary loops in the papillary dermis, corresponding to the loss of dermal papillae with advancing age. The remaining capillaries are shorter and tend to have relatively greater proportions of thickened basement membrane [54].

A number of studies have reported an age-associated diminution in the inflammatory response; thus the elderly will not experience the early warnings and will tend to fail to take appropriate action. The number of Langerhans' cells (LC) has been reported to decline in aged skin by approximately 50% from young adulthood to senescence [56]. This loss impairs the cell-mediated immune response. The effect of ageing on epidermal LC and on their response to a single ultraviolet (UV) exposure has been studied using skin biopsy specimens of healthy adults [56]. The data demonstrated an age-associated loss of epidermal LC and slowing of LC response to UV irradiation. A similar result was obtained in the study indicating a lower percentage of LC in the sacral epidermis of elderly patients with pressure ulcers than in age-matched elderly controls [57]. These structural changes associated with ageing probably contribute to reduction in tissue tolerance of external stimuli, including pressure.

Loss of autonomic nerve control, frequently seen in patients with spinal cord injury, generates loss of vasomotor control and muscle pumping action, subsequently leading to alteration in skin structure. Quantitative and qualitative changes in skin collagen synthesis and catabolism below the level of injury can lead to reduction of the skin's ability to resist mechanical insult.

Rodriguez and Claus-Walker [58] reported that the amino acid content and the activity of the enzyme lysyl hydroxylase were lower in the insensitive skin than in the sensitive skin of individuals with spinal cord injuries. The hydroxylation of lysine is an important first step in collagen cross-link formation. Decreased formation of hydrolysine will decrease cross-link formation and will result in structurally weaker collagen. Klein et al. [59] reported that 2–3 months after denervation followed by disuse, the newly synthesized collagen in adult rats had fewer cross-links, and was therefore probably biomechanically weaker, than the original collagen.

Rodriguez et al. [60] reported the excretion of collagen metabolites increased after injury, reaching a peak between 3 and 6 months, then declined gradually, reaching control values about a year after injury. Stover et al. [61] reported that type III collagen, distributed in a fine network in the papillary layer of the dermis, is less prevalent in the upper dermis, while type I collagen is more prevalent in the reticular dermis in the denervated skin of patients with spinal cord injury. This suggests skin thickening and clumping of collagen, flattening of rete pegs and hypertrophy of sweat glands and erector pilae muscle. Thickening skin associated with increase of collagen I may decrease the space available for tissue fluid transportation in the dermis, leading to reduced tissue viability.

When a region is disused, for example the paralysed area in patients with spinal cord injury, the affected tissue is alive but with a lower oxygen and nutrient supply, leading to alteration of skin structure. The epidermal–dermal junction becomes flattened, distribution of blood capillaries in the skin is scattered and arterio-venous shunt develops [62, 63]. If the shunt is developed, the blood flows via the "by-pass" route, not through the capillaries that supply nutrients to the tissue. Therefore, a threat to tissue viability is more likely, although observation suggests that skin blood flow is well maintained. Lymph flow is also impaired by paralysis. The lymph vessels of the skin of paraplegic patients with thromboembolic disease showed a dilated lumen surrounded by rarefied perivascular connective matrix characterized by dissociation and disruption of collagen and elastic fibres. Also the endothelial wall was generally attenuated and indented, and numerous open junctions along the endothelial cells were observed [41]. These alterations appear to be responsible for an impairment of interstitial fluid exchange, leading to reduced removal of tissue catabolites in paraplegics.

The mechanical tissue integrity of the skin is a result of the balance of solid structures (collagen, elastic fibres, etc.) and liquid components (lipids, water) [64]. The stratum corneum provides impermeability and resistance to mechanical insults. If the gross biophysical properties are altered due to environmental factors, e.g. humidity, the membrane's biological performance can be affected. When the skin is allowed to transmit moisture without excessive hydration, the mechanical integrity of the stratum corneum is maintained. The normal moisture content of stratum corneum is between 10 and 20% [65].

The tensile strength of the stratum corneum is reduced when it is wet. It has been demonstrated that the lower the frictional force, the greater the

amount of work required to rupture the epidermis. The frictional force on the skin depends on the amount of moisture at the skin surface. It has been reported that the breaking strength decreases with increasing relative humidity (RH) up to 90% RH [66]. Skin with such reduced strength may also be more prone to mechanical insult due to shear stress or abrasion.

