

# BIOENGINEERING OF THE SKIN

Skin Biomechanics



*Edited by* Peter Elsner  
Enzo Berardesca  
Klaus-P. Wilhelm  
Howard I. Maibach

DERMATOLOGY: CLINICAL & BASIC SCIENCE SERIES







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# Series Preface

Our goal in creating the *Dermatology: Clinical & Basic Science Series* is to present the insights of experts on emerging applied and experimental techniques and theoretical concepts that are, or will be, at the vanguard of dermatology. These books cover new and exciting multidisciplinary areas of cutaneous research; and we want them to be the books every physician will use to become acquainted with new methodologies in skin research. These books can be given to graduate students and postdoctoral fellows when they are looking for guidance to start a new line of research.

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We are working with these goals in mind. As the books become available, the efforts put in by the publisher, the book editors, and the individual authors will contribute to the further development of dermatology research and clinical practice. The extent to which we achieve this goal will be determined by the utility of these books.

**Howard I. Maibach, M.D.**



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# Preface

The skin plays an important role in maintaining the integrity of the living organism while allowing the interaction of the organism with its environment. To fulfill these functions, mechanical stability is as important as flexibility. The mechanical properties of skin are very diverse depending on the anatomical location, and they evolve throughout life from the fetus to old age. Both genetic and acquired skin diseases modify skin biomechanics, as do intrinsic and photoaging. Since aging is so closely linked with changes of skin mechanical properties that lead to wrinkles and furrows, the desire for eternal youth leads to attempts to modify skin mechanics by a variety of interventions, including cosmeceuticals, peeling, and laser treatments.

It is within this wide scope of interests that this book gathers up-to-date information on the noninvasive assessment of skin biomechanics by modern bioengineering technology. The editors are grateful that leading investigators have shared their experiences in the development and use of standard and new techniques, their applications in dermatology, and in the testing of pharmaceutical, cosmetic, and nonfood products for safety and efficacy. The editors are indebted to all authors for the knowledge and effort they have invested in this project. At the same time, we would like to thank Ms. Barbara Norwitz and Ms. Tiffany Lane of CRC Press, Boca Raton, for their help in the publishing process.

We sincerely hope that this book will provide valuable advice to our readers and that it will stimulate them to apply bioengineering techniques skillfully in their professional settings.

**Jena/Pavia/Hamburg/San Francisco, May 2001**

**Peter Elsner, M.D.**

**Enzo Berardesca, M.D.**

**Klaus-P. Wilhelm, M.D.**

**Howard I. Maibach, M.D.**



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# The Editors

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Dr. Elsner has published more than 200 original papers and 18 books. He is a member of more than 30 scientific societies; has served as chairman of the International Society for Bioengineering and the Skin (ISBS) and as a member of the Scientific Committee for Cosmetics and Non-Food Products (SCCNFP) of the European Commission and the European Group on Efficacy Measurement of Cosmetics and Other Topical Products (EEMCO).

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Dr. Berardesca has been chairman of the International Society for Bioengineering and the Skin from 1990 to 1996 and is a member of the Society for Investigative Dermatology, the European Society for Dermatological Research, the Italian Group for Research on Contact Dermatitis (GIRDCA), and the European Group for Standardization of Efficacy Measurements of Cosmetics (EEMCO group). He is currently vice chairman of the EEMCO group. He has organized several international meetings on skin bioengineering and irritant contact dermatitis in Europe.

Dr. Berardesca's current major research interests are irritant dermatitis, barrier function, and noninvasive techniques to investigate skin physiology (with particular regard to racial differences in skin function), sensitive skin, and efficacy evaluation of topical products.

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# *Section I*

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## *Introduction*





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# 1 Mechanical Properties of Human Skin: Biochemical Aspects

*Aarne Oikarinen and Anina Knuutinen*

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## INTRODUCTION

The mechanical properties of skin are due to the thickness and qualitative properties of epidermis, dermis, and subcutis. There are marked variations in these parameters in different parts of the body. During aging and in many diseases, qualitative and quantitative changes occur in epidermis and dermis. Since collagen and elastin are the major components of skin, this overview focuses on these proteins, emphasizing the synthesis, degradation, and genetic alterations that take place in them. Furthermore, certain physiological phenomena and diseases are illustrated that affect the quantity or quality of collagen and elastin and lead to alterations in the physical parameters and appearance of skin.

Human skin is composed of epidermal and dermal layers, each of which has its own functional importance. Epidermis consists mainly of keratinocytes and, to a lesser extent, melanocytes, Langerhans cells, Merkel cells, and unmyelinated axons. Dermis consists of eccrine and apocrine glands, hair follicles, veins, nerves, and a fine network of collagen fibers, elastic fibers, and other components of the extracellular matrix (ECM). ECM consists primarily of proteins and complex sugars, which form fibrillar networks and a ground substance. Collagen is an important structural component of skin connective tissue and provides the tensile strength of skin.

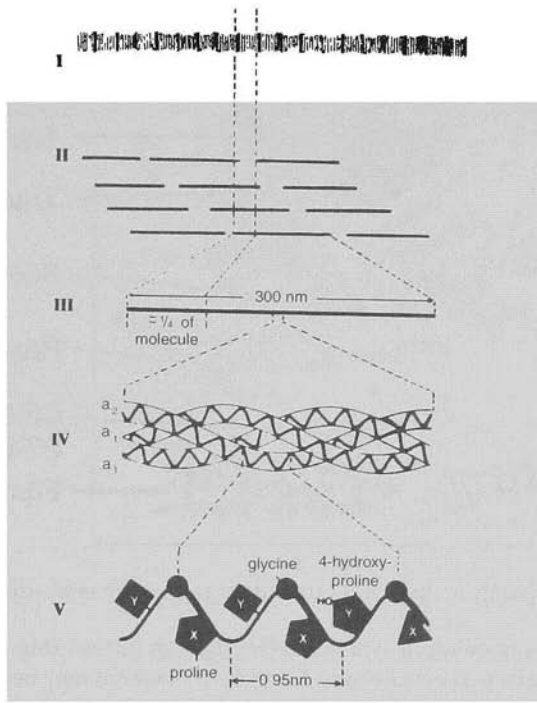
Approximately 70 to 80% of the dry weight of skin consists of collagen. The most abundant collagen types in skin are types I and III; the former accounts for 80% of the total collagen content of skin and the latter for approximately 15%.<sup>1</sup> The other collagen types present in skin include type IV collagen, which is abundant in the basement membrane (BM); type V collagen, which is located pericellularly; type VI collagen, which plays a role in matrix assembly and is present as microfibrils between collagen fibers; and type VII collagen, which is a structural component of anchoring fibrils.<sup>2</sup> Elastin accounts for only about 1 to 2% of the dry weight of skin but is important for the maintenance of skin elasticity and resilience. Glycosaminoglycans are of central importance for the maintenance of a water balance in skin, even though the quantities in ECM are small (0.1 to 0.3% of the dry weight of skin).<sup>3,4</sup> The BM of skin is a flexible sheetlike structure, which contains multiple different molecules.<sup>5</sup> Mutations in various BM components may cause variable clinical diseases, such as epidermolysis bullosa, in which the mechanical resistance of the BM is reduced.

In this overview, the synthesis and organization of collagen, elastin, and BM are elucidated. Furthermore, alterations in collagen and elastin are discussed in relation to changes in the mechanical characteristics of skin.

## COLLAGEN

A characteristic feature of the collagen molecule is a triple-helical conformation of three  $\alpha$  chains, which can be similar or dissimilar polypeptide chains. Type III collagen, for example, consists of three identical  $\alpha 1(\text{III})$  chains encoded by a single gene, whereas type I collagen is composed of two identical  $\alpha 1(\text{I})$  chains, which are synthesized from the same gene, and an  $\alpha 2(\text{I})$  chain, which is synthesized from another gene.<sup>6</sup> Each of the polypeptide chains forms a leftward helix, and the three helical chains wrap around each other to form a right-handed superhelix, which is stabilized in the extracellular space by cross-linking between chains and molecules (Figure 1.1). The triple-helical conformation of a collagen molecule requires the presence of glycine as every third amino acid in the polypeptide chains, which results in a series of Gly-X-Y, where X and Y can be any amino acid except glycine. The other amino acids essential for the triple-helical structure are proline and 4-hydroxyproline. Formation of 4-hydroxyproline and C-terminal disulfide bonds is crucial for the formation of the triple helix. Lysine is an amino acid also commonly found in the Y position, and it serves as a site for sugar attachment when converted into hydroxylysine by a specific enzyme.<sup>1,7,8</sup>

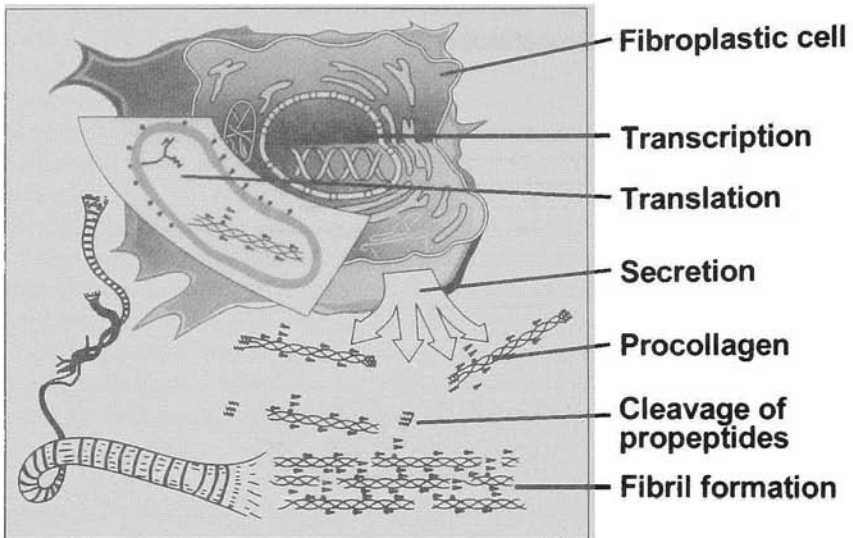
Skin collagen synthesis takes place mainly in fibroblasts. The synthesis of collagen has an intracellular and an extracellular phase, both of which involve post-translational modifications crucial for the formation of stable triple-helical collagen molecules, with appropriate cross-links (Figure 1.2). Intracellular modifications include hydroxylation of proline residues in the Y position into 4-hydroxyproline and of some proline residues in the X position into 3-hydroxyproline as well as hydroxylation of lysine residues in the Y position into hydroxylysine.<sup>7</sup> The reactions are catalyzed by specific enzymes, prolyl-4-hydroxylase, prolyl-3-hydroxylase, and lysyl hydroxylase, respectively, in the presence of  $\text{Fe}^{2+}$ , oxygen, 2-oxoglutarate, and



**FIGURE 1.1** Schematic presentation of the structure of collagen. (I) The collagen fibers in tissues demonstrate repetitive periodicity when examined by electron microscopy. (II) The fibers consist of individual collagen molecules aligned in a quarter-stagger arrangement. (III) Each collagen molecule is approximately 300 nm long. (IV) The collagen molecules consist of three individual polypeptides,  $\alpha$ -chains, which are twisted around each other in a right-handed, triple-helical conformation. (V) Each  $\alpha$ -chain has a primary sequence of amino acids in a repetitive X-Y-Gly sequence. As indicated, the X position is frequently occupied by a prolyl residue and the Y position by a 4-hydroxyproline residue. The individual  $\alpha$ -chains have a left-handed helical secondary structure with a pitch of 0.95 nm. (Modified from Prockop, D.J. and Guzman, N.A., Collagen diseases and the biosynthesis of collagen, *Hosp. Pract.*, 12, 61–68, 1977.)

ascorbate. Ascorbate is essential for the biosynthesis of collagen and acts as a cofactor in the hydroxylation of proline and lysine.<sup>9</sup>

Glycosylation of hydroxylysine and asparagine residues also takes place intracellularly. Both hydroxylation and glycosylation continue until the triple-helical conformation of the developing molecule is achieved. The procollagen molecules synthesized intracellularly are excreted into the extracellular space, where the large aminoterminal and carboxyterminal propeptides of the procollagens are cleaved *en bloc* by specific endoproteinases.<sup>10</sup> This cleavage of propeptides enables the initiation of fibril formation.<sup>11</sup> The molecular weights of the aminoterminal propeptides of type I and III procollagens (PINP and PIINP) are 35,000 and 45,000, respectively.<sup>10</sup> Since procollagens and mature collagens are synthesized in a ratio of 1:1, the amount of procollagen propeptides in serum and interstitial fluid reflects



**FIGURE 1.2** The intracellular and extracellular steps of the synthesis of fibrillar collagen.

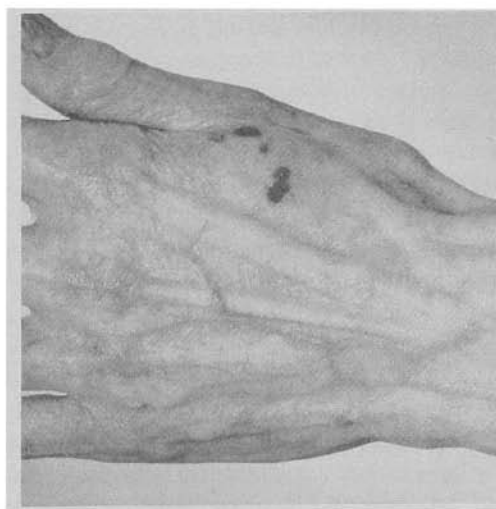
the rate of ongoing collagen synthesis.<sup>1,12,13</sup> In adult human skin, the ratio of type I to type III collagen is approximately 5:1 to 6:1,<sup>1</sup> but there may be a tendency toward an increased relative amount of type III collagen in the skin of elderly individuals.<sup>14</sup>

In living tissues, the existing collagen fibers gradually undergo chemical reactions that lead to the formation of covalent bonds between adjacent polypeptide chains, which make the fibers less soluble and more resistant to proteolytic enzymes. The first step in this reaction sequence is enzymatic, involving oxidation of the  $\epsilon$ -amino groups of lysine or hydroxylysine residues by the lysyl oxidase enzyme, which results in the formation of aldehydes derived from the corresponding amino acids. Two such aldehydes may, consequently, react with one another or one aldehyde may bind to another  $\epsilon$ -amino group. Either way, cross-links connecting two polypeptide chains, i.e., bivalent cross-links, are formed. The number of bivalent cross-links peaks at some point, after which their number begins to decline, as they develop into more-complicated structures connecting three or more polypeptide chains.<sup>15</sup>

Diseases with disturbed collagen metabolism include acquired diseases, such as scleroderma and scleredema, in which accumulation of collagen leads to thickening and stiffening of skin,<sup>16,17</sup> diabetic thick skin, presenting as thickening of skin, and keloids composed of excessive amounts of collagen (Table 1.1). In scleroderma and scleredema, increased synthesis of collagen results in thickening of skin.<sup>17,18</sup> In diabetic thick skin, nonenzymatic glycosylation of collagen is the most likely cause of the changes observed in skin.<sup>19</sup> A reduced amount of collagen can be found in skin atrophy, which may be a result of normal aging, or may be induced by topical or systemic glucocorticoids, or may be caused by genetic factors, such as focal dermal hypoplasia. In steroid-induced skin atrophy, the reduced amounts of collagen mRNA and the consequently reduced synthesis of collagen induce thinning of skin, as shown in Figure 1.3.<sup>20</sup> *Copyrighted Material*

**TABLE 1.1**  
**Mechanical Properties of Skin in Various Genetic and Acquired Diseases**  
**Resulting from Changes in Collagen**

Disease	Characteristics of Skin	Basic Biochemical Etiology
Steroid-induced atrophy	Thinning of skin	Reduced synthesis of type I and III collagens
Age-related atrophy	Thinning of skin	Reduced synthesis of type I and III collagens
Striae	Bluish /livid red lesions of variable size and shape	Not known, reduced collagen synthesis in steroid-induced striae
Focal dermal hypoplasia	Thinning of the dermis	Not known
Ehlers–Danlos syndrome (ED); includes at least ten different subtypes	Hyperextensible skin Thinning of skin Fragility of skin	Mutations in types I and V collagen, genes in type I and II ED, mutations in type III collagen gene in type IV ED, mutations in lysyl hydroxylase gene in type VI ED, defect in conversions of procollagen to collagen in type VII ED, defect in lysyl oxidase in type IX ED
Osteogenesis imperfecta	Thin, fragile skin	In most cases, mutations in type I collagen
Scleroderma	Thickening and stiffening of skin	Generally increased deposition of collagen
Keloids	Tumorlike thickening of skin	Increased deposition of collagen
Diabetic thick skin	Thickening and tautness of skin	Increase in nonenzymatic glycosylation of collagen



**FIGURE 1.3** Skin atrophy after topical glucocorticoid treatment. Skin thickness was 0.65 mm in a steroid-treated dorsum of the hand, whereas skin thickness in age-matched controls was 1.3 mm.

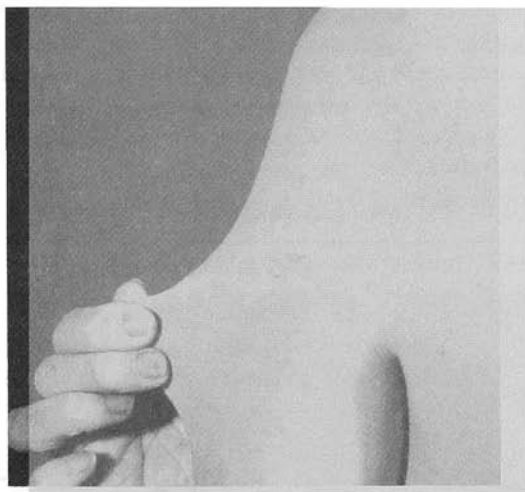
Changes in collagen are also found in various hereditary conditions. These include osteogenesis imperfecta, which involves changes in tissues rich in type I collagen, such as bones, ligaments, and skin, and Ehlers–Danlos (ED) syndrome, which has a wide variety of clinical manifestations, depending on the underlying defect in collagen metabolism.<sup>7,21,22</sup> Several gene defects associated with collagen-related diseases have been elucidated. For example, defects in the genes encoding the pro $\alpha$ 1(I) or pro $\alpha$ 2(I) chain of type I procollagen are commonly found in osteogenesis imperfecta, mutations in types I and V collagen genes have been found in ED types I and II,<sup>22</sup> and mutations in type III procollagen occurs in ED type IV.<sup>6,23</sup> The clinical picture in ED can vary from hyperextensible skin, as illustrated in Figure 1.4, due to abnormal fibrillogenesis of collagen, to thinning of the skin, as in ED type IV (Figure 1.5). This patient presented with a markedly reduced synthesis rate of type III collagen in the skin.<sup>24</sup>

## ELASTIN

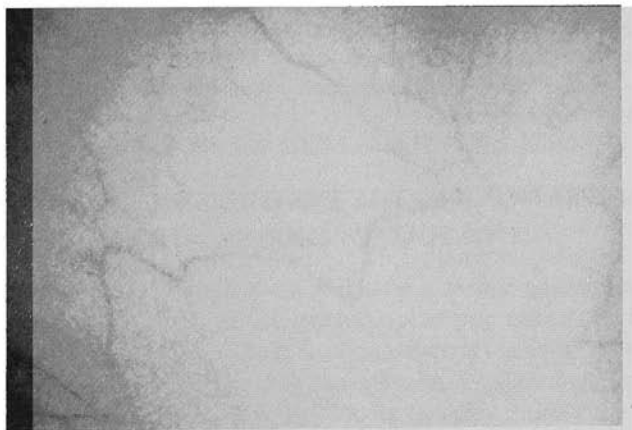
Elastic fibers are composed of an amorphous material, elastin, which accounts for 90% of the mature fibers, and of a microfibrillar component, which consists of microfibrils, 10 to 12 nm in size, primarily located around elastin, but partly also interspersed within it.<sup>25</sup> Microfibrils contain several glycoproteins; of these, fibrillin has been studied in most detail.<sup>26</sup> Elastic fibers are assembled in dermis as a three-dimensional net. Oxytalan fibers occur perpendicular to epidermis and are connected to elaunin fibers, which run parallel to epidermis.<sup>25</sup>

Elastin synthesis takes place in embryonic and rapidly growing tissues and in cells derived from these. Elastin is a polypeptide approximately 70 kDa in size, which is encoded by a single copy gene found in chromosome 7.<sup>27,28</sup> The elastin gene encodes tropoelastin, a precursor protein for elastin. Tropoelastin is synthesized intracellularly and then excreted into the extracellular space, where cross-linking takes place.<sup>26</sup> A high degree of cross-linking is characteristic of elastin, and the formation of desmosines is unique to it. A copper-dependent enzyme, lysyl oxidase, is involved in the cross-linking of both collagen and elastin.<sup>29</sup> In the cross-links of elastin, the lysine residues present as pairs in polyalanine sequences in such a way that there are always two or three amino acids, usually alanines, between two lysine residues, thus forming sequences of Lys-Ala-Ala-Lys or Lys-Ala-Ala-Ala-Lys. These alanine-rich cross-linking domains have an  $\alpha$ -helical conformation. In addition to the cross-linking domains, elastin has hydrophobic domains containing glycine, proline, and valine residues. The mechanisms of elastic fiber assembly are not well known, but microfibrils become visible first, after which elastin appears as an amorphous material that then coalesces and forms the core of the fiber. Most microfibrils are transferred to the outer aspect of the fiber, where they remain in mature tissue.<sup>26,27</sup> Abnormalities in elastic fiber morphology and assembly are seen in a number of congenital skin diseases, and specific gene defects behind genodermatosis have recently been found. Cutis laxa is a skin disease that presents in mild cases as predominant wrinkling and in severe genetic cases as widespread elastic fiber damage in skin and internal organs<sup>30</sup> (Table 1.2). Disturbed elastin cross-linking, due to defects in the copper metabolism and/or function of lysyl oxidase, has been suggested to cause X-linked cutis laxa.<sup>28</sup> A defect in the fibrillin1 gene is

found in Marfan syndrome.<sup>27,31</sup> In pseudoxanthoma elasticum, abnormal elastin fibrillogenesis occurs by an unknown cause and results in a lax and wrinkled appearance of the skin. Anetoderma involves local degradation of elastic fibers, causing sacklike protrusions.<sup>32</sup> In elastoderma, conversely, local accumulation of abnormal elastic fibers leads to delayed recoil and elasticity of the skin (Figure 1.6).<sup>33</sup>



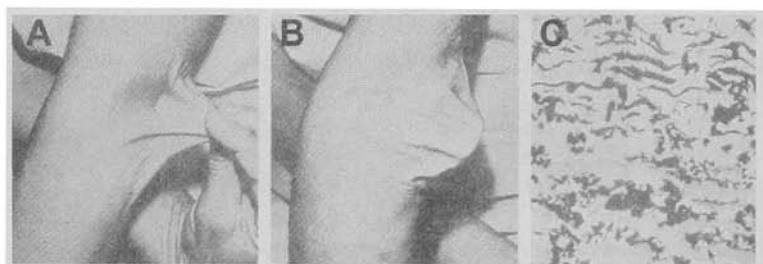
**FIGURE 1.4** The skin of a patient with ED type I is hyperextensible.



**FIGURE 1.5** The skin of a 20-year-old male with ED type IV is translucent with readily visible blood vessels. The concentration of type III collagen propeptide (PIINP) was 32.5  $\mu\text{g/L}$  in the suction blisters of the patient, whereas the mean value in the controls was 106  $\mu\text{g/L}$ , indicating markedly reduced synthesis of type III collagen in the patient's skin fibroblasts. Skin thickness was markedly reduced: 0.82 mm in the forearm of the patient and 1.49 mm in the controls.

**TABLE 1.2**  
**Skin Properties in Diseases Affecting Elastin**

Disease	Characteristic of the Skin	Biochemical Alterations
Cutis laxa	Loose, sagging skin	Decreased amount of elastin
Anetoderma	Sacklike lesions	Local degradation of elastic fibers
Pseudoxanthoma elasticum	Lax and wrinkled skin	Accumulation of abnormal elastin
Actinic elastosis	Diffuse thickening and wrinkling of sun-exposed skin	Accumulation of abnormal elastin in dermis; elevated levels of MMPs; decrease in collagen synthesis, increase in elastin synthesis
Marfan syndrome	Hyperextensible skin, striae	Mutations in fibrillin gene



**FIGURE 1.6** The right arm of a patient with elastoderma, demonstrating the laxity (A) and incomplete and delayed recoil (B) of skin. Histopathology revealed only a few normal-appearing fibers (the white arrow) and abnormal elastic structures (the black arrows) in the lower dermis (C) (Verhoeff–van Gieson stain). Modified from Kornberg, R.L. et al., *Elastoderma—disease of elastin accumulation within the skin*, *New Engl. J. Med.*, 312, 771–774, 1985. With permission.

## ALTERATIONS IN THE SYNTHESIS OF COLLAGEN AND ELASTIN DURING AGING

Along with increasing age, skin wrinkling gradually becomes evident, especially in sun-exposed areas, such as the face. Several distinct histological features have been observed within wrinkles, including reduction of oxytalan fibers in the dermis under wrinkles, profound collagen atrophy, and decreased amounts of type IV and VII collagens at the dermoepidermal junction as well as decreased amounts of dermal chondroitine sulfates, which are essential for balanced skin hydration.<sup>34</sup>

Skin collagen synthesis declines with aging and as the result of such external factors as long-term sun exposure and medications, for example, D-penicillamine and topical corticosteroids.<sup>35–37</sup> In aging skin, collagen fibers become thicker and less soluble and the synthesis of collagen declines.<sup>38</sup> Skin thickness remains quite constant between 10 and 70 years of age, after which a marked decrease in skin thickness occurs.<sup>39</sup> Precursors of both type I and III collagens also decrease in



photodamaged skin, and the degree of reduction in collagen production correlates with the amount of photodamage.<sup>40</sup>

The elastic properties of skin are also affected by aging. Along with increasing age, dermal elastic fibers become thicker and fragmented and oxytalan fibers appear fragmented and shortened.<sup>41</sup> Disintegration of elastic fibers is already seen in a minority of fibers between ages 30 and 70, but the changes become more profound after the age of 70 years, affecting a majority of the fibers.<sup>25</sup> As a result of the decreased number of elastic fibers in aged skin, the elastic recovery of skin decreases in elderly people.<sup>4</sup> Flattening of the dermo-epidermal junction is seen in both sun-exposed and sun-protected skin in elderly people.<sup>42</sup> Epidermal thickness declines with age in sun-protected areas, whereas sun-exposed regions develop an irregular epidermis with both thickened and atrophic regions.<sup>43</sup> A distinct feature of photoaged skin is a decrease in the ultrasound echogenicity of the upper dermis, which causes a subepidermal low-echogenic band.<sup>44-46</sup>

The ultraviolet (UV) radiation reaching the earth surface consists of UVA (320 to 400 nm) and UVB (280 to 320 nm) radiation. Shortwave UVC does not pass through the atmosphere.<sup>47</sup> UVA penetrates deep into tissues and has direct effects on dermal cells, including fibroblasts. UVB, on the other hand, has indirect effects on the ECM turnover by inducing the production of certain lymphokines and cytokines.<sup>13,48</sup> In actinic elastosis, the number of abnormal elastic fibers increases in the dermis, and the amount of collagen is reduced. *In vitro* studies have shown that the life spans of dermal fibroblasts and keratinocytes are shorter than normal in sun-exposed skin specimens.<sup>49,50</sup> It has also been demonstrated that elastin mRNA levels are elevated in photoaged skin, indicating transcriptional upregulation of the gene that codes elastin.<sup>51</sup> Reactive oxygen species activated by UV radiation are thought to play an important role in UV-induced DNA damage, cellular senescence, and aging.<sup>47</sup> Upon aging, the capacity to repair DNA decreases, thus increasing the risk of malignant transformations.<sup>52</sup>

## DEGRADATION OF COLLAGEN AND ELASTIN

Three major families of proteases degrade components of the extracellular matrix. These protease families are called serine, cysteine, and metalloproteinases, and they are important in the wound healing process and in tumor invasion and metastasis.<sup>53</sup> Matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) regulate the degradation of collagen, elastin, and other components of ECM.<sup>54</sup> It has been suggested that matrix metalloproteinases could have a crucial role in the degradation of collagen in actinic elastosis, since UV radiation has been shown to rapidly induce MMPs in skin and cell cultures. MMP-1, MMP-8, and MMP-13 (collagenases 1, 2, and 3) are the principal MMPs capable of initiating the degradation of fibrillar collagens I, II, III, and V. MMP-2 and MMP-9 are important in the final degradation of fibrillar collagens. MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, and MMP-12 are capable of degrading elastin.<sup>54,55</sup> MMP-1 degrades type III collagen at a faster rate than types I and II, whereas MMP-8 degrades type I collagen at a rate much faster than type III and, unlike MMP-1, is also important in the cleavage of type II collagen, which is abundant in cartilage.<sup>56</sup> The expression

of collagenase (MMP-1), 92-kDa gelatinase (MMP-9), and stromelysin has been shown to increase after a single exposure to UV radiation, and the activity of MMP-1 and MMP-9 remained maximally elevated for 7 days after four UV exposures at 2-day intervals. Topical tretinoin inhibited UV-induced MMP activity but did not counteract the induction of TIMPs.<sup>57</sup> Abundant evidence supports the use of topical tretinoin in the treatment of early signs of actinic damage.<sup>37,48,57-60</sup>

## FUNCTION AND ALTERATION OF THE BASEMENT MEMBRANE

Epithelial or endothelial cells and mesenchymal connective tissue are separated by a basement membrane (BM) or basal lamina, which is a flexible sheetlike structure approximately 50 to 100 nm thick.<sup>5</sup> Structurally, the BM consists of two layers: *lamina lucida*, which is adjacent to the basal plasma membrane of epithelial cells, and *lamina densa*, which is just below the *lamina lucida*. In skin, BM separates the epidermis from the dermis and forms a dermal-epidermal junction (DEJ). Depending on the type of tissue, the BM determines cell polarity, influences cell metabolism, organizes the proteins in adjacent plasma membranes, induces cell differentiation, and guides cell migration. The major components of BM are type IV collagen, a large heparin sulfate proteoglycan perlecan, and the glycoproteins laminin-1 and nidogen/entactin. Laminins are large flexible cross-shaped glycoproteins composed of three polypeptide chains. They bind to type IV collagen, heparan sulfate, nidogen, and cell surface laminin receptor proteins. Type IV collagen forms a network that is important in the maintenance of the mechanical stability of BM. The binding of another independent network, formed by laminin-1 on this network, is stabilized by nidogen-1 and nidogen-2. BM acts as a selective barrier to the movements of cells. BM beneath an epithelial layer prevents the fibroblasts in the underlying connective tissue from contacting the epithelial cells. The epithelial cells are linked to BM by integrins. In addition, the DEJ contains plaquelike hemidesmosomes at the surface of epithelial cells. Hemidesmosomes contain plectin, bullous pemphigoid antigen 1 (BPAG1), collagen XVII, and integrin  $\alpha 6\beta 4$ . They link the keratin cytoskeleton to laminin-5 in *lamina lucida*. Laminin-5 is linked to type VII collagen in *lamina densa*. Type VII collagen forms anchoring fibrils that firmly bind to the underlying connective tissue.<sup>61,62</sup>

There are several diseases, mostly inherited, in the epidermolysis bullosa (EB) disease group that affect the BM zone.<sup>63-65</sup> EB can be divided into four types, in which blister formation occurs at different levels. In EB simplex, the blistering is due to mutations in the keratins 5 and 14. As a consequence, keratinocytes are easily detached from each other, and blistering occurs within the epidermis.<sup>66</sup> In EB types where blistering occurs within the hemidesmosomes or between the basement membrane and the cell membranes, mutations may occur in type XVII collagen, plectin, or  $\alpha 6$  or  $\beta 4$  integrins. In junctional EB, the blistering takes place within *lamina lucida*, and mutations have been found in genes that code laminin 5. In dystrophic EB, the blistering takes place under BM and is due to mutations in type VII collagen.

## COMMENTS

Collagen and elastin are important for the structural integrity of skin. Thus, alterations in the quantity or quality of these proteins may cause changes in the mechanical properties of skin. Diseases involving a reduced collagen content of skin are characterized by atrophic skin, readily visible blood vessels, and easy bruising, which may result in paperlike scars. In contrast, if the quantity of collagen increases, skin becomes thick and taut and skin elasticity is limited, if not completely nonexistent. There are various genetic diseases in which collagen genes or enzymes participating in collagen biosynthesis are mutated. As a result, a wide range of diseases affecting skin and blood vessels may develop. Skin may, for example, be fragile, thin, or hyperextensible. Similarly, changes in the quantity or quality of elastin cause changes in the elastic properties of skin. If elastic fibers are fragmented or reduced in quantity, skin looks old and sags. If the quantity of elastin is increased, as in pseudoxanthoma elasticum or solar damage, skin may be thickened and inelastic.

There are several methods available to elucidate various aspects of collagen and elastin. Skin biopsies are useful in the assessment of collagen quantity, different types of collagen, and the rate of collagen synthesis. Histology, immunohistochemistry, and electron microscopy (EM) can be used to investigate changes in collagen fibers. Elastin can be studied by histological analysis and EM. Gene defects are best characterized by white blood cells, from which specific gene deletions and other mutations can be analyzed.

Similarly, the integrity of the BM zone can be studied by histological, immunohistochemical, and EM methods. If one wants to look at specific mutations of the BM components, there are several methods available to characterize the mutations in most of the proteins contributing to the integrity of BM.

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# 2 Mechanical Properties of Human Skin: Animal Models

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## INTRODUCTION

A significant question is whether animal models are suitable to predict mechanical properties in human skin. Can the results of animal studies be extrapolated to human skin, and are the basic approaches the same? Several attempts have been performed to describe the mechanical properties of skin by mathematical models (Ridge and Wright, 1964, 1965, 1966; Harkness, 1968, 1971; Hirsch and Sonnerup, 1968; Jamison et al., 1968; Viidik, 1968, 1969, 1973a,b, 1978, 1979; Frisén et al., 1969a,b; Veronda and Westman, 1970; Danielson, 1973; Soong and Huang, 1973; Wilkes

et al., 1973; Jenkins and Little, 1974; Lanir and Fung, 1974; Vogel, 1976, 1986; Barbanel and Evans, 1977; Barbanel et al., 1978; Lanir, 1979; Barbanel and Payne, 1981; Burlin, 1980, 1981; Fung, 1981; Sanjeevi, 1982; Potts and Breuer, 1983). Most of these authors used models derived from studies in polymers (Ferry, 1970). The simplest mechanical model analogous to a viscoelastic system is a spring combined with a dashpot, either in series (Maxwell element) or in parallel (Voigt or Kelvin element). Combinations of these elements were used to explain the mechanical phenomena in connective tissue, such as stress-strain behavior, relaxation and mechanical recovery, hysteresis, and creep phenomena (Jamison et al., 1968; Frisén et al., 1969a,b; Hirsch and Sonnerup, 1968; Vogel, 1976a, 1993a,b; Riedl and Nemetscheck, 1977; Vogel and Hilgner, 1979a; Viidik, 1968, 1969, 1973, 1978, 1979). Larrabee (1986), Larrabee and Sutton (1986), and Larrabee and Galt (1986) reviewed the theoretical and experimental mechanics of skin and soft tissue and proposed a mathematical model of skin deformation based on the finite-element method. A finite-element-based method to determine the properties of planar soft tissue was also described by Flynn et al. (1998). Unfortunately none of these models has been found sufficient to describe all properties of human and animal skin including the mechanical history before measurement and the time dependence during measurement. There is no comprehensive and unequivocally accepted model to describe completely the biorheology of skin.

Therefore, it is necessary to use several methods providing insight into clearly defined physical properties of skin.

## **STUDIES IN VITRO (EX VIVO)**

### **PREPARATION OF SAMPLES**

Subject animals, mostly rats, are sacrificed in anesthesia. The back skin is shaved and a flap of 5 × 5 cm removed. Subcutaneous fat is removed from the skin flaps and the sample placed between two pieces of plastic material with known thickness. In this way, skin thickness can be measured reliably with calipers to an accuracy of 0.1 mm. Perpendicular to the body axis two dumbbell-shaped specimens with a width of 4 mm in the middle of the sample are punched out (Vogel, 1969, 1970, 1989, 1993a). The samples are kept at room temperature on filter paper soaked with saline solution in petri dishes until testing. The specimens are fixed between the clamps of an INSTRON® instrument at a gauge length of 3 cm. All measurements are carried out within at least 1 hr. For long-lasting test procedures, such as relaxation or cyclic loading, the samples are wrapped with saline-soaked filter paper (Vogel, 1976a,b, 1989, 1993a,b).

### **STRESS-STRAIN CURVES IN VITRO**

After fixation of the specimens between the clamps of an INSTRON® instrument allowing a gauge length of 30 mm, stress-strain curves are registered at an extension rate of 5 cm/min; the curves show a characteristic shape (Figure 2.1). During low strain values, with a gradual increase of load, the curve has a concave section. The



stress-strain curve ascends according to an exponential function (Vogel and Hilgner, 1977). Afterward an almost straight section is reached indicating dependence on Hook's law. At this section, the *ultimate modulus of elasticity* (Young's modulus) can be calculated (increase of load divided by the cross-sectional area). Then, the curve yields somewhat, ending in a sudden break of the specimen. At this point, *ultimate strain* and *ultimate load* can be measured. From ultimate load divided by the cross-sectional area (specimen width times original skin thickness measured at the beginning of the experiment), *tensile strength* can be calculated.

The parameters skin thickness, ultimate strain, ultimate load, tensile strength, and modulus of elasticity are influenced by many factors.

Several studies on *age dependence* of mechanical parameters in rat skin were performed at age 2 weeks and 1, 4, 12, and 24 months. The period up to 4 months can be regarded as maturation, and the period between 12 and 24 months as senescence. Skin thickness increases to a maximum at 12 months of age and decreases thereafter. The ultimate strain values follow another shape. A small increase is found during puberty, a maximum after 4 months, and a decrease thereafter. Ultimate load, tensile strength, and modulus of elasticity show a very sharp increase during puberty, a maximum at 12 months, and a slight decrease thereafter (Vogel et al., 1970; Vogel, 1976b, 1978a, 1983a, 1988a, 1989, 1993a). Similar changes were found in human skin (Holzmann et al., 1971; Vogel, 1987a,b).

These parameters are also influenced by hormones and *desmotropic drugs*. The most-pronounced changes are seen after *glucocorticosteroids*, following both systemic and local application. Clinical experience unequivocally shows a decrease of skin thickness after long-term systemic or local treatment with corticosteroids. In rats, repeated administration of cortisol acetate in doses between 10 and 100 mg/kg cortisol acetate or 2 and 20 mg/kg prednisolone acetate induces a sharp dose-dependent increase of ultimate load and tensile strength up to 5 days. A continuous decrease of skin thickness and a decrease of ultimate load is noted up to 2 months. Ultimate load falls below controls, but tensile strength does not (Vogel, 1969, 1970a, 1974). From the increase of tensile strength after short-term administration, dose-response curves can be established for various corticosteroids vs. standard cortisol, allowing the calculation of potency ratios with confidence limits. The test can be used for

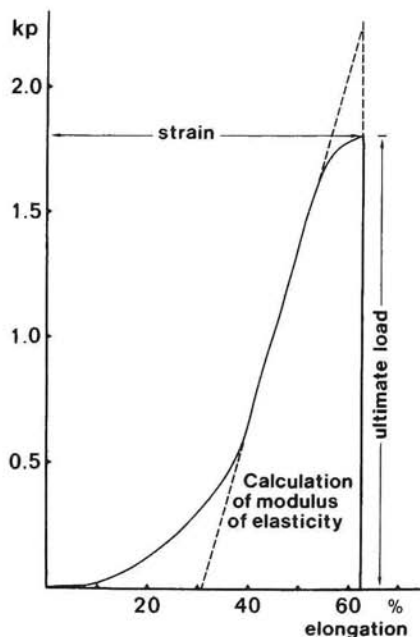


FIGURE 2.1 Original registration of a stress-strain experiment.

evaluation of topical corticosteroids (Schröder et al., 1974; Alpermann et al., 1982; Vogel and Petri, 1985). Similarly, Töpert et al. (1990) measured skin atrophy and tensile strength of skin after 30 days of local administration of corticosteroids in rats. Van den Hoven et al. (1991) and Woodbury and Kligman (1992) recommended the hairless mouse model for assaying the atrophogenicity of topical corticosteroids. Oxlund and Manthorpe (1982) found after long-term glucocorticoid treatment of rats an increase of strength and a decrease of extensibility of skin strips. In agreement with studies by Vogel (1974b, 1978a), these results were explained by a change in collagen cross-linking pattern.

Jørgensen et al. (1989) found a dose-dependent increase of mechanical strength in intact rat skin after treatment with biosynthetic human growth hormone. Andreassen et al. (1981) studied the biomechanical properties of skin in rats with streptozotocin-induced diabetes. An increased stiffness and strength were found: maximal stiffness was increased by 20% and the strain rate at maximum stress was decreased by 10%. Oxlund et al. (1980) found that the stiffness of rat skin was increased in the early postpartum period. This increase was also found in adrenalectomized animals. *Other hormones*, such as ACTH, thyroid hormones, androgens, estrogens, and gestagens, influence the mechanical parameters of rat skin to a lesser degree.

Among desmotropic drugs, *lathyrogenic* compounds, such as amino-acetonitrile, and D-penicillamine decrease ultimate load and tensile strength without major influence on skin thickness (Vogel, 1971a, 1972a, 1974a). A decrease of the strength of skin strips in rats after treatment with D-penicillamine was also found by Oxlund et al. (1984). A dose-dependent increase of tensile strength in skin after treatment was found with *nonsteroidal anti-inflammatory drugs* (Vogel, 1977a). Strain rate influences the values of ultimate load, tensile strength, and modulus of elasticity, but not the effects of age and corticosteroids (Vogel, 1972b). Changes in tensile strength are correlated with the content of insoluble collagen (Vogel, 1974b).

The mechanical parameters skin thickness, ultimate strain, ultimate load, tensile strength, and modulus of elasticity were used to evaluate the effects of *ultraviolet (UV-irradiation)* and the prevention of skin damage in hairless mice (Alpermann and Vogel, 1978; Vogel et al., 1981).

Fry et al. (1964) prepared skin rings from the lower part of the leg in rats and studied the age dependence of the mechanical properties. Nimni et al. (1966) measured tensile strength of excised skin samples in rabbits during aging. Pan et al. (1998) studied ultrasound and viscoelastic and mechanical properties in rabbit skin, including stress relaxation, creep, and Young's modulus as a function of strain. Lofstrom et al. (1973) described circadian variations of tensile strength in the skin of two inbred strains of mice. The effect of radiation therapy on mechanical properties of skin was studied in mice by Hutton et al. (1977) and by Spittle et al. (1980).

Schneider et al. (1988) measured tensiometric properties in guinea pig skin from flaps of normal dorsal skin and after implantation of an ovoid *tissue expander* filled for 4 days with saline. Belkoff et al. (1995) studied the mechanical properties of skin in pigs after subcutaneous implantation and inflation of silicone tissue expanders. Mustoe et al. (1989) compared the effects of a conventional tissue expansion

regimen of 6 weeks with the effects of an accelerated regimen of 2 weeks in a model in dogs; the study measured skin thickness, elasticity, creep, and stress relaxation.

### ANISOTROPY OF SKIN

As is the case with human skin indicated by Langer's lines (Langer, 1861; Gibson et al., 1969; Wright, 1971; Stark et al., 1977; Daly, 1982), the skin of rats exhibits *directional differences* (Hussein, 1972, 1973; Vogel and Hilgner, 1979a,b; Vogel, 1981a, 1983a, 1985a,b, 1988b; Belkoff and Haut, 1991). Stress-strain curves of rat skin displayed a different shape when excised perpendicularly vs. longitudinally to the body axis. At low loads, extension is higher in the longitudinal than in the perpendicular direction. The situation is reversed at medium and high stress values. Ultimate extension shows remarkable differences between longitudinal and perpendicular samples. Specimens obtained perpendicular to the body axis showed an increase during maturation, a maximum at 4 months of age, and a decrease during further aging. The behavior of samples obtained longitudinal to the body axis was quite different. After an initial rise, a maximum was found at 3 weeks. Afterwards a slight decrease was noted. Between 1 and 4 weeks all values of ultimate extension were significantly higher in samples punched out longitudinally to the body axis; between 4 and 12 months they were considerably lower (Vogel, 1981a). Analysis of the low sections of the stress-strain curve revealed a "step"-phenomenon (Vogel and Hilgner, 1977, 1979a,b; Vogel, 1988b). If samples obtained perpendicular to the body axis are extended, a gradual increase of load is observed at low degrees of extension, which is suddenly interrupted by a decrease of the registered curve. Then the curve increases again, and is interrupted by a second or third step. The phenomenon can be explained by the different orientation of collagen fibers in the dermis and by the presence of a muscular layer in rat skin. The muscular fibers are in a longitudinal direction to the body axis. If samples are obtained perpendicular to the body axis, the muscle bundles are cut transversally. In further studies the muscle layer was removed in one specimen and compared with a control with the muscle layer intact. Investigation of the directional variation showed that the step phenomenon is mainly due to the muscular layer oriented longitudinal to the body axis and the connective tissue between the muscle bundles, whereas the anisotropic behavior of extensibility and ultimate strain is caused by the directional variation of the collagenous bundles in the dermis.

Directional variations of the stress-strain curves were also described in the skin of tight-skin mutant mice (Menton et al., 1978).

### HYSTERESIS EXPERIMENTS

In hysteresis experiments not only the elastic but also the viscous properties of skin are measured (Vogel, 1978b, 1983b). Using the INSTRON instrument, the samples are stretched to a given extension degree (e.g., 20%) with an extension rate of 20 mm/min. When the given extension is achieved, the crosshead is immediately returned to the starting position with the same velocity. From the upward curve the stress and the modulus of elasticity at the end of the loading phase at the given strain

can be measured. When the sample is unstretched, the unloading curve shows a different pattern, reaching the baseline much earlier than the curve left it during the upward phase. From this point, the *residual extension* can be measured. Planimetry of the area below the upward curve, and of the area between the hysteresis loop, allows the calculation of the *energy input* and the *energy dissipation*, respectively, as well as the *ratio between energy dissipation and energy input* at each hysteresis cycle (Figure 2.2). Immediately after the first hysteresis cycle, the experiment is repeated to an extension degree of 30%, then to 40 and 50%, and finally to 60%. In rat skin, a maximum of the ratio between energy dissipation and energy input was found at 30 to 40% extension. This ratio is influenced by age. At low extension degrees, there is an increase with age, whereas at high extension degrees an age-dependent decrease is noted. The ratio of dissipation to input was slightly decreased by prednisolone, but definitively increased by D-penicillamine (Vogel, 1993b).