Incontinence is frequently noted as a contributing factor in pressure ulcer development. It is a major cause of moisture, local skin irritation and secondary infection. Urine, stool, perspiration and wound drainage contain substances other than moisture that may irritate the skin. It is unclear what causes increased susceptibility to skin injury: moisture only, as described earlier [68]; substances contained in urine and faeces, e.g. ammonia; or combination of these two factors. Allman et al. [67] reported that there was no association of urinary incontinence with pressure ulcers when patients with catheters were excluded, whereas faecal incontinence may be a more important risk factor. Berlowitz and Wilking [68] also studied risk factors for pressure ulcers, in which neither urinary nor faecal incontinence was associated with ulcer development. Overall, incontinence may be one of the contributing factors, but its possible relevance as an independent predictor remains unclear.

The precise relationship of cause-effect, e.g. in incontinent patients with diapers who develop pressure ulcers, should be clarified.

Effect of Repetitive Loading on Skin Structure/Composition

Loading stimulation also changes the skin's structure and composition leading to changes in the mechanical properties of the skin when it is repeated, depending on the degree and duration of pressure and how frequently it is applied to the skin. The site, the patient's age and the direction of loading are also important.

There are a number of published studies examining histologically, in animal models, how mechanical loading produces tissue damage [21, 26, 27]. However, at that time, not much attention was paid to how the tissue recovers following ischaemic insult. For example, if the loading stress is below the threshold, the tissue will recover completely. If the stress is the same order as threshold level, some compensation mechanism will take place within the tissue to maintain the tissue integrity or, if the stress is repeated, adaptation of the tissue will result. If the stress is severe and beyond the threshold, tissue damage or degeneration will be apparent. When the equilibrium between breakdown and regeneration cannot be maintained because of excessive duration or magnitude of force, catabolic processes overcome reparative mechanisms and the net result is tissue breakdown.

With the aim of preventing the destructive process, Sanders et al. [36] have attempted to address skin adaptation to mechanical stress by increasing load tolerance in rehabilitation practice. For example, spinal cord-in-

jured patients, when the spine is becoming stable, begin a wheelchair-sitting tolerance program. Sitting is limited to 30–60 min initially and increased periodically if hyperaemia resolves within 30 min [69].

Similarly, the ambulating protocol for a person with below-knee amputation is begun as early as 1–2 days postoperatively to stimulate wound healing and expose the antero-distal region of their residual limbs to high compressive and shear stress due to interaction with the prosthetic socket. Such protocols have been followed empirically for patients during the rehabilitation period.

Based on an extensive literature review, Sanders et al. [70] conducted animal experiments using the hind limb of the pig. Cyclic compressive and shear stress at 106.7±4.7 kPa and 22.6±5.9 kPa in the first session to 229.4±4.2 kPa and 53.0±0.8 kPa in the final session were applied at a frequency of 1 Hz for 1 h/day, 5 days/week for 4 weeks. Qualitative morphological analysis demonstrated that collagen fibril diameters were greater and fibril densities significantly lower in loaded skin than in control skin. Wang and Sanders [71] hypothesise that the adaptation occurs by forming new collagen fibrils with larger diameters as opposed to increasing diameters of existing fibrils. Such studies have been initiated only recently more extensive investigations are required.

Initial Damage Occurring in the Susceptible Areas

Whether the initial damage leading to pressure ulcers occurs at the surface of the skin or in muscle is controversial. Animal studies seem to indicate that pressure ulcers start from the muscle, because muscle is considerably less tolerant to ischaemia due to high metabolic need [24, 25, 28]. In contrast, clinical observation indicates that human pressure ulcers start from the skin [72]. Both may be true in certain situations. If an unconscious or immobilized person is left on the operating table for prolonged period of time [73], force is exerted perpendicularly (compression only), supporting the hypothesis that pressure ulcers start from muscle. However, in a conscious person or one with limited mobilization, force is exerted not only perpendicularly but also tangentially (compression and shear), supporting the hypothesis that pressure ulcers start from the skin. No reliable conclusion has yet been reached. There are unanswered questions: for example, if it is assumed that all human pressure ulcers develop from muscle, how can it be explained that some stage I pressure ulcers are resolved by effective pressure relief. Since muscle fibres, once damaged, cannot regenerate, fibrous tissues like collagen will replace the area, appearing as an irregular surface of the skin. In order to clarify these questions, more comprehensive research on the mechanism of pressure ulcer development is needed.