### RELAXATION EXPERIMENTS

In the relaxation experiment, viscous properties of skin are measured (Vogel, 1973, 1976a, 1983b, 1985a, 1993b). Skin strips were fastened between the clamps of an INSTRON instrument and extended with the high strain rate of 1000 mm/min to 20% extension. This extension was kept constant for 5 min. The chart speed was initially 1000 mm/min, then 10 mm/min. In this way, the initial tension and the stress values at 0.001, 0.01, 0.1, 1, and 5 min could be measured. As a result of relaxation, the stress values drop roughly with the logarithm of time. For each sample, the relaxation was calculated according to the formula:

$$\sigma(t) = A_1 + A_2 \times \log t$$

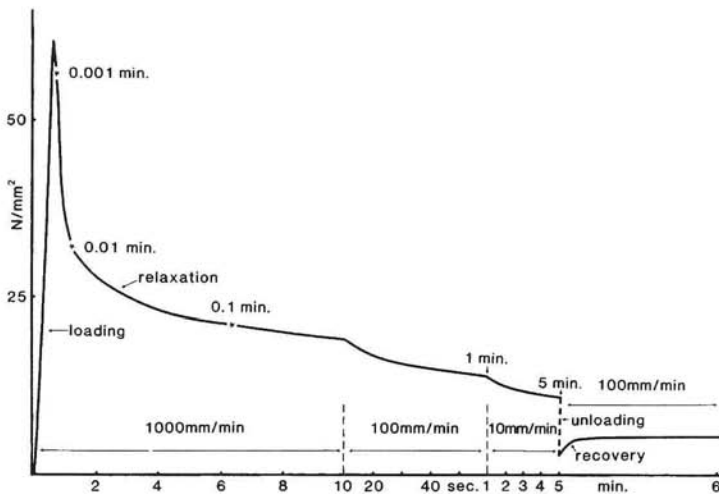
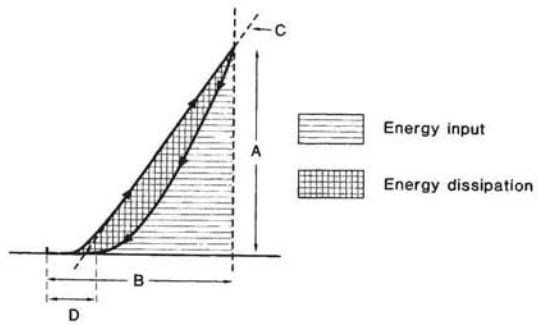
resulting in two constants ( $A_1$  and  $A_2$ ) for each sample, where  $A_1$  is the stress at  $t = 0$  and  $A_2$  the slope of the relaxation curve.

The ratio between the constants  $A_1$  and  $A_2$  must be considered the most characteristic parameter of the relaxation experiment. Furthermore, the *residual stress* after the 5-min relaxation period is measured and calculated as a percentage of the original stress. After 5 min the sample is returned to 90% of the original strain, for example, from 20 to 18%. The stress following such unloading is recorded and again calculated as percentage of the original stress. Immediately after unloading, the measured stress values rise again spontaneously, which is called *mechanical recovery* (Figure 2.3). Mechanical recovery is calculated as a percentage of initial tension and as a percentage of stress after unloading. The relaxation experiment is repeated with increasing degrees of extension of 40, 60, 80%, and eventually 100% until the specimen breaks.

In studies of age dependence in rat skin, a definitive decrease of the ratio of  $A_2$  to  $A_1$  is found at 40 and 60% extension degrees, indicating a decrease of plasticity with age. Mechanical recovery, as an indicator of secondary elasticity, at medium extension degrees is better in old animals than in young individuals. Stress relaxation is decreased after corticosteroids and increased after thyroid hormones and D-penicillamine (Vogel, 1973, 1993a,b).

Purslow et al. (1998) suggested that relaxation processes within the collagen fibers or at the fiber-matrix interface may be responsible for the viscoelastic behavior of skin.

**FIGURE 2.2** Original curve of the hysteresis experiment. A, Stress at the end of the loading phase; B, strain (%); C, line for calculation of the modulus of elasticity; D, residual extension.



**FIGURE 2.3** Original recording of the relaxation experiment.

## ISORHEOLOGICAL BEHAVIOR

Buss et al. (1976) demonstrated that the isorheological point is a valuable parameter for the mechanics of connective tissue. This method has been modified and elaborated for the skin strips of rats (Vogel, 1984, 1985b, 1987c). After fastening between the clamps of an INSTRON instrument, the specimen was expanded rapidly to 2 N and the corresponding strain measured. Keeping this strain constant, the load decay (relaxation) was measured for 5 min. Then the sample was again loaded to 2 N and a second relaxation period of 5 min was evaluated. In the third cycle, the sample was unloaded to 50% of the load observed after the 5-min relaxation period in the second cycle. The phenomenon of mechanical recovery was observed. With the crosshead driven up and down, the point was sought where neither immediate relaxation nor mechanical recovery could be observed. The load and strain at this point define the *isorheological point*, which is the point, under isometric conditions, that the measured load is constant for several minutes. Increasing and decreasing

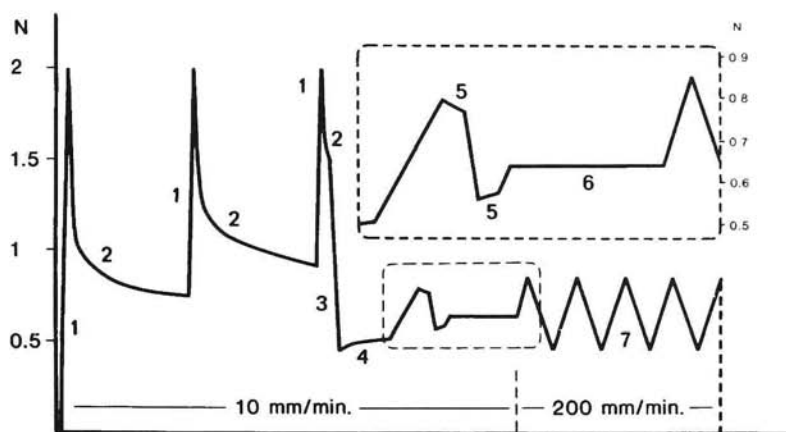
the load by 10% produced a sawtooth-shaped curve from which the modulus of elasticity at the isorheological point could be calculated (Figure 2.4). The same procedure was performed at higher initial loads such as 10 and 50 N. The product of percentage of strain multiplied by stress at the isorheological point indicates energy density. These values showed a decrease during maturation, a minimum at 12 months, and an increase during senescence. In studies with desmotropic compounds, the decreased viscosity after treatment with prednisolone acetate was more evident at the isorheological points than at the ultimate values. Similarly, the higher extensibility after treatment with D-penicillamine was indicated more clearly by the isorheological points than by the ultimate strain.

### REPEATED STRAIN

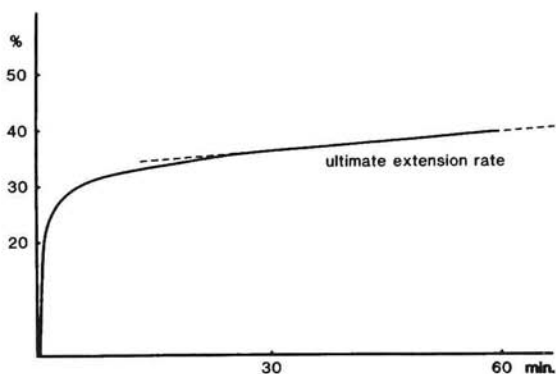
The method using repeated strain also measures mainly the viscous properties of skin (Vogel and Hilgner, 1978; Vogel, 1987b). Skin specimens are fastened between the clamps of an INSTRON instrument, extended with a strain rate of 100 mm/min up to 20% extension, and immediately unloaded; this procedure is followed by further cycles with the same strain rate and extension degree. The peak of the second cycle is considerably lower than the first, followed by a further decrease in the next cycles. The number of cycles are counted until the stress value is only one half that of the first cycle. Immediately afterward, the degree of extension is increased to 30%. Again, the number of cycles is counted until the stress value is only one half that of the first cycle. In this way, the *number of cycles indicating the half-life of tension* due to relaxation is counted at each step of 20, 30, 40, 50, 60, 70, 80, 90%, and eventually 100% extension. The number of cycles decreases from the first step (20%) to the third step (40%) and increases continuously until the last step. This increase is almost an exponential function of the number of steps. The parameters measured with this method are influenced by several factors. An increase is noted from an age of 1 month to an age of 24 months. The values are decreased by D-penicillamine and increased by prednisolone treatment. Again, this method showed that plasticity of skin is decreased by age and by corticosteroids and increased by D-penicillamine.

### CREEP EXPERIMENTS

In creep experiments, viscous behavior of skin is studied under constant load (Vogel, 1977b, 1987b). In a special apparatus, skin specimens are suddenly loaded with 100, 200, or 500 g and the extension degree measured. An immediate extension occurs, which is followed by a slow and almost continuous creep (Figure 2.5) that is measured as the *ultimate extension rate*. In addition, the extension achieved after 1 h is registered. An age-dependent decrease of these parameters was found in rat and human specimens indicating a decrease of viscosity or plasticity with maturation and age. Ultimate extension rate was decreased by prednisolone and increased by D-penicillamine.



**FIGURE 2.4** Repeated relaxation and determination of the isorheological point. 1, Loading to 2 N; 2, relaxation; 3, unloading; 4, mechanical recovery; 5, determination of the isorheological point; 7, sawtooth curve.



**FIGURE 2.5** Creep experiment in skin.

## STUDIES IN SKIN WOUNDS

The healing of skin wounds is a multiphasic process. The effect of drugs on the healing process was studied by measuring the mechanical strength at various time intervals after incision of the skin (Vogel, 1970b). Male Sprague-Dawley rats weighing  $120 \pm 5$  g were anesthetized with ether. After shaving of the dorsal skin, an approximately 3-cm-long incision was made down to the fascia in a craniocaudal direction in the dorsolumbar region. Immediately afterward, the wound was closed with wound clips. The rats were treated subcutaneously with test drugs beginning with the day of surgery. The clips were removed the day before the tensile strength was tested or at the latest at day 10 postoperation.

For the measurement of wound tensile strength, the rats were sacrificed on days 3, 6, 9, or 12 after surgery. Wound clips were fastened on each side of the incision and connected by means of threads with the load cell and the crosshead of an INSTRON instrument. Stress-strain curves were recorded at an extension rate of 5 cm/min. *Dehiscence of the wound* resulted in a sudden drop of the registered load. For experiments of 3-week duration, *skin strips* were punched and tensile strength was tested as described for evaluation of tensile strength in normal skin.

Changes of tensile strength of skin wounds following treatment with drugs is expressed as a percentage of vehicle-treated controls. The dose-dependent decrease found after immediate postoperative treatment and the dose-dependent increase found after treatment in prolonged experiments with corticosteroids serve as comparative parameters for new test compounds. A biphasic effect of corticosteroids on wound healing in rats was also found by Oxlund et al. (1979).

Many authors measured tensile strength of skin wound to follow the course of wound healing under various conditions. Most experiments were performed in rats (Holm-Pedersen and Zederfeldt, 1971; Holm-Pedersen and Viidik, 1972a,b; Andreasen et al., 1977; Greenwald et al., 1993; Seyer-Hansen et al., 1993; Jyung et al., 1994; Adamson et al., 1996; Quirinia and Viidik, 1998; Canturk et al., 1999), some of them also using the INSTRON instrument (Phillips et al., 1993; Maxwell et al., 1998; Jimenez and Rampy, 1999; Kim and Pomeranz, 1999). In addition, mice (Butler et al., 1991; Celebi et al., 1994; Kashyap et al., 1995; Vegesna et al., 1995; Gonul et al., 1998; Matsuda et al., 1998), guinea pigs (Bernstein et al., 1991; Drucker et al., 1998; Silverstein and Landsman, 1999), rabbits (Sandblom, 1957; Wu and Mustoe, 1995; Pandit et al., 1999), dogs (Howes et al., 1929; Scardino et al., 1999), or pigs (Langrana et al., 1982; Higashiyama et al., 1992; Chang et al., 1998; Fung et al., 1999) were used. In some studies polyvinyl alcohol sponges were simultaneously implanted to determine collagen accumulation (Langrana et al., 1983; Albina et al., 1993; Schaffer et al., 1996; Koshizuka et al., 1997; Bitar, 1998; DaCosta et al., 1998; Witte et al., 1998).

## THERMOCONTRACTION

If collagenous material such as skin or tendon is heated in a water bath, thermocontraction occurs. This phenomenon was described decades ago by Wöhlisch (Wöhlisch and du Mesnil de Rochemont, 1927; Wöhlisch, 1932). Verzár and other authors have used the phenomenon of thermocontraction of tendons and skin strips extensively to study the aging process (Verzár, 1955, 1956, 1957, 1964; Lerch, 1951; Rasmussen et al., 1964; Boros-Farkas and Everitt, 1967; Viidik, 1969, 1973b, 1975, 1978, 1979a,b; Vogel, 1969). With increasing temperature, a sudden increase of isometric force is found, which is followed by a decrease. To evaluate this phenomenon, either the *shrinkage temperature* or the stress at and above the shrinkage temperature can be measured. The decrease of sample strength can also be measured.

Joseph and Bose (1962) tested the shrinkage temperature of skin in newborn rats, at 10 months and 2 years and found an increase from 51.2 to 61.1°C. Elden (1970) found that the melting temperature in samples of rat tail skin did not consistently change with age. However, the zero stress length of melted collagen fibers



at 60°C relative to zero length at 50°C was greatly reduced with maturation and age. When isometric elevation of force at 60°C relative to that at 50°C was plotted against body weight, an increase was found. A decrease of percentage contraction of skin collagen melted at 60°C relative to that melted at 50°C was found, depending on age. Rupture stress of melted collagen fibers increased continuously with age.

Allain et al. (1977) tested pieces of dorsal skin of rats. The temperature of maximum tension was decreased from birth to 1 month, and then very slowly increased with age. A rapid relaxation was observed in young rats and in nonsenescent adult rats. Rundgren (1976) found changes of thermal contractility in skin of young and old female rats, as well as changes due to repeated pregnancies. Blackett and Hall (1980) found an increase of thermal shrinkage temperature in two strains of mice during the aging period.

Danielsen (1981) determined thermal stability measured as area shrinkage without tension during heating for membranes of collagen fibrils reconstituted from solutions of highly purified rat skin collagen. Le Lous et al. (1982a) and Flandin et al. (1984) applied the technique of differential scanning calorimetry to evaluate the denaturation process of collagen in rat skin.

Allain et al. (1980) built a device that measures not only hydrothermal shrinking but also swelling in rat skin. Le Lous et al. (1982b, 1983) studied hydrothermal isometric tension curves from rat and human skin and from different connective tissues. The curves obtained during a linear rise in temperature from 37 to 100°C at a rate of 1.15°C/min were classified into three major families, A, B, and C, depending on whether these curves show an early maximum, two shoulders, or a late maximum.

## STUDIES *IN VIVO*

### STRESS-STRAIN CURVES *IN VIVO*

In contrast to studies in humans, animal experiments allow measurement of mechanical properties both *in vivo* in anesthesia and later on *in vitro* (*ex vivo*) at the same site. This purpose required the development of special methods (Barbanel and Payne, 1981; Vogel, 1981b, 1982; Vogel and Denkel, 1982, 1985a; Denkel, 1983). The rats were anesthetized with 60 mg/kg Nembutal® i.p. The back skin was shaved mechanically. Skin thickness was measured by use of calipers on an elevated skin fold. Four small (14 × 14 mm) metal plates bearing a hook were used as tabs and were glued on the skin in both the longitudinal and perpendicular directions at a distance of 25 mm with a cyanoacrylate preparation. An operation table was mounted on the crosshead of an INSTRON instrument and a triangle was attached to the load cell. At the end of the triangle, threads were fastened that were conducted by reels and hooked to the tabs. The crosshead was moved down manually until the threads were stretched; however, no tension was yet measured. Then the crosshead was driven downward with a rate of 50 cm/min, which means that the actual extension rate was 100 cm/min. The load was measured only to limited values to prevent damage to the skin. In each rat the stress-strain curve was recorded in both directions, where the order (first longitudinal or first perpendicular) was changed from animal to

animal. In this way, the influence of the first extension on the results of the second extension should be eliminated.

In spite of similar conditions, differences between the stress-strain curves from *in vitro* and *in vivo* experiments were found. These findings confirmed the statements of other authors (Barbanel and Payne, 1981; Wijn, 1980) regarding the importance of tab distance and tab geometry (Vogel, 1981c). Analysis of the data showed that the higher the ratio of distance between the tabs to the area below the tabs, the higher were the stress values. These findings can be explained: although skin consists of several layers, only the upper layer (epidermis) is fastened to the tabs in the *in vivo* experiment. The forces transmitted to the lower layers are transmitted by a larger area if the area under the tabs is larger. The lower layer can slide over a larger area and is therefore less extended, resulting in lower stress values. No sliding is possible if the sample is fastened from both sides as it is in the *in vitro* experiments. By taking all experimental conditions including the strain rate into account, *the in vivo results are comparable with those obtained in vitro*. This holds true for the age dependence as well as for the influence of desmotropic compounds (Vogel and Denkel, 1985a).

Cook et al. (1977) compared tension/extension ratio curves *in vivo* and *in vitro* in rats using the suction-cup method. Baker et al. (1988) described an apparatus for testing mechanical properties of normal and irradiated pig skin *in vivo*. In their system, the pads were attached to the skin of the pig rump with double-sided tape. They were moved apart at a predetermined rate using a motorized unit. Force was assessed using an S-shaped, center-point, double-beam load cell mounted on a movable crosshead. Displacement of the pads was measured using a floating-core linear variable displacement transducer. Using this system, Baker et al. (1989) studied the effect of single doses of X rays on the mechanical properties of pig skin *in vivo*.

### REPEATED STRAIN *IN VIVO*

A special method has been developed to study the *mechanical properties of rat skin after repeated strain in vivo* and the course of recovery during different time intervals (Denkel, 1983; Vogel and Denkel, 1985; Vogel, 1988c). Tabs were fastened on the shaved back skin of anesthetized rats with a distance of 25 mm either perpendicular or longitudinal to the body axis. With an extension rate of 100 mm/min, the skin was extended 30 times for a 50% strain under anesthesia. Load was recorded and stress calculated by dividing of load by skin thickness measured from a skin fold obtained with calipers. Cycle 1, 5, 10, 20, 25, and 30 were recorded with more rapid paper speed to facilitate the evaluation of modulus of elasticity and stress values. The modulus of elasticity was calculated from the upper section of the stress-strain curve. Stress values decreased after repeated loading approximately with the logarithm of the number of cycles. The area under the curve of 30 cycles was evaluated by computerized calculation according to Simpson's formula (Hütte, 1915; Denkel, 1983; Vogel, 1988c). Stress values and the area under the curve were higher perpendicular than longitudinal to the body axis, as found in other *in vivo* experiments (Vogel and Denkel, 1985). The age dependence of the stress values was different

for the direction vs. body axis. In longitudinal samples the stress values fell from 1 to 12 months and increased until 24 months. In perpendicular samples a decrease of stress values was found followed by an increase at 12 months and a decrease until 24 months. During the experiment, the modulus of elasticity increased in both directions from the first to the fifth cycle. This may be explained by the so-called conditioning of connective tissue (Nemetscheck, 1980). From cycle 5 to 30, a decay of the modulus of elasticity approximately with the logarithm of the number of cycles was noted. Age dependence of the modulus of elasticity was similar to that of stress values. In both directions a decrease during maturation was found. The behavior between 12 and 24 months was different: in longitudinal samples an increase was noted and in perpendicular samples a decrease was noted. The area under the curve calculated from stress values closely resembled the pattern of initial stress, indicating that this value dominates for the area under the curve and that the decay is only of secondary importance. In the *in vivo* experiments the values of initial load, initial stress, the modulus of elasticity, and the area under the curve show the same tendency during senescence: a decrease in the perpendicular and an increase in the longitudinal direction. This indicates that the aging of the skin in rats is different in the longitudinal vs. the perpendicular direction.

#### **IN VIVO RECOVERY AFTER REPEATED STRAIN**

A method was developed to study the *in vivo recovery of mechanical properties of rat skin after repeated strain* (Denkel, 1983; Vogel and Denkel, 1985b; Vogel, 1988c, 1993a, 1993c). Full recovery, i.e., *restitutio ad integrum*, can be observed only by using *in vivo* experiments, not by using *in vitro* experiments. As in the experiment of repeated strain, tabs were fastened on the shaved back skin of anesthetized rats with a distance of 25 mm either perpendicular or longitudinal to the body axis. With an extension rate of 100 mm/min, the skin was extended 30 times for a 50% strain under anesthesia. Load was recorded and stress calculated by dividing load by skin thickness measured from a skin fold obtained with calipers. After the first run, the animals were returned to their cages with the tabs still in position. A second run of repeated strain was applied after different time intervals between 15 min and 16 h. The stress values in the second run were definitively lower than in the first run. When calculated as percentage of the first run, the differences diminished with extended time intervals. With this *in vivo* method not only the mechanical recovery, which also can be observed *in vitro*, but also the biological recovery, i.e., the *restitutio ad integrum*, could be measured. Almost full recovery was found after 16 h.

The age dependence as well as the influence of systemic treatment with desmotropic drugs on biological recovery was studied for both directions vs. body axis (Vogel, 1988c, 1993c). The stress values in the first cycle of the second run were calculated as a percentage of the first run. In both the longitudinal and perpendicular directions, the values were less than 50% after 15 min and 1 h, but rose continuously until 16 h, reaching or even exceeding 100% at this time. Apparently, the restoration process starts immediately and is detectable after 1 h. In both directions, the lowest values were for the youngest animals and the highest for 12-month-old rats. When cycle 30 was evaluated in the same manner, expressing the values of the second run

as a percentage of the first run, smaller differences were observed. The values of the second run were between 70 and 80% of the first run after 15 min. These values dropped further, reaching a minimum after 3 h, and rose thereafter to around 100%. This may indicate that restoration of the skin has at least two components, one of which appears immediately and is apparent after 1 h and a second in which the damage reaches a maximum later and restoration starts later.

When the modulus of elasticity at the first cycle of the second run was expressed as percentage of the corresponding value of the first run, the percentage values were much higher than those for tension, indicating that the modulus of elasticity was less affected. The changes were the highest in young animals and the lowest in 12-month-old rats in both directions. A minimum after 1 or 3 h was observed, followed by an increase to almost normal values after 16 h. When the area under the curve was compared, expressing the data of the second run as a percentage of the first run, the values were between 60 and 70%. A decline until 3 h was observed, followed by a steady increase. The time course for the modulus of elasticity and the area under the curve indicated that several processes of damage and restoration are involved.

Surprisingly, *restitutio ad integrum* was the most rapid in old animals. The ability of the dermis to reconstitute the fibrous structure is apparently not negatively influenced by age.

In another experimental series, the mechanical behavior of rat skin during repeated strain *in vivo* and the restoration process thereafter were studied following 10-day treatment with desmotropic drugs (300 mg/kg p.o. D-penicillamine or 10 mg/kg s.c. prednisolone acetate). Repeated (30 times) elongations to 40% were performed under anesthesia both longitudinally and perpendicularly to the body axis. Evaluation of the first run of 30 cycles showed that stress values as well as moduli of elasticity decreased after D-penicillamine, whereas they were greatly increased after prednisolone treatment. The decay of stress values during repeated strain revealed similar effects of treatment. The restoration process was evaluated by a second run of 30 cycles after 1, 6, and 16 h. In the late phase of recovery, an even better *restitutio ad integrum* was found in treated animals. In contrast to other biomechanical parameters, the restoration process was found to be only slightly influenced by treatment with desmotropic compounds.