Only a few studies using histological methods are available for understanding of human pressure ulcers [48, 74–77]. Witkowski and Parish [74], who attempted to investigate human pressure ulcer development extensively, re-

ported that the initial changes were found in the papillary dermis, where the capillaries and venules were greatly dilated showing blanchable erythema with intact skin. This change is completely reversible if adequate pressure relief is given. The next stage of pressure ulcers, which is called non-blanchable erythema, shows the consistent feature of red blood cell engorgement of the capillaries and venules, followed by perivascular and later diffuse haemorrhage; however, the epidermis still appears normal. The vessels in the reticular dermis may also be engorged with red blood cells. Some vessels show fibrin thrombi and degeneration of the eccrine sweat glands, and subcutaneous fat is more often seen. In addition, the sebaceous glands begin to show evidence of degeneration, There is loss of cell membranes and an inflammatory infiltrate.

Barnett [75] examined surgically excised human tissue samples in which a pressure ulcer was present and developed a diagrammatic representation of how a pressure ulcer develops and heals. At an early stage, thinning of the epidermis, death of the papillary layer and loss of elasticity and strength of collagen are characterised, probably due to impairment of blood/nutrient supply and lymph flow in the papillary layer of the dermis although the skin surface remains intact. At the next stage, equivalent to stage II pressure ulcer in the NPUAP classification, one finds breakdown of the epidermis ultimately resulting in an open ulcer and death of collagen leading to loss of integrity and thrombosed blood vessels.

Moore et al. [76] conducted a study using the edge of pressure ulcer tissues excised for flap surgery. They reported that irregularly sized and

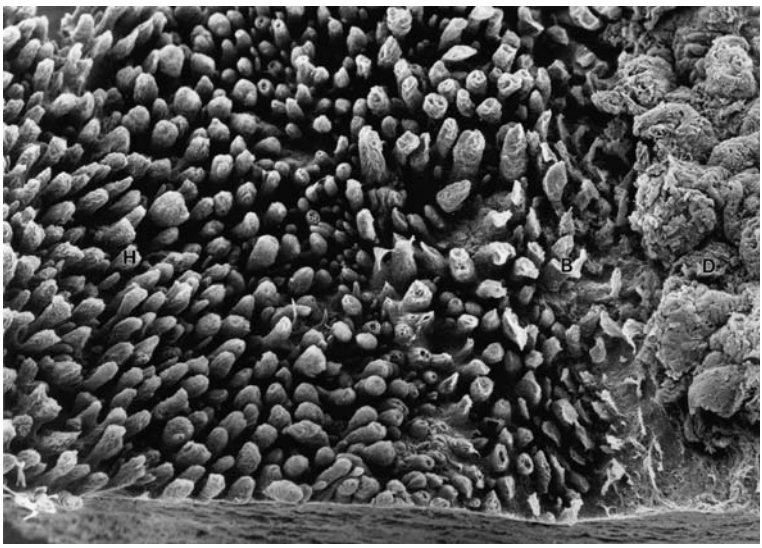

Fig. 11.10. Outer surface of the papillary dermis in the sacrum. Numerous dermal papillae with a finger-like profile are visible in the healthy (*H*) and boundary (*B*) areas. No papillae are seen in the damaged (*D*) area of stage II pressure ulcer. Age 84 years, female (×100)

shaped rete pegs were observed from the outer margin of the pressure ulcer through a transition zone of atypical rete pegs and finally disappear at the junction with granulation tissue.

Similar morphological findings were reported by Arao et al. [48], who carried out a post-mortem examination of the skin tissue of the sacrum of a subject who had stage II pressure ulcers, using light microscopy and transmission and scanning electron microscopy (Fig. 11.10).