## CONCLUSIONS

Studies on mechanical properties in animal skin are more advantageous than studies in human skin in several respects:

- They can be performed simultaneously *in vitro* and *in vivo*. Taking into consideration the different experimental and anatomical conditions, the results are comparable.
- Only in animal experiments can the biomechanical properties of the dermis at higher extension degrees be studied *ex vivo* or *in vivo* under anesthesia; studies in humans are limited by pain threshold or to tests in cadaver skin.

- Studies on age dependence show a similar pattern for skin thickness, ultimate load, tensile strength, ultimate extension, modulus of elasticity, hysteresis, relaxation, creep behavior, and biochemical data both in animal and human studies. Therefore, extrapolations from animal studies to behavior of human skin are justified.
- With the methods reported in this chapter, primarily the mechanical properties of the dermis are measured. Because of anatomical conditions (haired skin in animals), the biomechanics of the epidermis can be better studied in human rather than in animal experiments.

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# 3 Mechanical Properties of Human Skin: Elasticity Parameters and Their Relevance

*Jørgen Serup*

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## INTRODUCTION

Biologically, the elasticity of the skin is a simple bimodal parameter with only two major components: (1) the ability under the influence of stress to undergo distension or strain and (2) the ability to subsequently retract or recover to the original state (Figure 3.1).

Skin is composite and consists of layers with entirely different structures, functions, and mechanical properties. The low-humidity stratum corneum with densely packed keratin is thought to be quite resistant; the cellular stratum Malpighii and the papillar dermis with high proliferation and high perfusion are thought to be soft and pliable (albeit with a denser basement membrane zone interposed); and the reticular dermis packed with collagen bundles and some elastic fibers is thought to be highly mechanically resistant. Skin is mechanically a viscoelastic system, and it shows major histological and microanatomical variation in different anatomical sites, among individuals, and between men and women. Simple theories, developed by mechanical engineers from studies of nonliving materials, cannot be applied uncritically to a complex biological system such as full-thickness human skin.

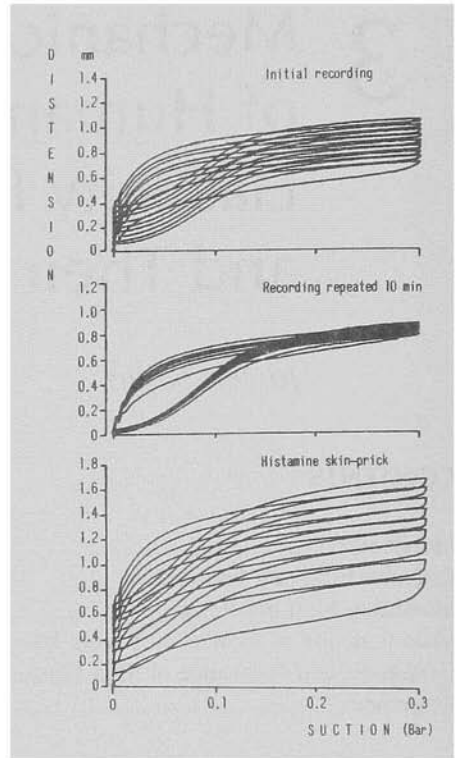
Elasticity parameters are manifold and can be measured and expressed in various ways *in vivo* and *ex vivo* depending on aims and usefulness. This chapter mainly addresses the background and aims related to usefulness in dermatology and cosmetology in an attempt to simplify and outline the essentials. Elasticity is considered from many different angles, and readers are referred to the chapters and the references given in the *Handbook of Noninvasive Methods and the Skin*.<sup>2</sup>

### ESSENTIAL ELASTICITY PARAMETERS

The essential parameters are, as mentioned, *distensibility* (or stress-strain) and *recovery* (or elastic retraction). These are both dependent on *time*, in particular with respect to recovery following a stress, which is “remembered” for quite a period (Figure 3.2).<sup>3</sup> Repeated stress results in further distension, a phenomenon known as *creeping* (or hysteresis); see Figure 3.1. This functional memory is probably a manifestation of the interstitial fluid and fiber network interactions in live skin, the expression of viscoelasticity of a highly specialized biological network.

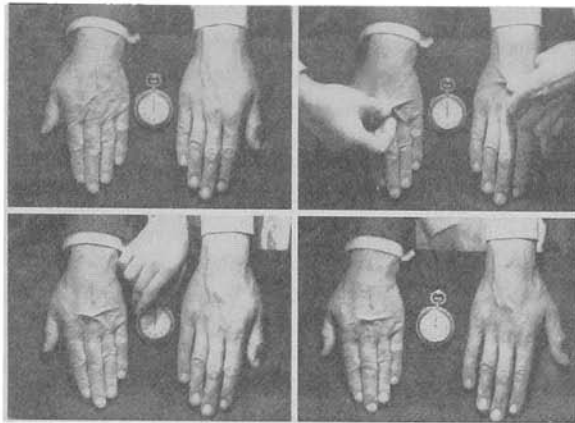
In the past it was often postulated, but never experimentally supported, that distensibility is related to collagen fibers and that retraction is related to elastic fibers. It is, of course, not possible in a complex system such as the skin to study isolated elements without intruding into the system; and the beauty of simplicity of opinion is no justification in itself in view of the present understanding of the complex nature of skin elasticity.

Experimental stress of skin has been induced as monoaxial elongation, as biaxial elongation (push, pull, and suction), by torsional maneuvers, and by elaborate testing such as applying different vibratory forces



**FIGURE 3.1** Examples of skin mechanics illustrating basic stress-strain functions, recorded with the suction chamber device Dermaflex A (Cortex Technology, Hadsund, Denmark). At initial recording, repeated suction results in further distension, so-called creeping or hysteresis. Re-recording after 10 min at the same skin site results in higher initial distension compared with initial recording but with less creeping. Recordings illustrate the functional mechanical memory. Histamine wheal and acute accumulation of water in the dermis result in markedly increased creeping. (From Serup, J. and Northeved, A., *J. Dermatol.* (Tokyo), 12, 52–62, 1985. With permission.)





**FIGURE 3.2** Elasticity of the skin in a man 68 years old (person on the left) contrasted to that of a man 26 years old (person on the right). At rest (upper left), stretched (upper right), immediately after release (lower left), and after 15 s (lower right). (From Lockhard, R.D., Ed., *Living Anatomy, a Photographic Atlas of Muscles in Action and Surface Contours*, 2nd ed., Faber & Faber, London, 1962. With permission.)

The value of a measuring system can be related to its usefulness in biological applications such as dermatology or cosmetology, and to its role in experimental research. The biaxial and monoaxial elongation systems have a fundamental rationale in biological situations and clinical states. Statements in the following sections mainly relate to this group of methods.

### MEASURING SKIN ELASTICITY

There is no general reference or standard for measuring the elasticity of live human skin, and the state of the art is — despite engineering sophistication — chaotic. There are no standard operating procedures regulating typical sources of variation and error during measurement, such as joint position, skin hydration state (epidermal and dermal), dermal perfusion and fluidity, intradermal texture, Langer line orientation, underlying adipose panniculus, skin temperature, effect of drinking/sweating, effect of stressful physical activity, etc. The state of the art is reflected by the range of elastometers available in the market, used in variable settings and by operators with variable educational backgrounds. Much activity is market-driven.

Most equipment operates on a suction-cup principle, where skin under a defined circular area is pulled in under the influence of negative pressure applied and released over a specific time (available systems typically have resistance in the pressure-regulating system with unknown pressure-to-time conditions in the suction chamber, and no tank with a negative-pressure reservoir). The circular area can vary from less than 1 to about 10 mm in diameter. With a small opening, the deformation of the skin is disproportionate; and only the epidermis and outer dermis can fold and undergo strain. With a larger diameter, the full-thickness skin can elongate.

Another type of equipment, torsional devices, induce only a few degrees of rotation and thereby typically only twist the very outer skin with a disproportionate

elongation. This is also the case with the gas-bearing electrodyamometer, which exerts repetitive monoaxial vibrations parallel to the skin. Thus, some devices operate with a suction pull exerted to a larger area and *proportionate elongation of the full-thickness skin*, whereas others operate with a small area and a tangential deformation with a *disproportionate elongation especially of the outer skin*. The devices and principles are not directly comparable. The former type of recording is directed toward dermatology and biology, the latter toward cosmetology.

Comparing healthy skin with abnormal skin involves a *reference/baseline problem*, which is difficult to solve. Aged skin is already sacked, elongated, and different from young skin before the device is applied. Measurements resulting from applied suction to these alterations are not directly comparable with measurements performed in a young person, who does not have the same structural abnormality and baseline. Measurement of aged vs. young skin typically demonstrates old skin to be equally distensible to young skin (but with poorer recovery) despite a sacked and obviously distended state on clinical inspection. The measured distensibility is technically correct, but experimentally not meaningful.

The *structure/elasticity relationship of skin* is complicated and seemingly very dependent on the structure and fluid relationship in the skin as exemplified by findings in scleroderma and histamine wheals. Interstitial fluid acts as oil between the fibers (see Figure 3.1). The more water, the softer and more distensible the skin and the easier the recovery following a strain. Skin *turgor* (from the Latin *turgor*, swelling) is the water tension of skin. In medicine, turgor is known to reflect the intradermal and general hydration state, as well as the fiber systems of the skin, particularly age-related changes (see Figure 3.2). Intradermal water and structural texture interactions are measured by ultrasound image analysis as low echogenic pixels with high precision. Intradermal water accumulates in most conditions in the outer dermis under the epidermis, rather than evenly throughout the skin. The skin is, among other tissues, a water reservoir that is mobilized when the body water balance is negative.

It is surprising that skin elasticity (distensibility) is variably or poorly correlated to thickness and that elasticity, even in normal skin (female vs. male, acral skin vs. truncal), is inversely correlated to thickness. The thinner and more echodense skin of extremities is less distensible compared with the thicker skin of the trunk. Females with thinner and more echodense skin show decreased distensibility compared with males. In addition, the thin skin of Pasini–Pierini atrophic morphea is less distensible. There is no expected gross difference in intradermal water content of thin skin compared with thick skin in different sites and in different genders; and the mentioned differences are likely to be related to the dermal structures and the way the fiber network is woven, rather than to total skin thickness.

## MAIN FUNCTION OF SKIN AS AN ELASTIC INTEGUMENT

The important mechanical functions of the skin can be outlined as follows:

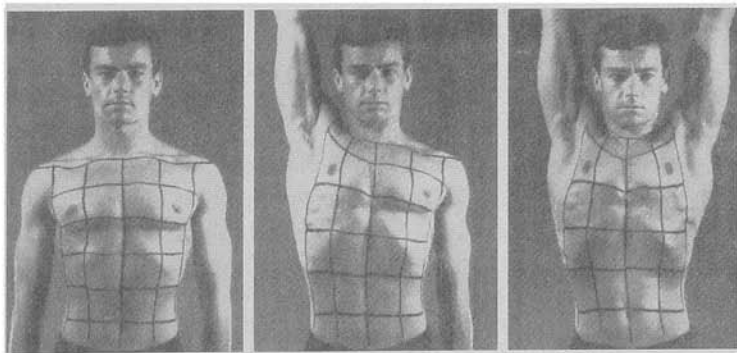
- To provide a protective and supporting cover of the body
- To remain tense but allow free motion of joints
- To counteract gravitation

- To be soft and pliable to allow effective contact with physical surfaces as a basis for simple and complex sensory perceptions (touch including stereological perception of objects, pain, heat, cold, and others)

The *protective function* is quite obvious. The skin must resist trauma and wounds must be avoided. The skin must support the adnexa, vessels, etc. Reduction of resistance related to connective tissue deficiency is seen in dermatosparaxis in cattle, in skin fragility during penicillamine treatment, in corticosteroid atrophy, and in aged skin as traction wounds or tangential wounds in the outer, less-resistant dermis, leaving pseudoscars.

The *function in relation to joint motions* (Figure 3.3) is vital in evolution and is directly reflected in the Langer lines, which are oriented in directions that clearly respect free motion of rotator joints and hinge joints. Langer systematically punctured cadaver skin with a round trocar and noted the direction of the resulting ellipsoid wounds. The lines represent the predominant direction of collagen and other fibers of the dermis. The Langer experiment at the same time demonstrated the variable pretension of the skin in different sites and directions, a pretension well appreciated in surgery and taken into account when incisions are made. Lichenification furrows in atopic dermatitis also follow the orientation of hinge joints. Fissures in chronic dermatitis do the same. Joint motion in acroscleroderma may be hampered by dermal sclerosis with excessive dermal collagen; conditions with loose connective tissue such as Ehlers–Danlos syndrome and pseudoxanthoma elasticum are associated with increased joint and skin motility. Increased skin distensibility may occur without altered joint motility.

*Counteraction of gravitation* is a function not well appreciated despite its fundamental significance. It has been known for decades that the giraffe, because of the tight connective tissue anatomy of its legs, avoids the development of orthostatic fluid accumulation despite its height. Valves of the veins have long been known to function to carry the hydrostatic force, and defective valves may result in swollen legs. In humans, it was clearly demonstrated in a study of 22 different body regions that there is a vertical vector in skin distensibility with increased spontaneous



**FIGURE 3.3** Elasticity of the skin relative to shoulder joint positions. Reproduced from Lockhard, R.D., Ed., *Living Anatomy, a Photographic Atlas of Muscles in Action and Surface Contours*, 2nd ed., Faber & Faber, London.

pretension of the skin from the head toward the foot.<sup>2</sup> This was confirmed in a study by Gniadecka, who also found a deficient vertical vector in sufferers of venous leg ulcers. Ultrasound image analysis of elderly persons shows an increase in low echogenic pixels in the morning 2 h after standing up, indicating orthostatic fluid accumulation in the legs. Recently, it was demonstrated that, in contrast, persons tilted in a negative-gravity bed develop fluid accumulation in the head, explaining the known phenomenon that astronauts develop significant head edema when they are no longer under the influence of earth's gravity. Russian astronauts applied cuffs around their thighs to avoid this problem. Thus, the vertical vector of skin elasticity in humans representing a systematic regional difference in the mechanical resistance of skin is, together with tense muscle fascia and venous valves, oriented to direct blood centrally, counteracting orthostatic pressure and gravity. It is a fundamental trait arising from evolution that is needed for physical performance and survival without swollen legs and leg ulcers at a young age.

A soft and pliable skin that can adjust to the surface of objects is a prerequisite in *sensory perception* including the different sensory modalities but particularly important for touch, which is sensed by Ruffini and Meissner end organs laid down in the skin texture. Touch is a three-dimensional modality that can become acutely sensitive as occurs in blindness, when touch replaces vision and may allow reading of complicated texts formed with letters made of small raised dots. Further, touch and the pressure exerted by pulses against an object are used as a "method" to assess the elasticity of objects. Resultant stress-strain of the skin replicates stress-strain of the object touched. Finally, touch combined with a tangential maneuver following the surface of the object serves to assess the three-dimensional surface contour and friction of objects, a highly developed function with central nervous system and even psychological elements. Tangential touch (and surface friction) plays an important role for feeling pleasure and for sexuality including sexual acts, well understood but little studied in spite of its huge importance in human interrelations from birth to death. Thus, surface, softness, pliability, and sensibility of the skin act together with intellect and psyche in different neurosensory functions important for daily life. In general, there is only a vague distinction between appreciation of stress-strain mechanics and surface friction of the skin.

### USEFULNESS AND RELEVANCE OF SKIN ELASTICITY PARAMETERS

Skin elasticity has no obvious, general, and direct user relevance except perhaps in some selected clinical situations. Elasticity is not commonly appreciated in normal life by healthy people or by patients. Aged people are more concerned about how their wrinkled and sacked skin looks than about some altered stress-strain measure when a piece of skin is pulled or twisted. A patient with scleroderma may be primarily concerned about the hampered joint motion, the fingertip ulcers, and the disability created by these than by the skin affliction itself. From this perspective, there is often limited relevance of measuring skin elasticity with very high precision

except perhaps in selected medical conditions to monitor disease course and the effect of medication.

Elasticity measurement in humans has the added limitation that a measurement is not very likely to be representative since normally only a small piece of skin is evaluated, typically a few square centimeters, and the whole skin is some 10,000 times larger and shows gross local site variations. Thus, the role of measuring skin elasticity mainly lies in experimental research when selected areas are treated or handled in a way that can illustrate general phenomena, effect of treatments, etc. that are due to a wider design perspective. However, extrapolation from observation in a small piece of skin to some broad field must be done with great reservation.

Elasticity methods have been somewhat overused to document efficacy of cosmetic products. This field is even more problematic because of the overlap in the appreciation of skin surface friction and surficial skin mechanics as depicted with a tangential movement by consumers spreading a cream or touching their skin (normally involves no twisting or vertical pull or push). The Young's modulus, valid for isotropic materials and widely used in engineering, does not appear meaningful in the biomechanics of anisotropic skin simply because the relation to thickness is variable and thus follows no generally applicable equation for skin as outlined in engineering texts.

There is a strong need for standardization in the field of skin elasticity measurement. It is a difficult variable to measure, and there are obviously many limitations and controversies related to instruments, experimental designs, preconditioning, data handling, and data interpretation. Skin elasticity measurement suffers a low status in the medical community and the techniques are generally not accepted by legal bodies. To some degree methods have been miscredited following their misuse. There are, nevertheless, a number of situations when elasticity measurements and proper experiments handled with excellence should receive the recognition they deserve. After decades of engineering and pragmatic use, it is time for bioengineers to review the field critically and to agree upon a set of realistic standards. Application, interpretation, and relevance must certainly be considered.

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# 4 Mechanical Properties of the Skin During Friction Assessment

*H. Zahouani, J. Asserin,  
and Phillippe Humbert*

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## INTRODUCTION

Previous studies on the tribology of human skin have attempted to demonstrate a correlation between certain tactile sensations and the friction between the skin surface and variety of probes.<sup>1-10</sup> In addition, friction measurements have been used to provide *in vivo* information about the effects of age, hydration, dermatitis, and cosmetic products<sup>11-15</sup> on both the interfacial and bulk properties of skin. Most previous studies on the friction of human skin, using sliding probes, have involved torque measurements on disks or flat cones rotating at constant velocity. Typical instruments have employed rotating wheels, oscillating disks, or adapted viscometers.

The physical nature of the forces involved during friction and the significance of the change of friction properties after cosmetic application are not clearly established.

The current techniques that simultaneously measure the normal load  $F_z$  between the contacting surfaces and the friction force  $F_x$  can be used to determine the skin friction coefficient defined as  $\mu = F_x/F_z$ . The survey of the published literature on skin friction shows a wide range of measured values of  $\mu$ . These differences emphasize that the assessment of the friction coefficient of skin is a highly complex problem. It involves skin elasticity (Young's modulus  $E = 10^5$  to  $10^7$  Pa for the forearm),<sup>16-18</sup> the anisotropy and the range of skin furrows, the physicochemical nature of skin (free energy of the skin  $\gamma_s = 38$  mJ m<sup>-2</sup>),<sup>19-21</sup> the hydrophobia of the sensor used, the normal load, speed, and the mean frequency deformation during friction.

This chapter describes measurements of the static and dynamic friction force of a spherical indenter on an inner human forearm. Through the results obtained by means of original *in vivo* tribometer,<sup>22</sup> which enables measurement of the components of friction force in a wide range of pressure and sliding, this study demonstrates the significance of the moisturization effect in terms of mechanical properties and changes in friction forces.

## FRICITION APPARATUS

### PROCEDURE

The equipment used in this study employs a more conventional tribological configuration based on a linear sliding action<sup>22</sup> on an inner human forearm (Figure 4.1). This system allows the control of the applied normal load, penetration depth, and sliding velocity, coupled with an accurate measurement of the frictional response. A smooth spherical indenter was selected as a probe to facilitate theoretical modeling, and to aid comparison with extensive earlier results on friction and lubrication of ball-*elastomer* contacts. During the friction test, the volar forearm axis was perpendicular to the sliding direction. The measured friction force corresponds to the friction of the probe on the skin, generating flexion of the two copper sheets. This flexion was transduced in an electrical signal by the strain gauges. The output signal was converted to digital data and collected by the computer, which displayed strain gauge deformations in related forces (mN).

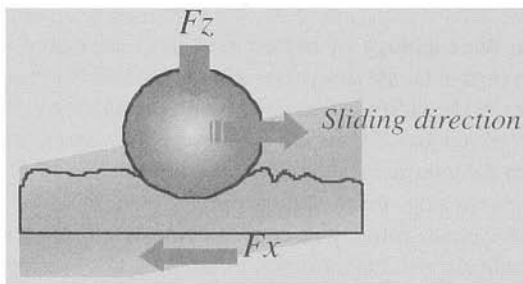


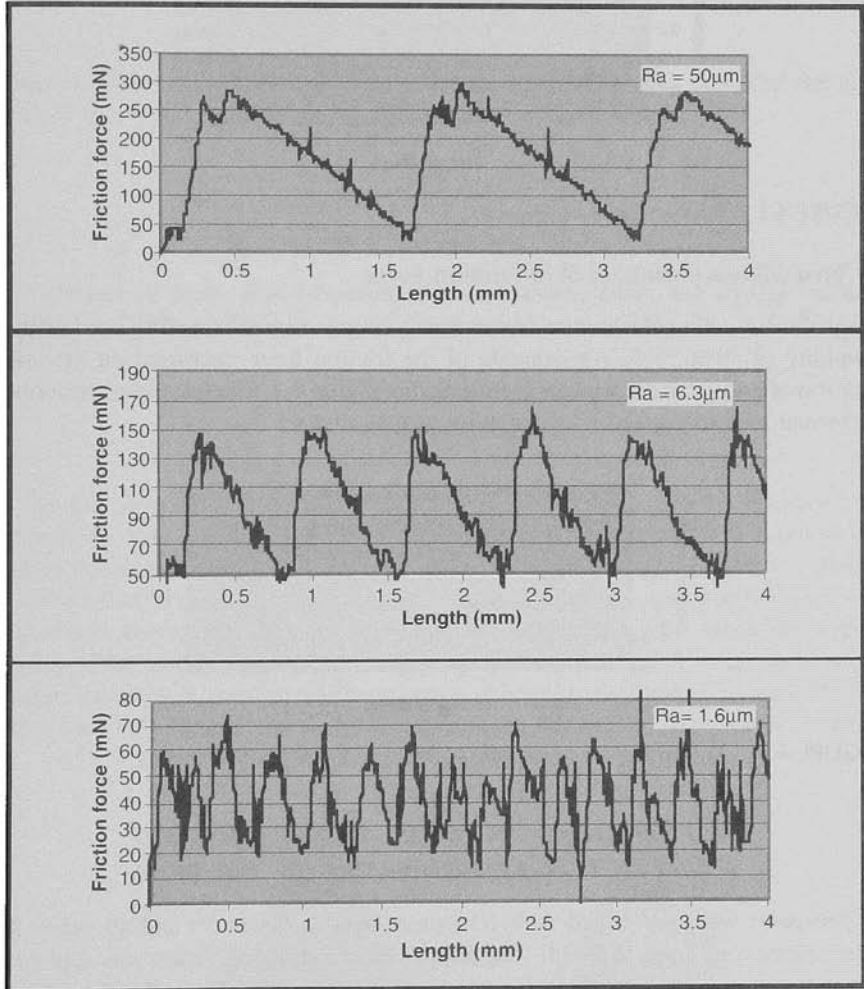
FIGURE 4.1 Measurement of skin friction force by linear sliding of a spherical indenter.