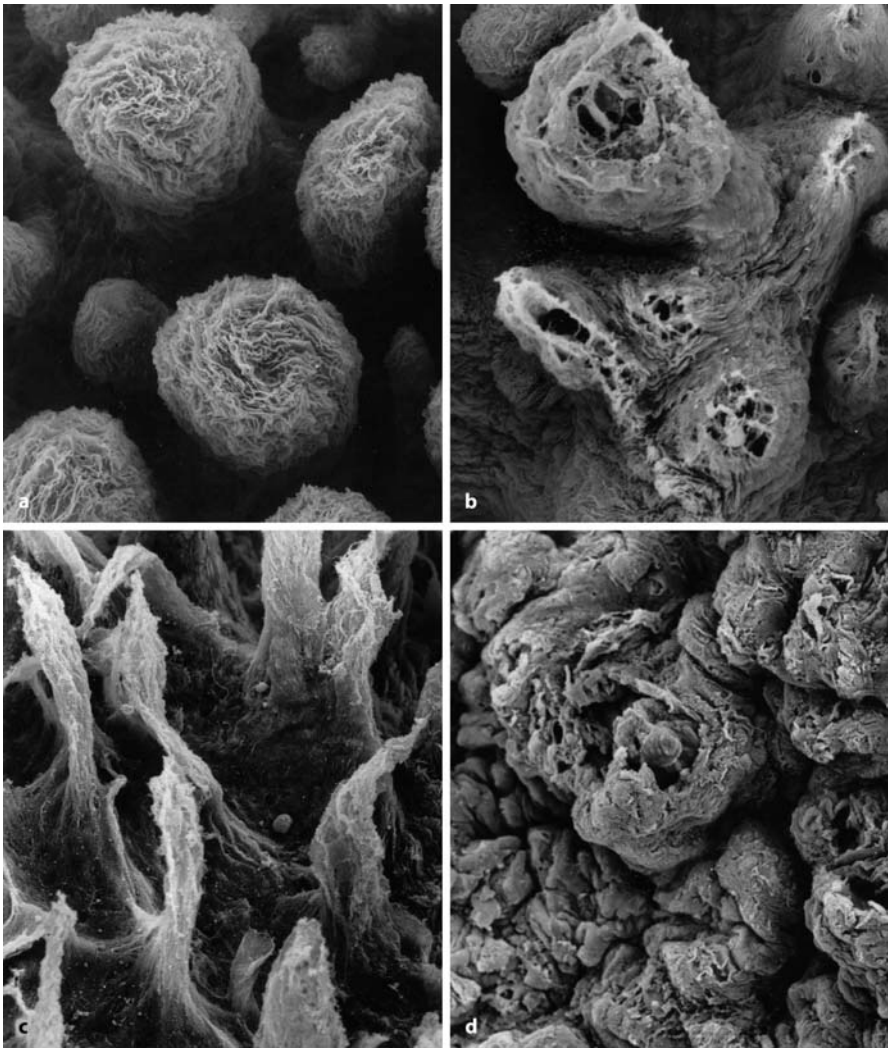

Fig. 11.11. Magnified view of dermal papillae observed in the healthy (**a**), boundary (**b**, **c**) and damaged (**d**) areas resulting from stage II pressure ulcer. The papillae in the healthy area all show a finger-like profile and are regularly arranged. In some papillae of the boundary area the top is broken (**b**), and others show atrophic changes (**c**). In the damaged area an irregular contour with no papillae is shown. Age 84 years, female (**a**, **b**, **c** ×700; **d** ×200)