## MEASUREMENTS OF THE FRICTION FORCE

### Friction Force Measurements of Calibrated Steel Roughness Plate

The ability of the equipment used is studied by measuring the friction force of rough steel, with different mean arithmetic roughness  $R_a = 1.6$  to  $50 \mu\text{m}$ . Tests were performed using a normal load of  $20 \text{ g}$ . All curves represent the friction force vs. displacement. The measured profiles indicated irregularities of the surface obtained by manufacturing which produced changes in the frictional force measurements (Figure 4.2).



**FIGURE 4.2** Validation of the friction force measurement with calibrated steel roughness plate.

### Friction Force of a Silicone

The friction forces vs. the normal load were measured on the polymeric material at a low velocity ( $v = 0.27 \text{ mm s}^{-1}$ ) (Figure 4.3). The static force, defined as the critical force required to allow friction, was higher than friction force with an observed relaxation.

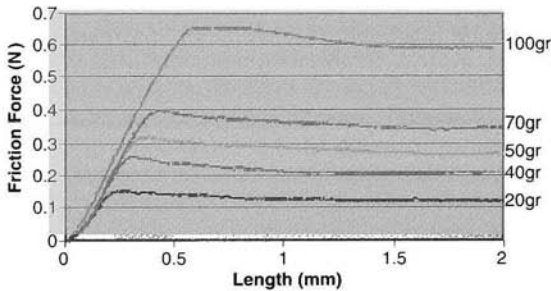


FIGURE 4.3 Friction force of silicone.

### *In Vivo* Measurements of Skin Friction Force

Measurements were obtained in a room with a temperature of 20 to 25°C and relative humidity of 40 to 50%. An example of the friction force measured on the volar forearm of a 45-year-old woman is presented in Figure 4.4. The tests were performed at normal load of 5 g and a low velocity of  $0.27 \text{ mm s}^{-1}$ .

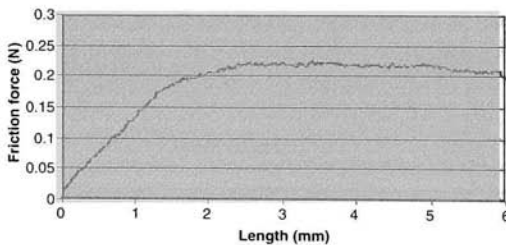


FIGURE 4.4 *In vivo* friction force measurement of a 45-year-old woman.

## MOISTURIZATION EFFECT IN MECHANICAL AND FRICTIONAL PROPERTIES OF THE SKIN

Experiments were performed with 10 women aged between 40 and 49 years. All participants were in good health. The insensitive moisturizing cream was applied to the volar forearm for 2 weeks. All measurements were performed after the subjects had been physically inactive for at least 15 min. Friction measurements were made on the volar aspect of their forearms before and after the application of the cream. The normal applied load used for mechanical and frictional properties was fixed at 50 mN. The contact was moved repeatedly along the arm over a length of about

6 mm, with imposed sliding velocity of 0.27 mm s<sup>-1</sup>. The mechanical and frictional parameters were assessed with ten tests.

**EFFECT IN MECHANICAL PARAMETERS**

During the first contact between the spherical indenter and skin surface under a normal load  $F_z$ , it was assumed that the skin deforms in an elastic manner. If the indenter has radius  $R$ , the radius of the circle of contact formed under a load is given by<sup>23</sup>

$$a^3 = \frac{3}{4} F_z R \frac{1 - \nu^2}{E} \tag{4.1}$$

where  $\nu$  is Poisson’s coefficient and  $E$  is Young’s modulus of the skin. The Hertzian theory<sup>24</sup> gives the pressure  $p$  at any point distant  $r$  from the center as

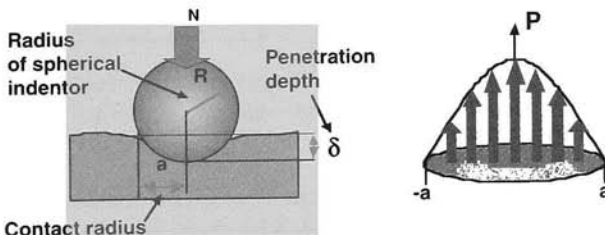
$$p = \frac{3}{2} \frac{F_z}{\pi a^2} \left( 1 - \frac{r^2}{a^2} \right) \tag{4.2}$$

The indentation depth,  $\delta$ , as a function of load, indenter radius, and skin parameters, is given by<sup>24</sup> (Figure 4.5)

$$\delta = \frac{a^2}{R} = \left( \frac{9}{16R} \right)^{1/3} \left( \frac{1 - \nu^2}{E} \right)^{2/3} F_z^{2/3} \tag{4.3}$$

In this first stage of contact, an approximate modulus can be evaluated by introducing into Equation 4.3 the measured value of the indentation depth  $\delta$ , the radius of curvature of the indenter  $R$ , and the skin Poisson’s coefficient ( $\nu \approx 0.45$ ).

The effect of moisturization in mechanical parameters is presented in Figure 4.6. The results show an increase of the mean contact radius and the mean indentation depth vs. the age group. On the basis of Equations 4.1 and 4.3, this increase in contact parameters was the result of Young’s modulus reduction (Figure 4.7). The reduction in the elastic modulus of the skin as the moisture content is increased has



**FIGURE 4.5** Contact parameters during a static contact between the spherical indenter and skin surface.

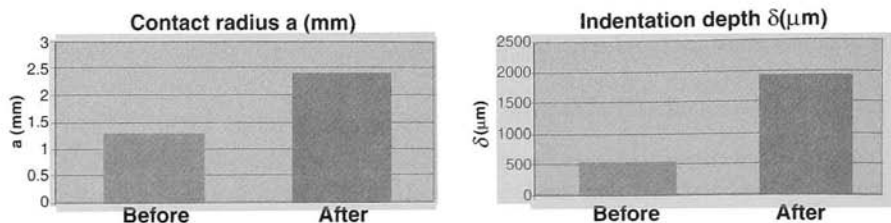


FIGURE 4.6 Effect of moisturization in contact mechanics.

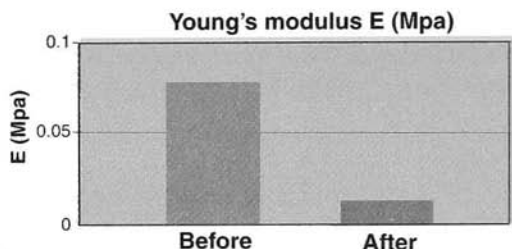


FIGURE 4.7 Effect of moisturization in elasticity of the skin surface.

been observed both *in vitro*<sup>25</sup> and *in vivo*. According to the literature,<sup>26</sup> water reduces the elastic modulus of skin in the range 2 to 2000. This study shows that after 2 weeks of application of an insensitive moisturizing cream, the factor of reduction of Young's modulus varies in the range of 4 to 7, depending on the age group.

#### EFFECT IN STATIC AND DYNAMIC FRICTIONAL PROPERTIES OF THE SKIN

When the contact is moved along the arm over a length of about 6 mm with a sliding velocity of about 0.25 mm/s, the friction force  $F_x$  of the skin surface can be characterized in three distinct phases (Figure 4.8).

In phase I the lateral force increases linearly to reach a maximum that corresponds to the static limit friction force. During this sliding resistance phase, the slope of the linear curve corresponds to the lateral stiffness of the skin  $K_x$  and the shear elastic modulus  $G$ .

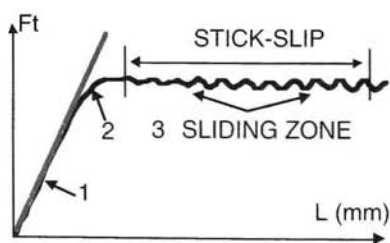


FIGURE 4.8 The three regimes of the skin friction force.

The slope change in the transition regime between the static and dynamic friction corresponds to phase II, which is controlled by the maximum of the lateral stress and the creep of the skin relief during the contact.

During the dynamic friction phase (phase III), an intermittent “stick–slip” motion can be observed depending on the conditions. The slopes of the “stick” phases of the motion provide information about the local stiffness of the skin. Figure 4.9 shows the result of the friction force before and after hydration over the course of 3 weeks. The increase of the friction force was observed for all participants, as shown in Figure 4.10. It is reasonable to conclude that the increase in friction force is due to the increase in the real area of contact and the reduction of the elastic modulus.

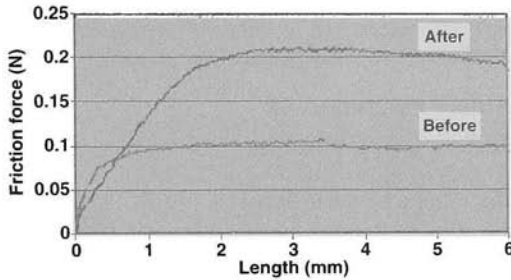


FIGURE 4.9 Effect of moisturization in the total friction force.

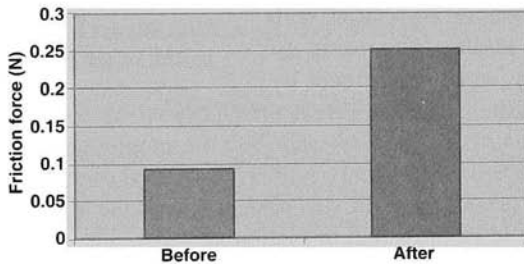


FIGURE 4.10 The increase of the friction force of moisturized skin surface.

## THE SKIN FRICTION MODEL

The total friction force,  $F_{\text{tot}}$ , may be given by the sum of two noninteracting terms — a deformation term,  $F_{\text{def}}$ , and an interfacial adhesion term,  $F_{\text{int}}$ ; thus,

$$F_{\text{tot}} = F_{\text{def}} + F_{\text{int}} \quad (4.4)$$

In general, the friction deformation term,  $F_{\text{def}}$ , of viscoelastic material is explained as a fraction of the frictional work done per unit sliding distance:

$$F_{\text{def}} = \alpha W \quad (4.5)$$

The parameter  $W$  describes the deformation work done; for example, per unit sliding distance, and  $\alpha$  the fraction dissipated.

The interfacial adhesion term,  $F_{\text{int}}$ , is the interface frictional work described by

$$F_{\text{int}} = SA \quad (4.6)$$

where  $A$  is the real contact area and  $S$  is a parameter termed the interface shear stress. This is the adhesion model of friction and it is supposed that the work is transmitted to the surface layer by the action of adhesive forces operating at the area of contact.

### DEFORMATION COMPONENT OF FRICTION

Friction may be usefully regarded as the energy dissipated per unit sliding distance. For a deformable substrate, which is expended at both the interface and in the bulk of the material during friction, the deformation component arises from the work dissipated by the rigid indenter in deforming the material. For viscoelastic materials, such as skin, the deformation–recovery cycle is associated with viscous energy losses. According to the experimental work examined by

Greenwood and Tabor,<sup>27</sup> the deformation component over the front half of the circle of contact (Figure 4.11) can be integrated over the annulus at constant point distance  $r$  from the center. Then the pressure  $p$  will be the same at every point of each annulus. The sum of the mean forces in the contact interval (0 to  $a$ ) gives the total deformation force in the direction of motion as

$$F_{\text{def}} = \frac{3F_z a}{16R} \quad (4.7)$$

by replacing Expression 4.1 in Equation 4.5, the total deformation force is given by

$$F_{\text{def}} = \left( \frac{9}{128R} \right)^{2/3} \left( \frac{1-v^2}{E} \right)^{1/3} F_z^{4/3} \quad (4.8)$$

If the skin were ideally elastic, the skin behind the sphere would yield an identical amount and no energy would be lost. If it is now assumed that, in fact, a constant fraction  $\alpha$  of the input elastic energy is lost as a result of elastic hysteresis in the skin, the deformation force is given by

$$F_{\text{def}} = \alpha \left( \frac{9}{128R} \right)^{2/3} \left( \frac{1-v^2}{E} \right)^{1/3} F_z^{4/3} \quad (4.9)$$

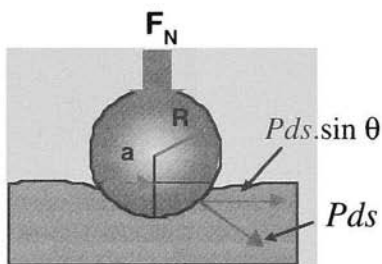


FIGURE 4.11 The deformation component of the friction force.

where  $\alpha$  is the viscoelastic hysteresis loss fraction. For sinusoidal-solicitation systems,  $\alpha$  is equivalent to  $\pi \tan \gamma$ , where  $\gamma$  is the loss tangent of the viscoelastic substrate and is given by the ratio of the loss and storage modulus.

Some cyclic loading–unloading measurements similar to the normal indentation test have shown that for rates of deformation the first cycle involved an energy loss due to hysteresis, which varied in the range of  $\alpha = 20$  to 35% of the total elastic energy deformation. On the basis of Equation 4.7, the deformation component was determined for each subject before and after hydration. The result shows an increase of the deformation component as a result of the change of Young's modulus and contact parameters after hydration (Figure 4.12).

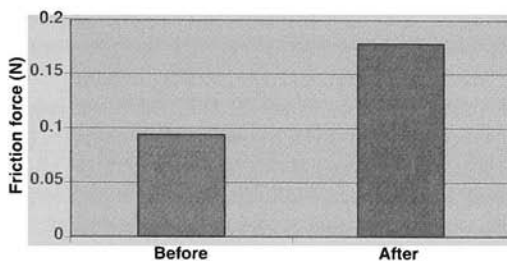


FIGURE 4.12 Effect of moisturization on skin deformation.

## CONCLUSIONS

The present study describes the physical significance of the friction force in the static and dynamic regimes by computing the functional parameters connected with the intrinsic response of the skin surface. The equipment used employed a more conventional tribological configuration based on a linear sliding of a rigid spherical probe under a small load, on an inner human forearm. The large increase in friction of moisturized skin is a result of moisture-dependent mechanical properties of the stratum corneum. A better interpretation of the frictional property changes can be achieved by taking into account the physicochemical properties of the skin area tested.

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# *Section II*

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## *Elasticity and Viscoelasticity*



# *Part 1*

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## *General Aspects*



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# 5 Hardware and Basic Principles of the Dermal Torque Meter

*Jean de Rigal*

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## INTRODUCTION

Complete determination of the mechanical properties of a material requires exposing it to a stress that is as clearly defined as possible over a perfectly determined geometry. The simplest example is in determination of the mechanical characteristics of an isotropic material that can be simply deformed by elongation in a single direction. The use of geometrically well-defined test assays then enables determination of all the intrinsic characteristics.

If the material is not homogeneous, anisotropic, and, like the skin, is subject to natural stresses, the problem becomes particularly complex. It is necessary to conduct a large number of tests under different configurations to stress the test specimen in

all directions. Failing that, determination of the intrinsic parameters can only be approximate. A structure consisting of a pile of layers, as is the case with the skin, cannot be isotropic. At best, if the layers are isotropic, the structure will exhibit transverse isotropism, necessitating determination of five elastic constants to characterize it completely. A certain number of finite-element modeling procedures<sup>1</sup> have shown that that degree of asymmetry is not sufficient to describe the behavior of the skin, which is at least orthotropic (8 elastic constants) or even completely anisotropic (21 elastic constants). It should also be noted that the skin is not elastic, but viscoelastic, and so the viscous characteristics must also be determined to describe completely the mechanical behavior of the skin. That approach, already highly complex *in vitro*, on test assays well-defined, becomes even more difficult *in vivo* when the material is attached to deep lying layers such as the adipose tissue. In addition, measuring skin properties *in vivo* is further complicated because only one surface of the sample is accessible.

It is thus clear that it is impossible to use simple means to characterize the skin fully. The objective will thus be to determine its properties using a rheological model that is as pertinent as possible, while clearly stating the set of measurement conditions (geometry, stresses, stress mode, etc.).

Numerous methods have been proposed to resolve the problem of *in vivo* determination of the mechanical characteristics of the skin. Several modes of applying stress have been proposed, such as uniaxial extensometry; in the plane<sup>2</sup> of the skin, or perpendicular to that plane; as in ballistometry,<sup>3</sup> the propagation of mechanical or sound waves,<sup>4</sup> and torque deformations.<sup>5</sup>

Concerning the most widely used methods, the general principles of determination are of two types: (1) constant-force stress and measurement of the deformation (i.e., creep mode) or (2) deformation of imposed amplitude and measurement of the stresses (i.e., relaxation mode). The stress or deformation may be imposed abruptly or slowly. The rate of imposition will condition the accounting for, and hence the determination of, the viscosity phenomena and the associated time constants.

The Twistometer and the Dermal Torque Meter (DTM), the latter a copy of the former, thus attempt to resolve certain of the above problems. The deformations are applied in the plane of the skin to minimize the contribution of the deep layers, as Wlasbloom<sup>5</sup> has shown. The stresses are applied in rotation, hence with an axis of symmetry. This solution does not eliminate the contribution of natural tensions, but averages them and makes measurement independent of the orientation of the imposed stress relative to the natural tension lines (Langer's lines), in contrast to uniaxial methods.<sup>6</sup> The general principle of the DTM is of the creep type, with an abrupt rise in stress.

Torsion methods have been available for some time.<sup>7-9</sup> The development of miniaturized electromechanical components enabled design of the Twistometer, then the DTM. Those instruments are now portable and can be used on all body areas of sufficient flatness and width (about 5 cm). The applications are in the fields of cosmetics (determination of hydration of the *stratum corneum*,<sup>10</sup> effects of sun,<sup>11,12</sup> effects of aging,<sup>13</sup> and effects of photoaging<sup>14</sup>) and dermatology (follow-up of disease course<sup>15</sup> and treatment effect monitoring).<sup>16</sup>

## BASIC PRINCIPLE OF THE HARDWARE

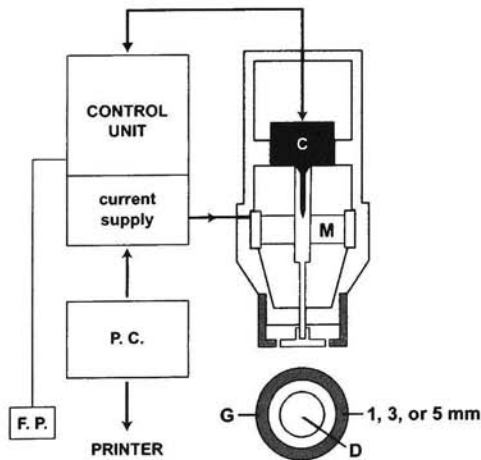
### THE PROBE

The probe consists of a torque motor and an angle sensor (Figure 5.1). The torque motor is rigidly locked to a flat disk at the probe head, which is referred to as the "torque disk." A ring, referred to as the "guard ring" or "torque ring," surrounds the disk. Both are glued onto the skin by means of two-sided adhesive tape. The torque disk imposes the stress on the skin and the immobile guard ring limits the propagation of the deformation.

The gap between the torque disk and the guard ring is the "operating gap" (OG). Three torque rings are available; depending on the question asked and the problem to be solved, a 1-, 3-, or 5-mm ring may be selected. For assessment of the mechanical properties of the skin surface, a 1-mm OG is required. For determination of deeper mechanical properties, a 3- or 5-mm OG is required. It should be borne in mind that the reproducibility of the measurements decreases as the OG width increases.

When the torque is applied for a given duration the torque disk moves to a degree dependent on the suppleness and viscosity of the tissue, and the resulting angular deformation is recorded. When the torque is switched off, the remaining tensile strength of the skin moves the torque disk back toward the initial position, and this phase of the response is recorded. During this phase, the skin is the only source of the forces acting in opposition to the mechanical friction of the probe. The deformation angle recording stops when the equilibrium between the two opposing forces is reached, so the remaining deformation is not simply a pure characteristic of the skin.

A two-way switch on the body of the probe enables one to zero the torque motor before measurement, and the second position of the switch applies the torque. The



**FIGURE 5.1** Diagrammatic representation of the DTM; C = rotational sensor, M = torque motor, D = torque disk, G = torque ring, D = operating gap.

period when the torque is applied is referred as the “torque-on” phase, and when the torque is removed is referred to as the “torque-off” phase. A complete measurement consists of these two phases.

## THE CONTROL UNIT

The control unit (see Figure 5.1) contains all the electronic circuits necessary to power the torque motor, the amplifier, the rotating sensor, and for relaying data to and from the computer. A foot pedal connected to the control unit enables the operator to initiate the measurements. The probe cable is also connected to the control unit. Thus, all the instructions and characteristics of the measurement or the set of determinations are controlled by computer via the control unit.

## COMPUTERS, PRINTERS, AND PLOTTERS

The DTM is connected to the serial port of a computer (see Figure 5.1), which cannot be used in stand-alone mode. Rather, a PC with a printer or a plotter to print the results or curves is required. The setup enables a standard computer to be used with no change in hardware. The user-friendly program contains all the functions commonly used to collect, store, and analyze the response curve of the skin submitted to the torque. The program is window-based and consists of various menus for the main functions.

All the measurement parameters (torque value, duration of the torque-on phase, duration of the torque-off phase) are defined and activated by the computer. The response curve is divided into two sections; torque-on and torque-off, which are analyzed separately on the basis of a rheological model. The essential parameters are extracted from each of the curves and stored.

## BASIC MECHANICAL PRINCIPLE OF THE TWISTOMETER AND DTM

The two systems may be considered electromechanical oscillators connected to a spring exhibiting a variable degree of viscous recoil in the skin. The oscillator has its own inertia, friction, and viscosity characteristics, which may be added to those of the skin or may oppose them (friction in the torque-off phase). The dynamic response of the mobile equipment may be described by a differential equation of the following type (harmonic oscillator-type response):

$$Jd^2\theta/dt^2 + \eta d\theta/dt + K_o\theta = C_o$$

where  $J$  is the moment of the inertia of the mobile component,  $C_o$  the imposed torque,  $K_o$  the stiffness of the recoil spring (the skin), and  $\eta$  the coefficient of viscous friction of the system skin plus mobile component.

The solution of this differential equation is given by

$$\theta(t) = C_o/K_o + A \exp(-at) \sin(bt + c)$$

where  $a = \eta/2J$  and  $b = 1/2J(4K_oJ - \eta^2)^{1/2}$ .



In the creep direction (torque-on), there is an inertial system with a recoil torque (skin). In the torque-off direction, there is an inertial system with no recoil torque but with friction.

For very short time periods, the profile of the response thus depends on the ratio between the values of the two parameters,  $J$  and  $\eta$ . If damping is marked, relative to the inertial moment, the response will have a continuous profile (Figure 5.2). If the damping is very small, an oscillating response will occur with duration depending on the ratio of the inertia to the damping. In a purely elastic material, the limit value for a long time period is  $C_o/K_o$ . These considerations show that analysis of the signal recorded by the DTM or Twistometer over very short time periods are conditioned by the ratio between the inertia and damping. If damping is marked, the elastic response,  $U_e$ , can never be achieved; the response would pass continuously from the elastic phase to the viscous one. For short time intervals, the determination is related more to the apparatus and the viscous response of the skin and less to the elastic component.