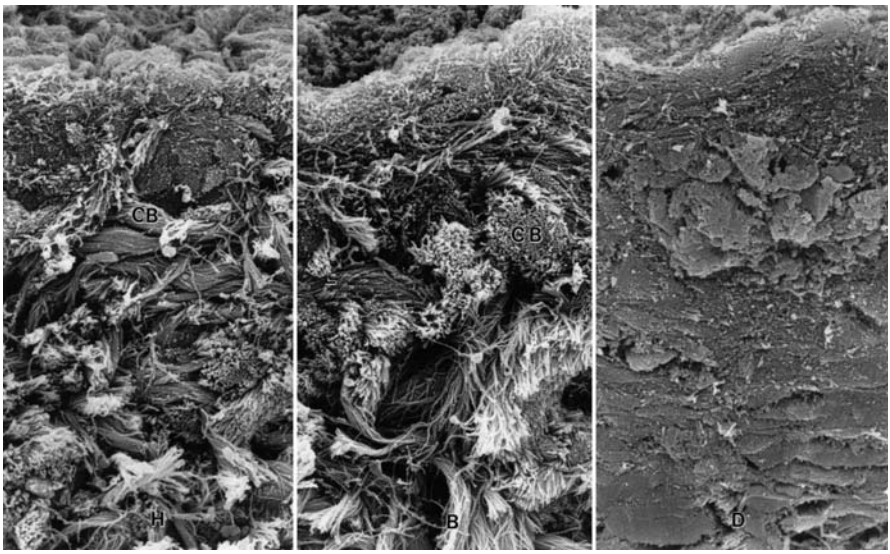

Fig. 11.12. Cut surface of the papillary layer showing the bundles of collagen fibrils (*CB*). These bundles are larger in the boundary area (*B*) than in the healthy area (*H*). In the damaged area (*D*) resulting from stage II pressure ulcers, the fibrils are densely packed and individual fibrils cannot be identified. Age 84 years, female (×3,300)

It was found that the atrophic, irregularly shaped dermal papillae – partially broken, with foramina – were characterised in the boundary zone between healthy and damaged areas (Fig. 11.11).

In addition, a relatively dense network of collagen fibres in the papillary layers was observed, in contrast with the healthy area, where collagen fibres were scarce (Fig. 11.12).

In the area damaged by pressure ulcer, no epidermis and no dermal papillae were observed, and the fibrous elements of the dermis were exposed to the surface (Fig. 11.11). These findings suggested that the morphological changes of the papillae observed in the boundary area impairs tissue viability of the epidermis and papillary by inhibiting nutritive blood supply and by accumulating metabolites which predispose to tissue damage.

Shimamura and Watanabe [77] examined 23 tissue samples of the sacrum in mostly elderly humans with pressure ulcers post mortem. They reported that the earliest sign of tissue damage occurs in the superficial layers and subsequently extends towards the deeper layers. They assumed that the damage in the subcutaneous tissue and deep fascia may extend more easily since there is no structural diffusion barrier in those tissues. In this regard, the meshwork of collagen and elastic fibres of the papillary and reticular layers may play an important role in preventing the transmission of external pressure to deeper tissues.

Further Studies

Studies of the following nature would be beneficial:

1. More systematic and comprehensive animal studies are needed to enhance our understanding of the whole mechanism of tissue damage-recovery following loading. The results of previous animal studies are not comparable; therefore, the protocols of future experiments should be similar. For example, studies should use the same kind of animal (e.g. pig) or in-vitro model, the same indentor shape and loading system, the same site for indentation, and continuous loading of predetermined pressure and duration, examined using physiological, biochemical and immunohistological techniques. Once the threshold curve between magnitude and duration of pressure has been established, then the effect of repetitive loading can be investigated.
2. Characterization of the altered mechanical properties of the skin accompanying altered structure/composition in susceptible individuals, for example the elderly, patients with spinal cord injury and those with disuse syndrome. In addition, characterization of the altered mechanical properties of the skin due to repetitive loading.
3. Qualitative and quantitative analysis of tissue viability using more sensitive morphological tools, for example immunohistochemical analysis or non-invasive techniques (e.g. magnetic resonance imaging) that provide such information.
4. In-vitro investigation using a vital soft tissue model, that needs to be established, to clarify how the force is transferred to the individual layers of the soft tissue and how a given layer behaves differently when the force is applied to the skin.

One of the reasons why the aetiology of pressure ulcers has been investigated so little over the past decades is a lack of involvement of basic medical scientists or biologists in pressure ulcer research. In order to facilitate these studies, a multidisciplinary approach is needed involving biologists, basic medical scientists, bioengineers, clinicans, and other medical care specialists. This approach would provide significant advances in the pathogenesis of pressure ulcer.