An illustration of the profile of the response recorded on skin using the Twistometer is given in Figure 5.3. The recording was conducted at two different rates to clearly image the dynamic section (176 ms) and the quasi-static section (5 s). The recording was obtained at "critical" damping, yielding a single oscillation or incipient oscillation for an amplitude of rotation,  $U_e = 10.32^\circ$ . The dynamic phase is even more clearly imaged in the torque-off section since the resisting forces are weak. In the case of the skin, which is not a pure elastic material, the viscous deformation takes over and is added to the elastic deformation, as can be observed in the curve in Figure 5.3.

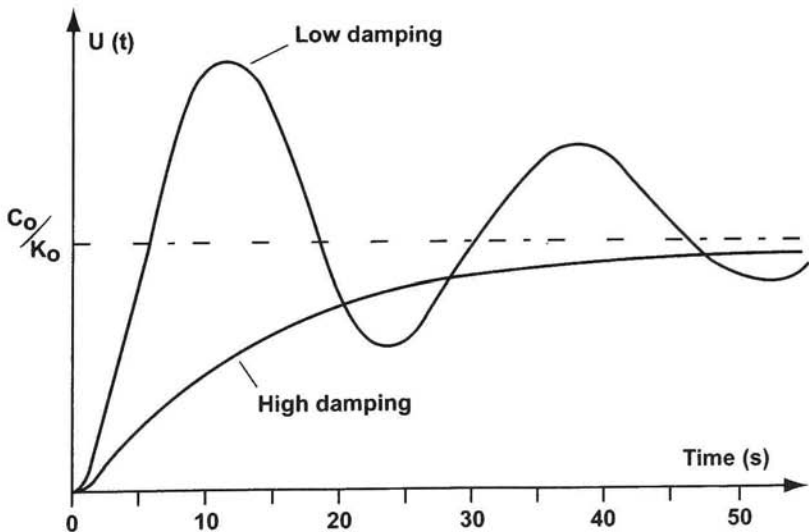


FIGURE 5.2 Response profile for a harmonic oscillator with a force scale.

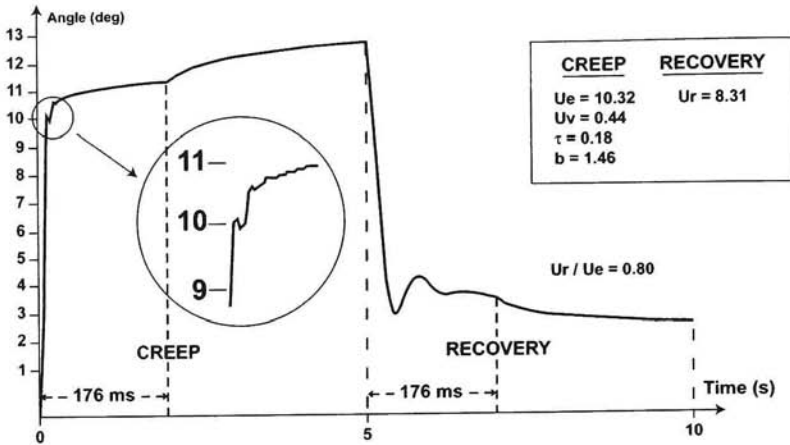


FIGURE 5.3 Skin response profile recorded using the Twistometer (critical damping mode) and parameters calculated using the rheological model of Equation 5.3.

## INTERPRETING THE RESULTS

### THE VARIOUS RHEOLOGICAL MODELS

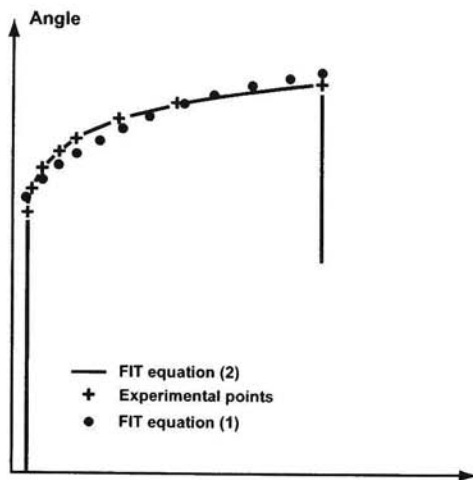
Numerous analytical methods for the response of skin subjected to stress have been proposed. Their aim is to extract the extrinsic parameters that characterize the behavior of the tissue under study, based on the simplest rheological model possible, but a model that describes all the properties of the skin. The oldest rheological model consists in the following equation:

$$U(t) = U_e + U_v(1 - \exp(-t/\tau)) \quad (5.1)$$

The correspondences between the main parameters and their physical significance are outlined in Figure 5.5b below.

This model, consisting of an immediate elastic response,  $U_e$ , and a delayed viscoelastic deformation, is not totally satisfactory. Comparison of the curves generated experimentally with the mathematical fit (Equation 5.1) shows that a bias is present and the deviations between the two curves are not randomly distributed. The model systematically overevaluates the values at the start and end of deformation and underevaluates those in the middle (Figure 5.4). The bias is more marked the greater the OG and/or the torque.

Another equation, proposed by Pichon et al.,<sup>17</sup> and based on Burger's rheological model with a non-Newtonian damper in series and hence corresponding to Equation 5.2, yields a markedly superior fit between the experimental response and the rheological model. Pichon et al.<sup>17</sup> studied the response curve of the skin using the finite-element method proposed by de Lacombe in 1939.<sup>18</sup> The method has the advantage of independence of immediate extensibility. Pichon et al.<sup>17</sup> have shown that the value of  $1/3$ , commonly known as Andrade's constant,<sup>19</sup> applies equally



**FIGURE 5.4** Comparison of the rheological models for Equations 5.1 and 5.2 with the experimental curve.

well to determinations of the mechanical properties of the dermis (OG = 3 or 5 mm) and epidermis (OG = 1 mm) and that the value is a mean valid for all subjects.

$$U(t) = U_e + U_v(1 - \exp(-t/\tau)) + bt^{1/3} \quad (5.2)$$

The term  $U_e$  is the elastic response, the term  $U_v$  is the fast or transient creep, and the term  $bt^{1/3}$  is the stationary creep (Figure 5.5c).

A diagrammatic representation of Burger's model and the fit between the model and the calculated parameters are given in Figure 5.6.

Another value for the time dependence of the stationary creep term has been proposed by Sanders,<sup>7</sup> Wjin,<sup>8</sup> and Finlay,<sup>9</sup> who all assigned it the value of 1. This becomes a Newtonian Burger model:

$$U(t) = U_e + U_v(1 - \exp(-t/\tau)) + bt \quad (5.3)$$

The model can be enhanced by adding Voight's component to the Burger model.

Much more recently, another model was proposed by Salter et al.,<sup>20</sup> based on Weibull's theory. The equation is as follows:

$$U(t) = A(1 - \exp(Ct)^n) \quad (5.4)$$

In this equation, it is much more difficult to provide a physical interpretation for parameters A, C, and  $n$ . Wickett and Murray<sup>21</sup> have shown that the equation does not generate any additional information and is not totally satisfactory.

The publication presenting the model<sup>20</sup> based on Weibull's theory shows that it is impossible to image and measure the component of elastic deformation denoted  $U_e$ . The impossibility is due only to the markedly damped response of the mobile

component (see Figure 5.2). Thus, the model is only applicable under those conditions and will not fit a system with little damping and with oscillations.

Fundamentally, the rheological models, as presented above (Equations 5.1 through 5.3), cannot take into account the dynamic part of the response and only apply to static or quasi-static deformations. The analysis of the dynamic response, skin plus mobile equipment, necessitates modeling the differential equation indicated above and separating the specific contributions of the apparatus and the skin. Currently, no one has advanced in that direction.

## THE DATA PROCESSING MODES USED BY THE DTM

Two processing modes are available on the DTM:

1. The basic model tool
2. The Pexp curve fit tool

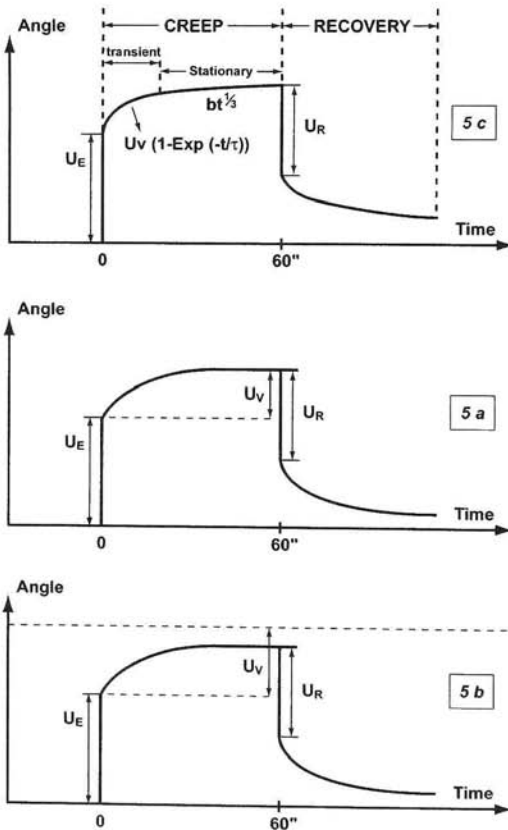


FIGURE 5.5 The various parameters and their physical significance for each of the rheological models covered.

Those data processing modes can be run online or subsequently. The program processes the torque-on and torque-off phases separately.

**The Basic Model Tool**

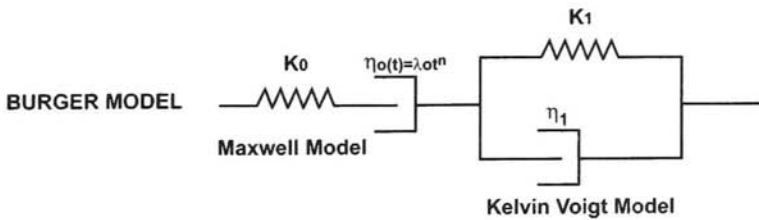
The determination of parameters  $U_e$ ,  $U_v$ ,  $U_r$ , and  $U_r/U_e$  is conducted directly on the curve recorded 50 ms after application or discontinuation of the torque (Figure 5.5a). Normally the measurement times have been defined to minimize the influence of the dynamic response.

**The PEXP Curve-Fit Tool**

The DTM uses the Equation 5.3 model (linear dependence over time for stationary creep). To ensure the condition for static or quasi-static deformation, processing does not take into account the first 100 ms in the torque-on or torque-off phases. It is clear that, in the example given in Figure 5.3, in the torque-off phase, the dynamic phase is not complete and the  $U_r$  determination will be subject to error.

**PRECAUTIONS AND REMARKS**

It is important to note that the parameters determined, while they bear the same name, do not all have the same significance. In fact, the basic model parameters,  $U_e$  and  $U_r$ , may include some viscosity (Figure 5.5a). Parameters  $U_v$  and  $U_f$  are deformation amplitude parameters determined for a given time period and are only meaningful if the duration of torque application is specified. As is the case with all mechanical properties, the results of the determinations depend on the geometric



**MATHEMATICAL MODEL**

$$U(t) = U_o + a \exp(-t/\tau) + b t^{1/3}$$

**RHEOLOGICAL MODEL**

$$\epsilon(t) = \frac{\sigma}{K_o} + \frac{\sigma}{K_1} \left[ 1 - e^{-\frac{tK_1}{\eta_1}} \right] + \frac{\sigma}{\lambda_o(n+1)} t^{n+1}$$

**RHEOLOGICAL PARAMETERS**

$$K_o = \frac{C}{(U_o - a)} = \frac{C}{U_e} \quad K_1 = \frac{C}{a}$$

$$\eta_o = \frac{\lambda_o}{3} = \frac{C}{b} \quad \eta_1 = \tau K_1 = \tau \cdot \frac{C}{a}$$

**FIGURE 5.6** Burger’s model and the rheological parameters calculated from the mathematical model, fitting the response curve

characteristics of the test assay, in this case the thickness of the skin and the width of the OG. It is tempting to calculate the ratios between the various magnitudes determined to obtain independent parameters for the thickness and/or without dimensions. That is the case, for example, with  $U_f/U_e$  (elasticity).

In contrast, the parameters  $U_v/U_e$ ,  $U_f/U_e$ , and  $U_f/U_v$  are not dimensionless magnitudes and depend on time and the duration of torque application, if generated using the basic model. Using those parameters, it is possible to calculate the intrinsic magnitudes, taking into account the thickness of the skin. The latter should be measured in all long-duration tests in which a variation in tissue thickness may be suspected and in all tests in which differences in thickness exist (solar effect, age, disease, etc.). The formulas enabling calculation of those intrinsic magnitudes (modulus of elasticity or Young's modulus and shear modulus) are obtained by considering the material to be isotropic (but that is an approximation).

For example, for elastic parameters and in the case of torque determination, the formula for the shear modulus is given by

$$G = (1/r^2 - 1/R^2) (C \sin \theta) / 4\pi e$$

where  $e$  is the thickness of the tissue,  $C$  the torque applied,  $\theta$  the angle of rotation, and  $r$  and  $R$  the internal and external radii of the crown of skin.

Other parameters concerning the viscous phase may be calculated.<sup>22</sup>

In the measurement probe, mechanical friction is inevitable. For the torque-on phase, friction normally remains negligible in view of the imposed torque. That does not apply, however, in the torque-off phase, at the end of which the equilibrium between the recoil force of the skin and mechanical friction restricts the return to the initial position. During the torque-off phase the values of the residual deformation and the viscous deformation phase are thus to be considered with caution.

## STANDARD PRECAUTIONS

The stress applied to the skin is transmitted to it through the two-sided adhesive tape used; thus, the tape must be capable of transmitting the torque. It is further necessary to ensure that the adhesive forces are sufficient and that, in the case of cosmetic or other formulation efficacy tests, the presence of product traces does not interfere with or influence the measurement.

## INFLUENCE OF PROBE POSITION

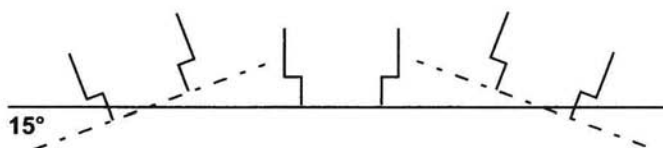
As in all determinations, the probe must not interfere with the measurements. The probe should be applied to the measurement zone with the weakest pressure possible, thus allowing the skin to retain its natural plane. The influence of pressure (Table 5.1) and an angle of inclination relative to the skin of the forearm are great (Figure 5.7). The effects induced on the measurement results by positioning errors are more marked, the greater the OG. An almost complete block may occur with a 1-mm OG.

The position of the measurement zone on the body must be clearly specified. Numerous property gradients exist in the forearm with the forearm (Figure 5.8). The

same applies to the top and bottom of the back. Concerning determinations on the forearm of athletic subjects, a laterality effect exists (Figure 5.8). The skin is normally subject to natural tensions. Muscle contraction induces variations (Figure 5.9), which, as above, are a function of the OG.

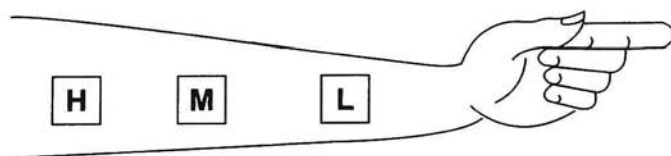
**TABLE 5.1**  
**Influence of Probe Application Pressure**  
**on the Skin during Determination**  
**(relative to the no-pressure value)**

Applied Pressure, g/cm <sup>2</sup>	Operating Gap	
	5-mm	1-mm
0	1	1
50	0.81	0.96
150	0.77	0.80
500	0.70	0.40



<b>O.G.: 5 mm</b>	<b>1.07</b>	<b>1</b>	<b>1.45</b>
<b>O.G.: 1 mm</b>	<b>0.96</b>	<b>1</b>	<b>1.07</b>

**FIGURE 5.7** Influence of measurement probe angle of inclination (expressed relative to the normal value).



	<b>H</b>	<b>M</b>	<b>L</b>
<b>Left</b>	<b>175 ± 15</b>	<b>156 ± 7</b>	<b>109 ± 11</b>
<b>Right</b>	<b>151 ± 15</b>	<b>135 ± 15</b>	<b>120 ± 15</b>

**FIGURE 5.8** Influence of forearm measurement zone and laterality effect (OG = 3 mm, mean ± SEM, nine models).

### INFLUENCE OF PRECONDITIONING OR SERIAL STRESSES

The statement that the skin should be prestressed before recording and measuring the mechanical characteristics is sometimes encountered. Some call the procedure normalization. If the torque is applied serially several times, the profile of the curves recorded complies with that in Figure 5.10. This type of test is conducted in mechanics, when it is used as a fatigue test designed to determine the ability of a material to withstand serial stresses. Under those conditions, parameter  $U_e$  is no longer the immediate extensibility but includes an increasing viscosity component. It will be observed, using, for example, the model of Equation 5.2, that the sum,  $U_e + U_v$ , remains constant, but the  $U_e$  value increases at the expense of the  $U_v$  value.

A study (Table 5.2) was conducted on two groups of 12 models (mean age: 30 and 50 years, respectively). Torque duration was 10 s and each torque was separated from the next by 1 min, without removing the probe from the skin ( $OG = 3$  mm). The rheological model used was that of Equation 5.3. It is clear that repeated stresses impair the mechanical properties, with the decrease in elasticity particularly marked at high torque values. The mechanisms for transfer of viscosity toward extensibility are different for low and high torque and are also a function of skin condition.

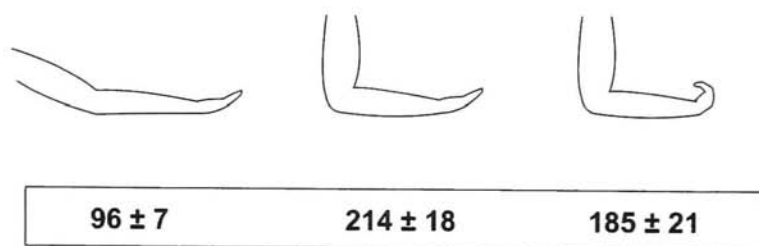


FIGURE 5.9 Influence of forearm position: relaxed extended arm, arm bent  $90^\circ$  and relaxed, arms and hands bent and muscles contracted ( $OG = 3$  mm, mean  $\pm$  SEM, nine models).

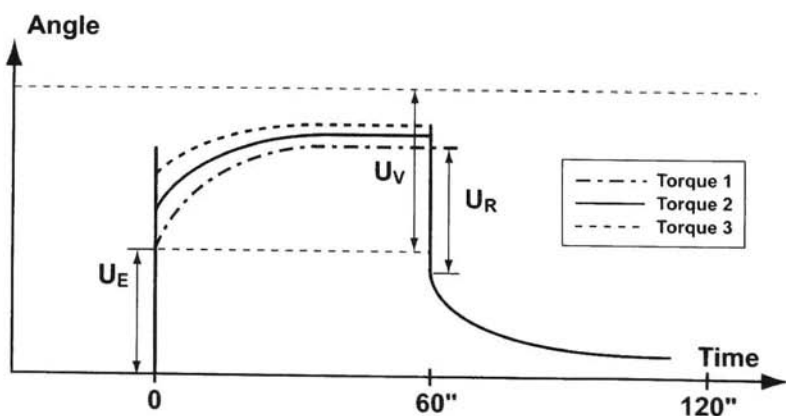


FIGURE 5.10 Diagrammatic representation of the influence of serial application of torque.



**TABLE 5.2**  
**Influence of Three Serial Applications of Torque**  
**(relative to the initial value, mean  $\pm$  SEM)**

Applied Torque	Parameter	"Young Population"		"Old Population"	
		Torque 2 / Torque 1	Torque 3 / Torque 1	Torque 2 / Torque 1	Torque 3 / Torque 1
Low torque, 60 cm·cN	$U_e$	1.11 $\pm$ 0.01	1.15 $\pm$ 0.02	1.12 $\pm$ 0.02	1.15 $\pm$ 0.03
	$U_v$	0.95 $\pm$ 0.05	0.57 $\pm$ 0.07	0.64 $\pm$ 0.2	0.43 $\pm$ 0.12
	$b$	0.82 $\pm$ 0.10	0.75 $\pm$ 0.05	0.86 $\pm$ 0.05	0.82 $\pm$ 0.09
	$U_v/U_e$	0.98 $\pm$ 0.01	0.97 $\pm$ 0.02	0.96 $\pm$ 0.02	0.93 $\pm$ 0.03
High torque, 90 cm·cN	$U_e$	1.17 $\pm$ 0.01	1.24 $\pm$ 0.01	1.16 $\pm$ 0.03	1.21 $\pm$ 0.03
	$U_v$	0.71 $\pm$ 0.04	0.75 $\pm$ 0.06	0.81 $\pm$ 0.07	0.75 $\pm$ 0.06
	$b$	0.81 $\pm$ 0.01	0.76 $\pm$ 0.02	0.79 $\pm$ 0.03	0.73 $\pm$ 0.03
	$U_v/U_e$	0.91 $\pm$ 0.01	0.87 $\pm$ 0.02	0.92 $\pm$ 0.01	0.90 $\pm$ 0.01

## CONCLUSIONS

Although the effect that incorrect handling may induce must be taken into account, use of the DTM or Twistometer is relatively simple. The reproducibility of the determinations is good and enables study of numerous phenomena, particularly in the cosmetic field. Caution is nonetheless required with respect to comparing the results derived by different methods, since a full understanding of the meaning of the parameters and the stress modes is necessary. Interpretation of the results is not always easy, and the researcher must exercise both caution and a precise understanding of the phenomena and techniques involved.

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# 6 *In Vivo* Tensile Tests on Human Skin: The Extensometers

*Paul Vescovo, D. Varchon, and Phillippe Humbert*

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## INTRODUCTION

Dermatologists conduct physical measurements on skin to diagnose and to follow the development of pathologies. They also need, as do cosmetologists, to measure the efficacy of the treatments they apply to skin. The measurement of skin mechanical properties can offer a wealth of information to this field but, at the present time, studies are too often carried out in a qualitative way, which leads to relatively subjective assessments. It is essential to quantify precisely the evolution of at least one mechanical parameter of skin representative of its state. When studies are

conducted in hospitals or in research laboratories, the means used can be sophisticated, whereas the methods must be rather simple when they are intended to be used by practitioners in their offices.

## MECHANICAL PROPERTIES MEASUREMENTS

The mechanical behavior of a material is defined by rheological equations linking loadings, deformations, and such external or internal parameters as temperature, hygrometry, material constituents, etc. In the simplest case the behavior is considered linear elastic. In many applications and to simplify the equations, it is possible to assume that the state of stress is plane; then the behavior can be modeled as follows:

$$\begin{pmatrix} \sigma_1 \\ \sigma_2 \\ \sigma_6 \end{pmatrix} = \begin{bmatrix} C_{11} & C_{12} & 0 \\ C_{12} & C_{22} & 0 \\ 0 & 0 & C_{66} \end{bmatrix} \begin{pmatrix} e_1 \\ e_2 \\ e_6 \end{pmatrix} \quad \text{or} \quad \begin{pmatrix} e_1 \\ e_2 \\ e_6 \end{pmatrix} = \begin{bmatrix} S_{11} & S_{12} & 0 \\ S_{21} & S_{22} & 0 \\ 0 & 0 & S_{66} \end{bmatrix} \begin{pmatrix} \sigma_1 \\ \sigma_2 \\ \sigma_6 \end{pmatrix} \quad (6.1)$$

Terms of rigidity  $C_{ij}$  and suppleness  $S_{ij}$  are often written according to elastic constants that characterize material in an elastic range. An isotropic material is completely defined by two constants called Young's modulus  $E$  and Poisson's ratio  $\nu$ , with

$$S_{11} = S_{22} = \frac{1}{E}; \quad S_{12} = S_{21} = -\frac{\nu}{E}; \quad S_{66} = \frac{1}{G}; \quad G = \frac{E}{2(1+\nu)} \quad (6.2)$$

In the case of an anisotropic material, the number of independent constants is higher, nine for an orthotropic material.<sup>1</sup> Experimental determination of the constants requires that the number of independent experiences equal the number of parameters to be determined. When the behavior is more complex (viscous, for example), the types of tests are identical but the loadings to implement are different (creep experiment, stress relaxation, etc.). Human skin is a material that can be considered isotropic or transverse isotropic. In its plane, two Young's moduli  $E_1, E_2$ , one Poisson's ratio  $\nu_{12}$ , and one shear modulus  $G_{12}$  can be calculated.