References

1. Osborne S (1987) A quality circle investigation. Nurs Times Feb 18:73–76
2. Goode HF, Burns E, Walker BE (1992) Vitamin C depletion and pressure sores in elderly patients with femoral neck fracture. BMJ 305(17):925–927
3. Exton-Smith AN, Sherwin RW (1961) The prevention of pressure sores: Significance of spontaneous bodily movements. Lancet II:1124–1126
4. Defloor T (1999) The risk of pressure sores: A conceptual scheme. J Clin Nurs 8:206–216

5. Allman RM (1989) Pressure ulcers among the elderly. N Engl J Med 320(13): 850–853
6. Anderson TP, Andberg MM (1979) Psychosocial factors associated with pressure sores. Arch Phys Med Rehabil 60:341–346
7. Krouskop TA (1983) A synthesis of the factors that contribute to pressure sore formation. Med Hypotheses 11(2):255–267
8. Schubert V, Fagrell B (1991) Evaluation of the dynamic cutaneous post-ischemic hyperemia and thermal responses in elderly subjects and in an area at risk for pressure sores. Clin Physiol 11:169–182
9. Hagisawa S, Ferguson-Pell M, Cardi M, Miller SD (1994) Assessment of skin blood content and oxygenation in spinal cord injured subjects during reactive hyperemia. J Rehabil Res Dev 31(1):1–14
10. Bader DL (1990) The recovery characteristics of soft tissues following repeated loading. J Rehabil Res Dev 27:141–150
11. Bogie KM, Nuseibeh I, Bader DL (1992) Transcutaneous gas tension in the sacrum during the acute phase of spinal injury. Proc Inst Mech Eng [H] 206(1):1–6
12. Holloway GA (1984) Physiological causes of skin breakdown, In National Symposium on the Care, Treatment and Prevention of Decubitus Ulcers. Conference Proceedings, Virginia, pp 13–16
13. Ferguson-Pell M, Hagisawa S (1988) Biochemical changes in sweat following prolonged ischemia. J Rehabil Res Dev 25(3):57–62
14. Polliack AA, Taylor R, Bader DL (1991) Sweat analysis of soft tissue under load. Annual Report 18, Oxford Orthopaedic Engineering Centre, pp 19–24
15. Hyman WA, Artigue RS (1977) Oxygen and lactic acid transport in skeletal muscle effect of reactive hyperemia. Ann Biomed Eng 5:260–272
16. McCord JM (1985) Oxygen- free radicals in postischemic tissue injury. N Engl J Med 312(3):159–163
17. Gute DC, Ishida T, Yarimizu K, Korthuis RJ (1988) Inflammatory responses to ischemia and reperfusion in skeletal muscle. Mol Cell Biochem 179:169–187
18. Cotran RS, Kumar V, Collins T (1999) Acute and chronic inflammation. In: Pathologic basis of disease, 6th edn. Saunders, Philadelphia, pp 50–88
19. Sundin BM, Hussein MA, Glasofer S, El-Falaky MH, Abdel-Aleem SM, Sachse RE, Klitzman B (2000) The role of allopurinol and deferoxamine in preventing pressure ulcers in pigs. Plast Reconstr Surg 105:1408–1421
20. Houwing R, Overgoor M, Kon M, Jansen G, Asbeck ACV, Haalboom JRE (2000) Pressure-induced skin lesions in pigs: reperfusion injury and the effects of vitamin E. J Wound Care 9(1):36–40
21. Husain T (1953) An experimental study of some pressure effects on tissues with reference to the bed-sore problem. J Pathol Bacteriol 66:347–358
22. Kosiak M (1961) Etiology of decubitus ulcers. Arch Phys Med Rehabil 42:19–29
23. Wilms-Kretschmer K, Majno G (1969) Ischemia of the skin. Am J Pathol 54(3):327–343
24. Nola GT, Vistnes LM (1980) Differential response of skin and muscle in the experimental production of pressure sores. Plast Reconstr Surg 66(5):728–733
25. Groth KE (1942) Klinische Beobachtungen und Experimentelle Studien über die Entstehung des Decubitus. Acta Chir Scand 87[Suppl 76]:1–203
26. Kosiak M (1959) Etiology and pathology of ischemic ulcers. Arch Phys Med Rehabil 40:62–68