## IN VITRO AND IN VIVO TESTS

Skin studied by *in vitro* tests comes from cadaver or plastic surgery; the number of experiments, the variety of skins which can be tested, and the variety of their original localizations on the body are thus very limited. In contrast, with *in vivo* experiments it is easy to conduct a great number of tests on various kinds of skin anywhere on the body. From a mechanical point of view, experimental conditions are better during *in vitro* tests than during *in vivo*. Because of the specimens used, it is possible to have homogeneous stress fields on large surfaces, which allow accurate measurements of mechanical properties. However, human skin does not lend itself at all well to these kinds of experiences because it is very difficult to obtain samples of good

quality. Indeed, skin used for experiment comes from cadavers or plastic surgery. In the first case, the mechanical behavior of the skin may have been modified by time; in the second, the skin is often greatly damaged by stretch marks and may exhibit behavior close to that of pathological skin. Several research teams have focused on that subject; Schneider et al.<sup>2</sup> even carried out biaxial tensile tests with a good instrumentation. Vescovo et al.<sup>3</sup> brought to the fore the difficulties involved in obtaining specimens that would allow proper measurements and interpretation of results, because the initial conditions of the skin specimens are different from those of skin *in vivo*. The main problems with *in vivo* tests are the poor experimental conditions, which make analysis very complex. Despite their disadvantages, *in vivo* tests can certainly bring a better understanding of skin mechanical behavior than *in vitro* experiments can provide.

Several kinds of apparatus have been designed in the past; few have been marketed. One of the most-developed devices is the Cutometer. It is a suction apparatus marketed by Courage and Khazaka (Cologne, Germany); results are analyzed by a developed software. However, it is unfortunate that results are not provided via intrinsic parameters like Young's modulus by means of a simple modeling as are those proposed by Vescovo et al.<sup>4</sup> or Diridolou et al.<sup>5</sup> Another interesting apparatus is the Twistometer, which has not been as important as the Cutometer. However, it is quite easy to measure the coulomb modulus in the skin plane with the Twistometer. These two devices have the same disadvantage: they cannot provide information about the anisotropy of skin. Therefore, it is necessary to use another type of apparatus to measure this important feature of skin.

## MEASUREMENT OF MECHANICAL PROPERTIES OF SKIN WITH AN EXTENSOMETER

The principle of the test is simple: either two pads fixed on skin are moved with respect to each other and forces applied on them are measured, or the forces are applied on pads and the displacements between them are measured. The test seems easy, but reduction of the results is rather complicated. Indeed, the specimen boundary conditions are not well defined and the test is not a pure uniaxial tensile test. However, it is a directional test, which allows measurements in the plane of skin and thus a quantification of anisotropy. This feature makes the extensometer very different from the other devices, and is the reason this process is especially interesting and is analyzed more thoroughly later in this chapter.

### EXTENSOMETERS: EXAMPLES

Extensometers are not used commonly at the present time; however, several research teams have taken an interest in this technique in the past. The technologies used did not allow a large enough optimization of the apparatus and the process was partially abandoned. A few examples of devices that seem to be more representative and accomplished are presented here.

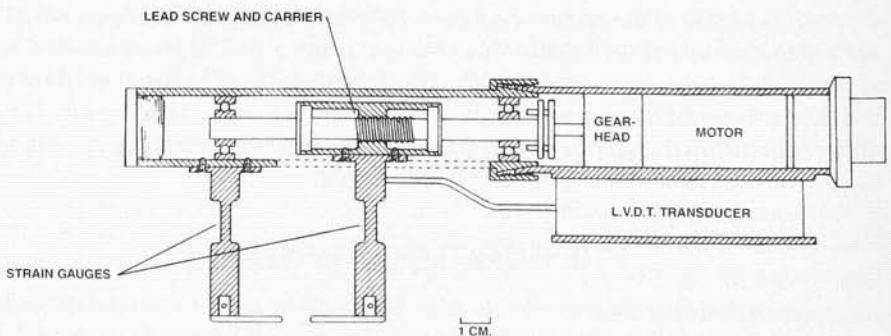
### THE PORTABLE HAND-HELD EXTENSOMETER

The extensometer was built by Gunner et al.<sup>6</sup> in 1978; it is a development of a device reported previously.<sup>7</sup> It can apply a uniform extension rate to skin *in vivo*. Its functioning principle is relatively simple (Figure 6.1). Two arms, one fixed, the other movable by means of a motor-driven lead screw, have at their ends rectangular pads that are stuck to the skin surface by means of double-sided adhesive tape. Strain gauges attached at the reduced section on each arm and a linear variable differential transformer sensor (LVDT) measure the forces applied to the pads and their displacements. The force–displacement curve can be worked out easily.

The main advantage of that apparatus is its simplicity, which makes it very easy to use; its disadvantages are its size, weight, and significant dissymmetry, which can disrupt the results because of interference forces. The main features of this apparatus are listed in Table 6.1.

The device can conduct tests with loadings at an imposed extension rate with subsequent relaxation. To analyze the recovery appearing after the end of the loading the same authors propose a device that can measure the return of skin to its initial state.<sup>8</sup> This apparatus consists of two pads; one is fixed to the device body, the other is free on a slide rail and has an LVDT sensor attached on it to measure the displacement (Figure 6.2). It can be used alone; the displacement of the mobile pad is then applied manually or with the extensometer described previously. It is then possible to record loading, relaxation, and recovery (Figure 6.3). The simplicity of this apparatus, its light weight (50 g), and the fact that it can be used without being held by the experimenter or placed on a stand are its main advantages. Friction is certainly a disadvantage for its proper functioning.

These two apparatuses allowed their designers to conduct many tests on various zones of the human body. Their experiences allowed the designers, for example, to propose a rheological model identified on normal and pathological skin and to measure the effect of treatments on the mechanical behavior of human skin.



**FIGURE 6.1** Schematic diagram of the extensometer designed by Gunner et al.<sup>6</sup> (From Gunner, C.W. et al., *Br. J. Dermatol.*, 100, 161, 1979. With permission of Blackwell Science.)

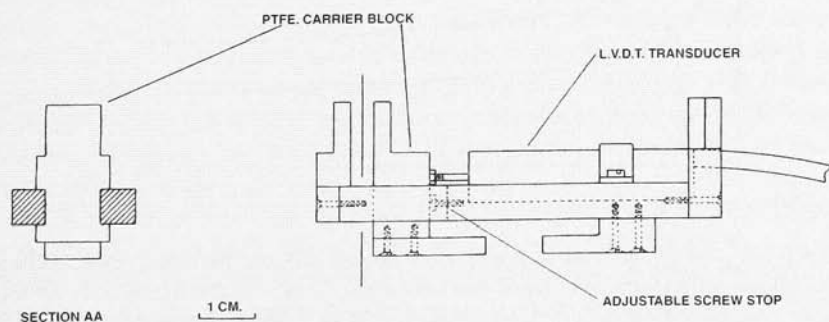
## MAGNETIC EXTENSOMETER

This apparatus was described in 1979 by Wijn et al.<sup>9</sup> and was used in 1986 by Manschot et al.<sup>10</sup> Two pads are stuck to the skin surface by means of double-sided adhesive tape or cyanoacrylate adhesive; the force producing the displacement of the movable pad is obtained with a magnet situated inside a coil. The force applied is then proportional to the electric current, and the displacement is measured with an LVDT-type transducer (Figure 6.4).

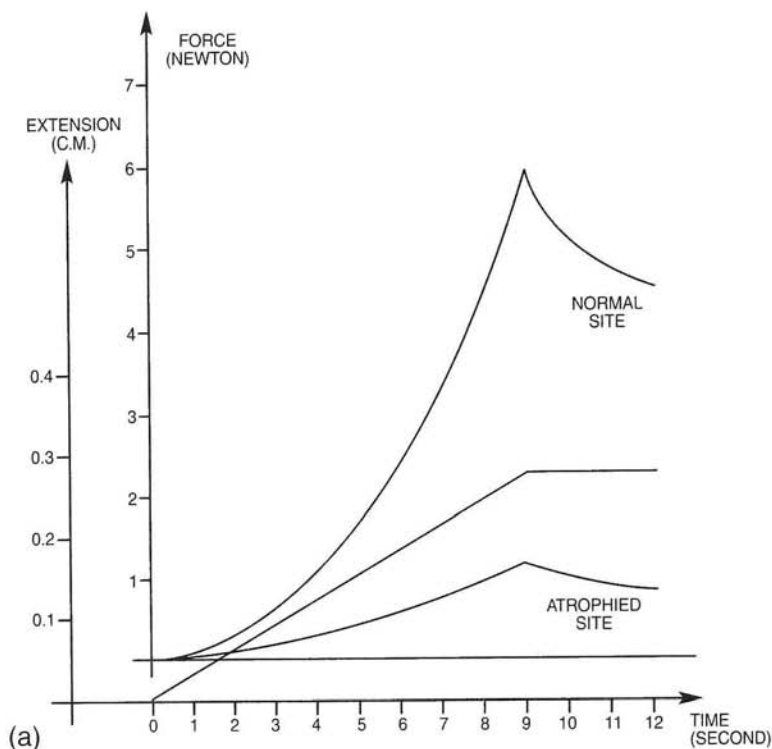
The principal advantage of the device is its operating mode, which allows creep tests to be conducted because it works by imposing force. Its disadvantages are due to its large weight, which requires fixing the apparatus on a table. Thus, it is not possible to carry out tests on all locations on the body. Tests are mostly performed on arms and legs. Friction may disrupt the measurements.

**TABLE 6.1**  
**Features of the Various Presented Extensometers**

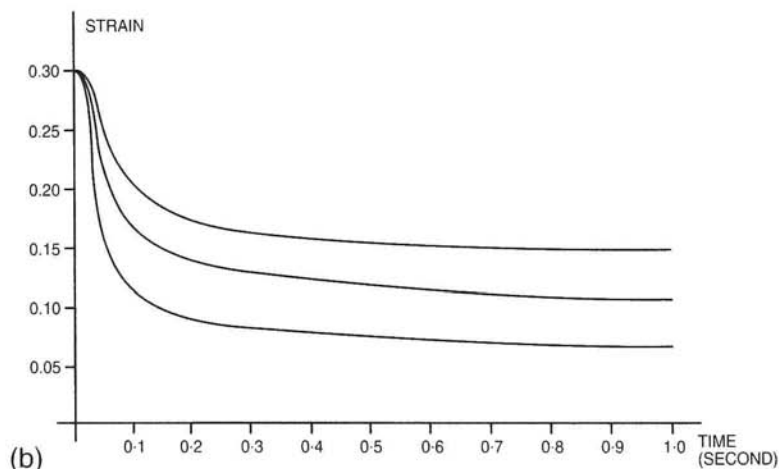
Study (extensometer's name)	Gunner et al., <sup>6</sup> 1979	Gunner et al., <sup>8</sup> 1979 (Recoil apparatus)	Manschot et al., <sup>10</sup> 1986	Baker et al., <sup>11</sup> 1988	Vescovo, <sup>13</sup> 1998 (Cutech)
Pads anchorage on skin	Double-sided adhesive tape	Double-sided adhesive tape	Cyanoacrylate	Double-sided adhesive tape	Double-sided adhesive tape
Portable	Yes	Yes	No	Yes	Yes
Initial tab distance (mm)	10	10	3–20	4	6
Tab size (length × width) (mm)	25 × ?	?	10 × 10	10 × 20	17.8 × 10
Maximum strain (%)	40	30	Up to 50	50	40
Maximum force (N)	6	10	12	5	3
Loading	Uniform extension rate (0.35 mm/s)	Manually or with the extensometer used by Gunner et al. <sup>6</sup> in 1979	Sawtooth-shaped force loading	Uniform extension rate (0.05 or 0.33 mm/s)	Uniform extension rate (0.1 or 0.33 mm/s)



**FIGURE 6.2** Schematic drawing of the *in vivo* recoil apparatus designed by Gunner et al.<sup>8</sup> (From Gunner, C.W. et al., *Med. Biol. Eng. Comput.*, 17, 142, 1979. With permission of IEE Publishing.)



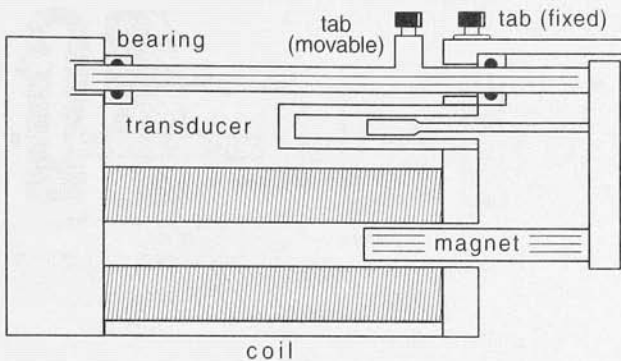
(a)



(b)

**FIGURE 6.3** (a) Comparison of extensometer outputs obtained from skin severely affected by steroid atrophy and adjacent normal skin near axilla. Tests were carried out with the extensometer designed by Gunner et al.<sup>6</sup> (From Gunner, C.W. et al., *Br. J. Dermatol.*, 100, 161, 1979. With permission of Blackwell Science.) (b) Recoil characteristics obtained from adjacent sites on the forearm of a normal subject with the recoil apparatus designed by Gunner et al.<sup>8</sup> (From Gunner, C.W. et al., *Med. Biol. Eng. Comput.*, 17, 142, 1979. With permission of IEE Publishing.)





**FIGURE 6.4** Schematic drawing of the uniaxial strain apparatus.<sup>10</sup> (From Manschot, J.F.M. and Brakkee, A.J.M., *J. Biomech.*, 19, 511, 1986. With permission of Elsevier Science.)

### EXTENSOMETER OF BAKER, BADER, AND HOPEWELL

This apparatus was built and used in 1988 by Baker et al.<sup>11</sup> Here, again, there is a screw and bolt system with an LVDT sensor. But force measurement is performed differently by means of a load cell placed between the movable pad and the apparatus body (Figure 6.5). This device has been used to carry out stiffness measurements in parallel with A scan ultrasonic tests to study irradiated pig skin. It is heavy and has not been optimized.

### THE CUTECH EXTENSOMETER

Two 10 × 18 mm pads are adhered to skin 6 or 9 mm apart. The pads are moved closer together (tension test) or farther apart (compression test) at a constant but adjustable speed (from 3 to 10 mm/s). The arms supporting the pads have gauges attached to them that make it possible to measure the applied load (4 N max.) (Figures 6.6 and 6.7). The apparatus can be used with or without a support plate, which is a plate with a rectangular hole in it through which the pads are adhered to skin surface. This support plate is fixed to the device body and is also adhered to skin by means of double-sided adhesive tape. When the support plate is used, skin around the investigated zone is fixed to the apparatus. The apparatus can carry out loading followed by creep and recovery; with analog recording. This device was marketed by Cotech and the Stiefel Laboratories about 10 years ago, but is no longer available. Its design is similar to that of the Gunner et al. apparatus, but with improved performance.

This apparatus was used by Asserin<sup>12</sup> to investigate the anisotropic properties of human skin. His study was carried out *in vivo* on arms, by means of a finite-element model whose meshing used the natural patterns of skin. He was able to prove that an isotropic model does not properly represent the elastic behavior of skin. Analysis of deformations in every direction allows optimization of skin mechanical constants when modeled as an isotropic material. Vescovo<sup>13</sup> completely validated this extensometer through tests carried out on materials whose mechanical

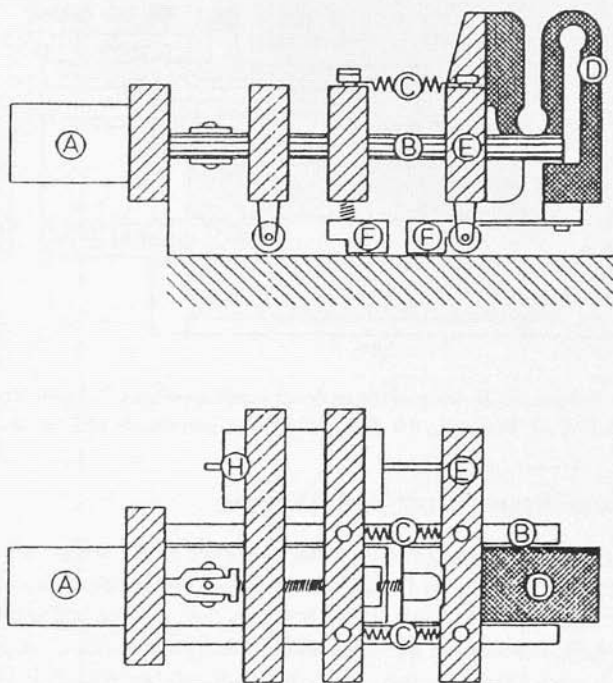


FIGURE 6.5 Diagrammatic representation of the transducer in plane and side view.<sup>11</sup> (From Baker, M.R. et al., *Bioeng. Skin*, 4, 87, 1988. With permission of Kluwer Academic Publishers.)

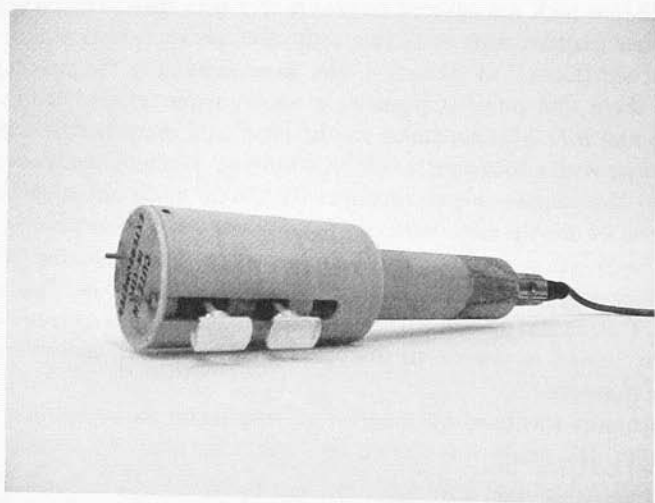


FIGURE 6.6 View of the Cutech extensometer.

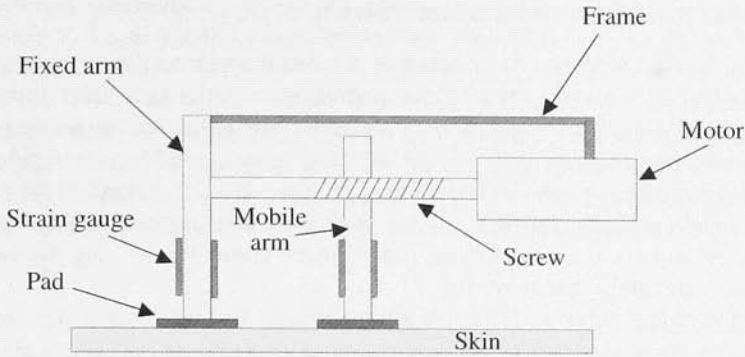


FIGURE 6.7 Schematic diagram of the Cutch extensometer.

behaviors are simpler and easier to work out by means of standard tensile tests. He showed the performance limits of this apparatus and highlighted operating instructions leading to quality results.

The main features of the extensometers presented here are summarized in Table 6.1. The devices and the research conducted with them are similar because designers used the same-generation technologies.

## USE OF AN EXTENSOMETER

In the case of physical measurements, environmental influences cannot be completely suppressed. No matter the apparatus, the material, or the experimenter, environmental influences always disrupt the measurements. The best device is the one yielding results closest to reality, while being accessible to all practitioners. Whatever their differences, the devices presented here all have a very important mission. The main problems can be overcome or, at least, they can be taken into account in the results analysis.

### BOND WITH SKIN

Measurements are correct only if the pad displacements represent those of the skin. This is valid for every type of device (including the Cutometer, Twistometer, and so forth) and is possible only if the pads are properly anchored on skin. Because tests are carried out *in vivo*, invasive techniques are not acceptable and most of the time double-sided adhesive tape is simply used. However, this process is not completely satisfactory if the forces applied are large. Especially during creep tests, the measured displacements are incorrect because of adhesive coat creep. So it is necessary to check the bonding quality before carrying out experiments. Other techniques are being studied at the present time but the results are not yet final; however, a rapid improvement in this fundamental issue can be anticipated.

## MOVEMENTS AND INTERFERENCE VIBRATIONS

Except for the device designed by Gunner et al.<sup>8</sup> (recoil apparatus), the extensometers presented here have to be held by the experimenter or fixed to a stand during the tests. When the device is held during the tests, low-amplitude movements and vibrations are created between the device and the skin area tested, which significantly disrupt the force measurements. When the apparatus is fixed to a stand, if the patient is put in a good position (which is in practice difficult to achieve; indeed, it requires a system suitable for every body type), interference vibrations are very low but the body areas that can be tested are few.

The future lies either in sufficiently miniaturized and lightweight devices that do not have to be held or in devices fixed to a stand via a mechanical system allowing tests to be carried out on a very large number of body zones.

## TYPES OF TEST CONDUCTED AND PRECISION OF RESULTS

Apparatus designed in the past allowed either loading with imposed forces or displacements, but no one device could do both. Moreover, for most extensometers, loading is not programmable (except, for example, the device used by Manschot et al.<sup>10</sup>), which significantly restricts the number of feasible tests (for example, the device used by Baker et al.<sup>11</sup> can have constant extension rates of only 0.05 or 0.33 mm/s). Conducting combined tests, such as creep and relaxation tests, is of great interest to identify the parameters of skin rheological equations. With the aid of current technological means it seems possible to design high-performance devices allowing every type of loading.

User aims are of two types:

1. Conducting simple tests that allow a qualitative assessment of skin mechanical behavior during pathology or medical or cosmological treatment. If experimental conditions are always identical, result comparison is possible and sufficient.
2. Working out intrinsic mechanical constants essential to identify models which can greatly help to understand biological phenomena, forecast pathology evolution, or optimize surgery. It is then necessary to carry out tests with high precision on the loading applied and the measurements performed. Because of the viscoelastic behavior of skin, the apparatus must be able to perform tests with a closed-loop servo on force or displacement; only those having these advanced technologies are suitable.

## RHEOLOGICAL EQUATIONS

Because rheological equations are solved at the level of the representative volume element, it is necessary to know all stresses and deformations at work. These constants are tensorial-type constants; in the case of skin it is often possible, to simplify, to model the state of stress as a plane one. The equation between stresses

and deformations in the elastic range is then written as Equation 6.1. It is, of course, necessary to know the three stresses and the three deformations to calculate the elastic constants.

In the case of an *in vitro* tensile test, because of the experimental conditions, the state of stress is sufficiently homogeneous to have tensile stress alone in the investigated zone. It is possible to work out stresses and strains applied to a volume element from the forces and displacements applied to the specimen. Under these conditions, it is possible to work out the engineering constants directly.