27. Dinsdale SM (1973) Decubitus ulcers in swine: Light and electron microscopy study of pathogenesis. Arch Phys Med Rehabil 55:51–56, 74
28. Daniel RK, Priest LD, Wheatley DC (1981) Etiologic factors in pressure sores: An experimental model. Arch Phys Med Rehabil 62:492–498
29. Reswick JB, Rogers JE (1976) Experience at Rancho Los Amigos Hospital with devices and techniques to prevent pressure sores. In: Kenedi RM, Cowden JM, Scales JT (eds) Bedsore biomechanics. University Park Press, London, pp 301–310
30. Rose EH, Vistnes LM, Ksander GA (1977) The panniculus carnosus in the domestic pig. Plast Reconstr Surg 59(1):94–97
31. Le KM, Madsen BL, Barth PW, Ksander GA, Angell JB. Vistnes LM (1984) An in-depth look at pressure sores using monolithic silicon pressure sensors. Plast Reconstr Surg 74(6):745–754
32. Dodd KT, Gross DR (1991) Three-dimensional tissue deformation in subcutaneous tissues overlying bony prominences may help to explain external load transfer to the interstitium J Biomechanics 24(1):11–19
33. Sangeorzan BJ, Harrington RM, Wyss CD, Czerniecki JM, Matsen FA (1989) Circulatory and mechanical response of skin to loading. J Orthop Res 7:425–431
34. Todd BA, Thacker JG (1994) Three-dimensional computer model of the human buttocks, in vivo. J Rehabil Res Dev 31(2):111–119
35. Hagisawa S, Shimada T, Arao H, Asada Y (2001) Morphological architecture and distribution of blood capillaries and elastic fibres in the human skin. J Tissue Viability 11(2):59–63
36. Sanders JE, Goldstein BS, Leotta DF (1995) Skin response to mechanical stress: adaptation rather than breakdown – a review of the literature. J Rehabil Res Dev 32(3):214–226
37. Pasyk KA, Thomas SV, Hassett CA, Cherry GW, Faller R (1989) Regional differences in capillary density of the normal human dermis. Plast Reconstr Surg 83(6):939–947
38. Ryan TJ (1983) Cutaneous circulation, In: Goldsmith LA (ed) Biochemistry and physiology of the skin., Oxford University Press, New York, pp 828–831
39. Liu X, Zhang Y, Liao J (1998) Regional differences in density of children's skin – an enzyme histochemical and stereological study, Zhonghua Zheng Xing Shao Wai Ke Za Zhi 14(6):448–451
40. Tsuchida Y (1987) Regional differences in the skin blood flow at various sites of the body studied by Xenon 133. Plast Reconstr Surg 80(5):705–710
41. Scelsi R, Scelsi L, Bocchi R, Lotta S (1995) Morphological changes in the skin microlymphatics in recently injured paraplegic patients with ilio-femoral venous thrombosis. Paraplegia 33:472–475
42. Reddy NP (1990) Effects of mechanical stresses on lymph and interstitial fluid flows, In: Bader DL (ed) Pressure sores: clinical practice and scientific approach. Macmillan Scientific & Medical, London, pp 203–220
43. Shimada T, Morita T, Oya M.(1991) Structures and architectures of lymphatic capillaries: Morphological differences from blood capillaries. Jpn Soc Electron Microsc 26(1):66–71
44. Reddy NP, Patel K (1995) A mathematical model of flow through the terminal lymphatics. Med Eng Phys 17(2):134–140
45. Miller GE, Seale J (1981) Lymphatic clearance during compressive loading, Lymphology 14:161–166
46. Ghadially R (1998) Aging and the epidermal permeability barrier: implications for contact dermatitis. Am J Contact Dermatitis 9(3):162–169

47. Gibson T, Kenedi RM, Craik JE (1965) The mobile micro-architecture of dermal collagen. Br J Surg 52:764–770
48. Arao H, Obata M, Shimada T, Hagisawa S (1998) Morphological characteristics of the dermal papillae in the development of pressure sores. J Tissue Viability 8(3):17–23
49. Parry DAD, Barnes GRG, Craig AS (1978) A comparison of the size distribution of collagen fibrils in connective tissues as a function of age and a possible relation between fibril size distribution and mechanical properties. Proc R Soc Biol Sci 203:305–321
50. Silver FH, Kato YP, Ohno M, Wasserman AJ (1992) Analysis of mammalian connective tissue: relationship between hierarchical structure and mechanical properties. J Long-Term Effects Med Implants 2(2,3):165–198
51. Richey M, Richey HK, Fenske NA (1988) Aging-related skin changes: development and clinical meaning. Geriatrics 43(4):49–64
52. Lavker RM, Zheng PS, Dong G (1986) Morphology of aged skin. Dermatol Clin 4(3):379–389
53. Fenske NA, Conard CB (1988) Aging skin. Am Fam Physician 37(2):219–230
54. Smith L (1989) Histopathologic characteristics and ultrastructure of aging skin. CUTIS 43:414–423
55. Daly CH, Odland GF (1979) Age-related changes in the mechanical properties of human skin. J Invest Dermatol 73:84–87
56. Gilchrest BA, Murphy GF, Soter NA (1982) Effect of chronologic aging and ultraviolet irradiation on Langerhans cells in human epidermis. J Invest Dermatol 79(2):85–88
57. Kohn S, Kohn D, Schiller D (1990) Epidermal Langerhans' cells in elderly patients with decubital ulcers. J Dermatol 17:724–728
58. Rodriguez GP, Claus-Walker J (1988) Biochemical changes in skin composition in spinal cord injury: a possible contribution to decubitus ulcers. Paraplegia 26:302–309
59. Klein L, Dawson MH, Heiple KG (1977) Turnover of collagen in the adult rat after denervation. J Bone Joint Surg 159-A(8):1065–1067
60. Rodriguez GP, Claus-Walker J, Kent MC, Garza HM (1989) Collagen metabolite excretion as a predictor of bone- and skin-related complications in spinal cord injury. Arch Phys Med Rehabil 70:442–444
61. Stover SL (1987) Arthritis related interests in spinal cord injury J Rheumatol 14[Suppl 15]:82–88
62. Tanaka K (1963) Structural changes in the capillary of the skin in chronic spinal cord injured patients examined with vital microscopy. Scientific Report of National Hakone Sanatorium, Japan, pp 222–231 (in Japanese)
63. Van Den Hoogen F, Brawn LA, Sherriff S, Watson N, Ward JD (1986) Arteriovenous shunting in quadriplegia. Paraplegia 24:282–286
64. Fischer TW, Wigger-Alberti W, Elsner P (2001) Assessment of 'dry skin': Current bioengineering methods and test designs. Skin Pharmacol Appl Skin Physiol 14:183–195
65. Blank IH (1953) Further observation on factors which influence the water content of stratum corneum. I Invest Dermatol 259–269
66. Wildnauer RH, Bothwell JW, Douglass AB (1971) Stratum corneum biomechanical properties. I. Influence of relative humidity on normal and extracted human stratum corneum. J Invest Dermatol 56(1):72–78

67. Allman RM, Laprade CA, Noel LB, Walker JM, Moorer CA, Dear MR, Smith CR (1986) Pressure sores among hospitalized patients. Ann Int Med 195:337–342
68. Berlowitz DR, Wilking SVB (1989) Risk factors for pressure sores: A comparison of cross-sectional and cohort-derived data. J Am Geriatr Soc 37:1043–1050
69. Yarkony GM (1993) Aging skin, pressure ulcers and spinal cord injury, In: Whitenock GG et al (eds) Aging with spinal cord injury. Demos, New York, pp 39–52
70. Sanders JE, Goldstein BS (2001) Collagen fibril diameters increase and fibril densities decrease in skin subjected to repetitive compressive and shear stresses. J Biomechanics 34:1581–1587
71. Wang YH, Sanders JE (2003) How does skin adapt to repetitive mechanical stress to become load tolerant? Med Hypotheses 61(1):29–35
72. Shea JD (1975) Pressure sores classification and management. Clin Orthop 112:89–100
73. Vermillion C (1990) Operating room acquired pressure ulcers. Decubitus 3(1):26–30
74. Witkowski JA, Parish LC (1982) Histopathology of the decubitus ulcer. J Am Acad Dermatol 6:1014–1021
75. Barnett SE (1987) Histology of the human pressure sore. CARE – Science and Practice 5:13–18
76. Moore JC, Ray AK, Shakespeare PG (1993) Ultrastructure of human dermis and wounds. Br J Plast Surg 46:460–465
77. Shimamura K, Watanabe H (2001) Histological study of pressure ulcers from cadaver sacral skin with special reference to the site of initial pathological changes and the progress of the tissue damage. Jpn J P U 3(3):305–314 (English abstract)