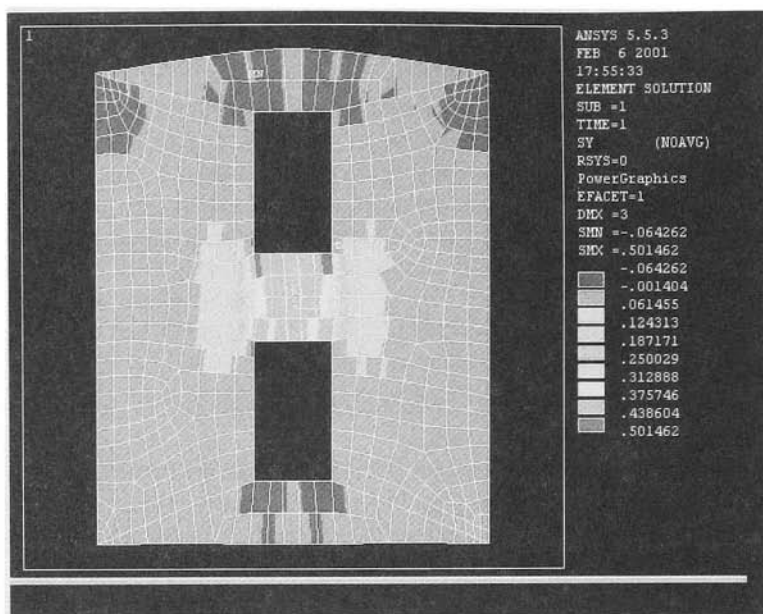
$$F = ES \frac{\Delta l}{l} \Rightarrow \sigma_1 = E\varepsilon_1 \quad (6.3)$$

where  $F$  = tensile force,  $E$  = Young's modulus,  $S$  = specimen section,  $\Delta l$  = elongation,  $l$  = initial length,  $\sigma$  = stress,  $\varepsilon$  = strain.

For a test carried out *in vivo* with an extensometer, the area of skin that is loaded depends on the test geometry and cannot be defined easily. The specimen is very different from that used in a standard tensile test, and movement of the pads creates a state of strain (stress) between them that stretches the whole skin area. The strain (stress) decreases when the distance from central zone increases and theoretically becomes zero to infinity. In practice, as was shown by Vescovo et al.,<sup>4</sup> the loaded zone can be modeled as finite, but even so it is not easy to work out the stress level from the force applied to the pads.

A skin sample was modeled with the software Ansys 5.5 (Figure 6.8). The skin was taken as a pure elastic material with a Young's modulus  $E$  of 1 MPa. In many studies, the authors consider that only the area of skin between pads is loaded, which means that they model the test as a standard tensile test (specimen width = pad width, specimen length = distance between pads). With this model there is only a longitudinal stress, which is constant in the specimen and is equal to 0.87 MPa. It can be seen with the finite-element modeling that the longitudinal stress is not constant and that its maximum level is about 0.5 MPa, which is far less than the value calculated previously with the simple model. Moreover, finite-element modeling shows that there are shear and cross stresses. With an optical method to measure the strain field and finite-element modeling, it is possible to work out mechanical constants correctly. Finite-element modeling of an *in vivo* extensometer test presents many problems that are due to the specific mechanical behavior of skin. For most standard materials, it is acceptable to consider that their elastic behavior is identical in tension and compression. This hypothesis is not true for skin. Indeed, when skin undergoes compression loading, it creases; its effective stiffness is very low. Skin has a mechanical behavior similar in a way to that of a tissue. Retel et al.<sup>14</sup> have taken that particular feature into account to model the state of stress around a scar with ablation. Few experimenters take into account the state of heterogeneous stress when calculating skin mechanical constants (Asserin<sup>12</sup>).

Rigorous study of the extensometer test shows that it can provide information about skin anisotropy, but it shows as well that its analysis is tricky.



**FIGURE 6.8** Finite-element modeling of a skin zone undergoing a test by extensometer. Each grayscale tone represents a longitudinal stress level.

### EFFECT OF HYPODERMA

During a test with an extensometer *in vivo*, not only skin is loaded but also hypodermis. The problem is to work out skin mechanical constants from a test carried out on a structure composed of two materials, skin and hypodermis, whose mechanical behaviors are unknown. The hypothesis posed most of the time to solve that problem is that hypodermis, during an extensometer test, is much less loaded than skin and that its stiffness is much lower than that of skin.

### USE OF A SUPPORT PLATE

A support plate can be used to define more precisely the skin area that is loaded. This process must be used with care because it can be a source of error. For some devices, the measurement of forces applied to the pads are calculated by means of gauges on the two arms. This technique is appropriate when the test is symmetrical (forces applied to the two pads are identical), which is not the case when only one arm moves and when a support plate is used. Another problem with a support plate that completely frames the tested area is that the compressed zone is situated behind the pads, which can alter the force calculation. To avoid that, the support plate can be open behind the pads.

## PROSPECTS

At the present time, extensometer tests are not commonly used. However, these authors think that the extensometer can offer practitioners precious information, especially on the anisotropic nature of human skin. To expand, this technique must improve by offering easier-to-use devices with higher performance. An up-to-date apparatus should meet the following requirements:

- It should be miniaturized (present microtechnologies should allow great improvements).
- It should carry out force or displacement servo-controlled tests.
- It should fit to an optical device that can analyze in real time the tested zone in order to get the strain field.
- It should fit to an ultrasonic device.
- It should be sufficiently simple and easy to use to allow common practitioners to conduct comparative tests.
- It should be a high-performance apparatus to allow researchers to study and analyze precisely skin mechanical behavior.

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# 7 Hardware and Measuring Principle: The Cutometer®

*Undine Berndt and Peter Elsner*

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## INTRODUCTION

The biomechanical properties of human skin are a complex combination of elastic and viscous components. Elasticity correlates with the function of elastin fibers; viscosity is controlled by the collagen fibers and the surrounding intercellular ground substance, which consists primarily of water and proteoglycans.

The Cutometer allows the measurement of the viscoelastic properties of the skin *in vivo*, which provides valuable information on physiological and pathological changes of human dermis as well as on the efficacy of topical treatments. It is recognized as a standard tool in dermatological and cosmetic research.

## MEASURING PRINCIPLE

The measuring principle of the Cutometer is based on suction. A defined negative air pressure is created and applied on the skin surface through the opening of a probe drawing the skin into its aperture. The resulting vertical deformation of the skin surface is measured by determining the depth of skin penetration into the probe. This is achieved by a noncontact optical system that consists of a light transmitter

and a light recipient. Two glass prisms project the light from transmitter to recipient, where the diminution of the infrared light beam depending on the penetration depth of the skin is measured (Figure 7.1).<sup>1</sup>

## MEASURING DEVICE

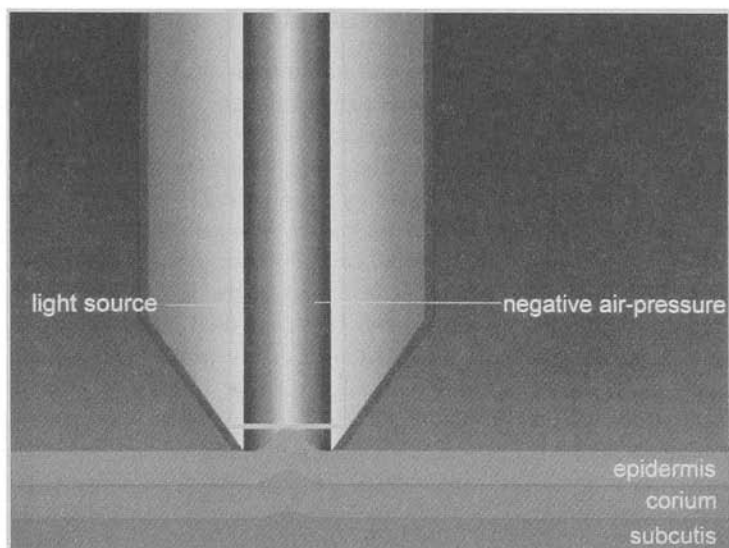
The Cutometer consists of a hand-held probe that is connected to the main unit through an air tube and an electric cable (Figure 7.2). The hand-held measuring probe is a  $3 \times 10$  cm cylinder with a weight of approximately 90 g. It contains the optical measuring system and the evaluation electronics. The suction head is centered in the probe shield. The diameter of its circular aperture measures 2 (standard), 4, 6, or 8 mm depending on the skin area and purpose of the examination. The probe is applied perpendicularly to the skin under constant pressure with an elastic spring.

The main unit contains a vacuum pump, a pressure sensor, and an electronic circuit controlling the pump and the analog/digital data conversion. The load of the vacuum can be regulated between 20 and 500 mbar, and the rate of pressure increase or decrease can be selected between 10 and 100 mbar/s. The suction interval (on-time) as well as the relaxation interval (off-time) can be varied between 0.1 and 60 s. Within one measurement cycle as many as 99 measurement repetitions are possible, each with a duration limited to a maximum of 320 s.

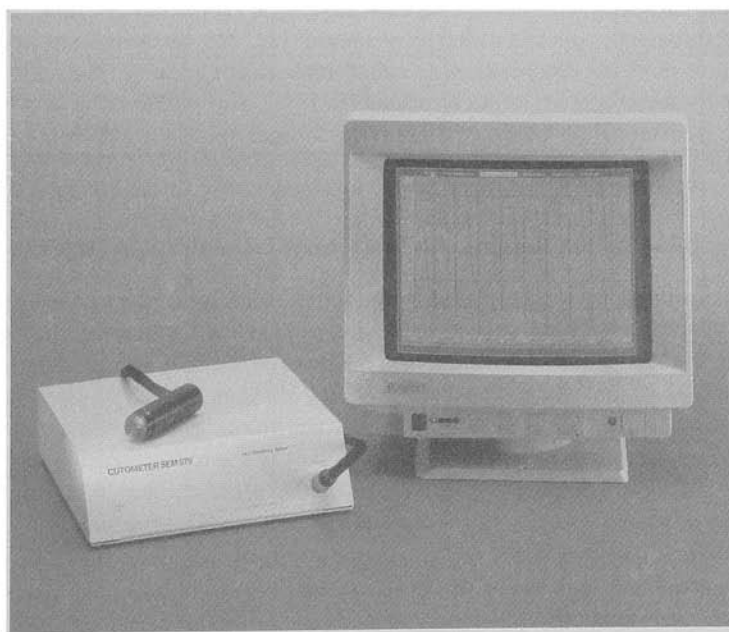
The Cutometer is designed for operation with an IBM-compatible personal computer (interface RS-232-C). The delivered standard software allows automatic calculation and storage of measuring results. In addition, data concerning the volunteer or patient, skin area, date and time of measurement, relative humidity, external temperature, and other information can be entered. All data are saved on an ASCII data file for external statistical evaluation. During the measurement process a corresponding curve is displayed showing the depth of the skin penetration into the probe and its retraction as the skin recovers during the relaxation period.<sup>1</sup>

## MEASURING MODES

Two measuring techniques are available, a stress-strain mode and a time-strain mode. In the stress-strain mode, the vacuum is increased over a selected period of time, and the deformation (in mm) is displayed as a function of negative pressure (in mbar). In the time-strain mode, which is mostly used to study viscoelastic properties of human skin, a selected vacuum is applied for a chosen time period. The skin deformation is shown as a function of time. The Cutometer offers four different measuring possibilities as the result of the choice of either immediate or slow linear increase and decrease of the applied vacuum. Applying mode 1 (-), the skin is drawn into the probe with constant negative pressure, which is immediately cut off after a certain time period. In mode 2 ( $\wedge$ ), deformation and retraction of the skin are achieved by a linearly increasing and decreasing vacuum. Mode 3 (-) begins with a constant abrupt strain of the skin followed by a slow decrease of pressure, and mode 4 (/) combines a linear increase of vacuum and a sudden total release of the skin.<sup>1</sup>



**FIGURE 7.1** Schematic view of the optical measuring system within the probe. (From Courage and Khazaka Electronic GmbH, Cologne, Germany. With permission.)



**FIGURE 7.2** Cutometer SEM 575. (From Courage and Khazaka Electronic GmbH, Cologne, Germany. With permission.)

## MEASURING RESULTS

Figure 7.3 shows a typical curve obtained in the time–strain mode (mode 1). The deformation curve is composed of rapid deformation representing a purely elastic section, followed by a viscoelastic section, and finally by a purely viscous section. The same elements can be differentiated in retraction of the tissue.<sup>2</sup>

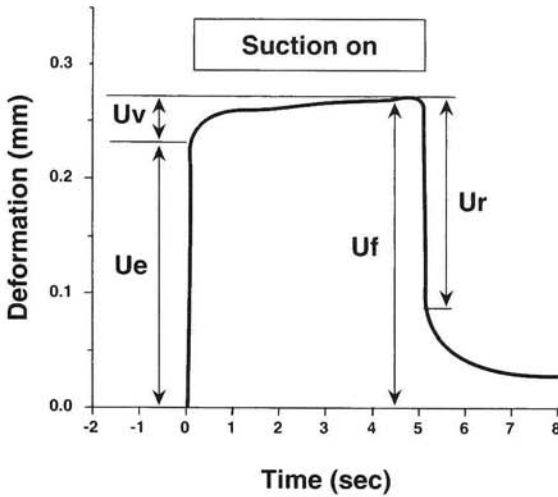
Following the nomenclature proposed by Agache et al.,<sup>3</sup> the deformation parameters used in most viscoelastic studies on human skin are  $U_e$ ,  $U_v$ ,  $U_f$ ,  $U_r$ , and  $U_a$ .  $U_e$  is defined as immediate deformation, or skin extensibility;  $U_v$  as the delayed distension reflecting the viscoelastic contribution of the skin;  $U_f$  as the final skin deformation; and  $U_r$  as the immediate and  $U_a$  as the final retraction after removal of the vacuum. The Cutometer program offers a cursor mode for the measurement of these parameters directly from the graphical display.

All these parameters are a function of skin thickness. Therefore, it is not meaningful to compare their absolute values between test sites or subjects. Instead, the experimental values should be standardized for skin thickness, which is preferably determined by ultrasound. If data on skin thickness are not available, ratios of the above parameters instead of the parameters themselves can be determined. Certain ratios of these parameters are biologically meaningful, do not depend on skin thickness, and can be compared between sites and subjects.  $U_v/U_e$  is the ratio between delayed and immediate deformation and indicates the relative contributions of the viscoelastic plus viscous and the elastic distension to the total deformation. The value of this ratio increases with decreasing elasticity.  $U_a/U_f$  is the ratio of total retraction to total deformation, which is called gross elasticity.  $U_r/U_f$ , as the ratio of immediate retraction to the total deformation, is called biological elasticity. The ratio  $U_r/U_e$ , proposed by Agache et al.,<sup>3</sup> closely resembles  $U_r/U_f$  and is also used as a measure of elastic recovery. High values of these ratios — maximum = 1 (100%) — indicate a high level of elasticity.

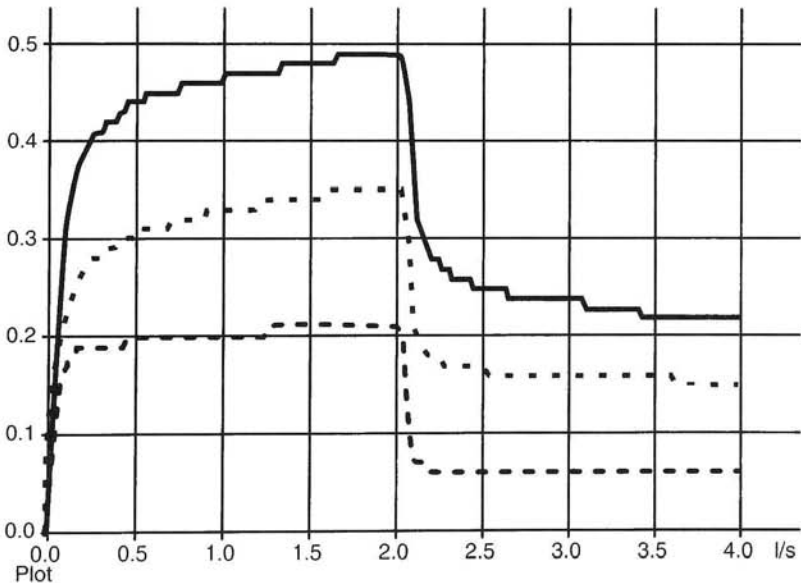
## DERMATOLOGICAL AND COSMETIC APPLICATIONS

Age and anatomical region are important factors influencing the viscoelasticity of human skin and have been studied extensively using the Cutometer. Biological as well as actinic aging is accompanied by a decrease of the biological elasticity of the skin indicated by the decreasing values of the  $U_r/U_f$  and  $U_r/U_e$  ratios.<sup>4-7</sup> On the other hand, an increase in  $U_v/U_e$ , the ratio between viscoelastic and elastic extension, indicates a greater contribution of the viscous part to the total extension with age.<sup>7,8</sup>

Reflecting the differences in structure of the papillary and reticular dermis, significant differences of the viscoelastic properties of skin of different anatomical regions were found in various studies. Comparison of the biomechanical qualities of vulvar and forearm skin, for example, showed that  $U_v/U_e$  and  $U_r/U_f$  were both significantly lower in vulvar than in forearm skin.<sup>5,6</sup> Differences of the viscoelasticity parameters of three different anatomical skin areas, i.e., eyelid, temple, and forearm, are graphically shown in Figure 7.4. However, significant sex-dependent biomechanical differences were not observed during the studies of physiological influences on skin elasticity.<sup>4,5,7</sup>



**FIGURE 7.3** Typical graphical registration of a strain–time curve obtained on vulvar skin. 2 mm probe, on-time 5 s, off-time 3 s, load 500 mbar. The parameters used to describe the deformation are as follows:  $U_e$  = instantaneous deviation length;  $U_v$  = viscoelastic and viscous deviation length (creep);  $U_f$  = final deviation length; and  $U_r$  = instantaneous recovery length.



**FIGURE 7.4** Three different curves of a 50-year-old person taken under the eye, at the temple, and on the forearm (from top to bottom). Time–strain mode 1 (- -); probe aperture = 2 mm, load = 500 mbar, on-time = 2 s, off-time = 2 s. (From Courage and Khazaka Electronic GmbH, Cologne, Germany. With permission.)

In addition to the influence of physiological factors on the viscoelasticity of human skin, pathological changes underlying various dermatological diseases have been studied in recent years. Thus, the Cutometer has been used to study mechanical properties of skin affected by, for example, psoriasis,<sup>9</sup> systemic sclerosis,<sup>10-12</sup> Ehlers-Danlos syndrome,<sup>13</sup> striae distensae,<sup>14</sup> and hypertroph scars.<sup>15</sup> In addition, objective and quantitative evaluation of the effectiveness of therapeutic strategies has been made utilizing this bioengineering technique.

Furthermore, changes of biomechanical properties following the application of ultraviolet radiation,<sup>16</sup> laser treatment,<sup>17</sup> reconstructive dermal substitutions,<sup>18</sup> and liposuction<sup>19</sup> have been studied. Studies regarding the activity and safety of dermatocosmetics, such as emollients, moisturizers, chemical peelings, and antiaging creams, are another important application.<sup>20,21</sup>

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# 8 Hardware and Measurement Principles: The Gas-Bearing Electrodynamometer and Linear Skin Rheometer

*Paul J. Matts*

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## MEASURING PRINCIPLES

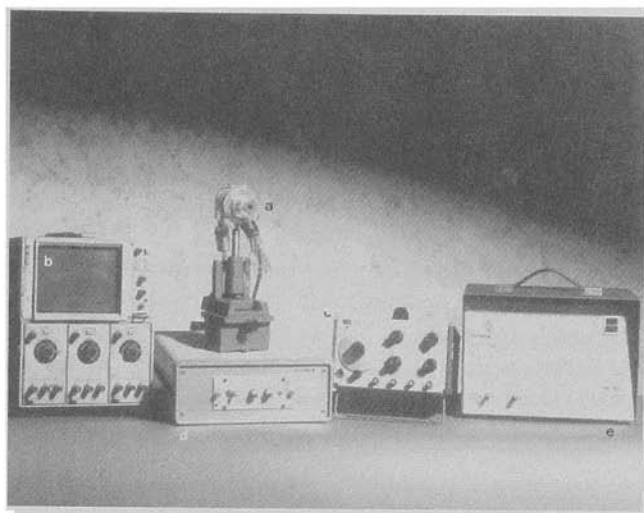
The Gas-Bearing Electrodynamometer (GBE<sup>1-5</sup>) has been used for the last 20 years to obtain sensitive measurements of the stratum corneum. The Linear Skin Rheometer (LSR<sup>6</sup>) is a new instrument for measuring the mechanical properties of the stratum corneum that incorporates all of the measurement principles of the GBE but none of its components. A force-controlled miniature DC servo, gearing, and lead screw replace the magnet/solenoid arrangement of the GBE. Error resulting from conversion of an electrical signal to a mechanical force is automatically compensated for. Consequently,

this control renders the need for a friction-free bearing redundant. The original Linear Variable Differential Transformer (LVDT) has been replaced with a unit with a sensitivity of 0.01% and force is now measured by a calibrated 100 g load beam. The function generator, signal conditioner, and storage oscilloscope have been replaced by user-friendly software run by a small portable computer. The new design offers greater inherent accuracy than the GBE and requires minimal servicing. The new LSR instrument has been shown to provide sensitive measurements of stratum corneum mechanics. A simple case study is presented in which the LSR was used to measure the mechanical responses of the stratum corneum to two topical moisturizing treatments of differing relative hydration performance (as determined by impedance measurements using the Nova<sup>®</sup> DPM9003). The relative performance of the two products as measured by the LSR compared favorably with corresponding impedance data, indicating the ability of the LSR to differentiate varying degrees of stratum corneum plasticization in response to hydration.

In measuring subtle changes in the mechanical properties of human stratum corneum, it is essential to use instrumentation that does not induce overly large surface displacement (either parallel or perpendicular to the skin surface). Excessive surface displacement will involve underlying tissue to an unacceptable degree, effectively rendering the measurement void.

With this in mind, one of the instruments to have been most widely used over the last 20 years to obtain sensitive measurements of the stratum corneum, is the Gas Bearing Electrodynamicometer (GBE<sup>1-5</sup>). It is able to apply a sinusoidal loading stress of less than 5 g parallel to the skin surface, with a resulting displacement of less than 1 mm in each direction. These force/displacement values are, indeed, sufficiently small to allow investigation of stratum corneum mechanics. This is achieved by suspending an armature in a gas bearing to create near friction-free movement. Changes in the magnetic field generated by a surrounding coil cause the armature to oscillate at a known frequency and amplitude. The coil is activated by a sinusoidal signal from a low-frequency function generator or from a suitable software trigger. The armature of the instrument is typically attached to the skin surface by a stiff wire probe bent to 90° at its free end. A small plastic stub is usually cemented to the free end of the probe and used to attach the probe to the skin surface using a circular piece of double-sided adhesive tape. Displacement of the armature is measured by a sensitive LVDT, mounted coaxially with the coil. Coil and LVDT outputs (force and displacement) are amplified and then supplied for analysis to either a storage oscilloscope or a computer equipped with suitable software. Equipment used in a "classic" GBE workstation is shown in Figure 8.1.

Results of force and displacement measurements of skin are typically displayed as a hysteresis loop (Figure 8.2). Analysis of the gradient of the loop (force/displacement or displacement/force) yields derivatives of the dynamic spring rate (DSR) usually expressed as g/mm (a measure of the force required to stretch or compress the skin per unit extension), mm/N or  $\mu\text{m/g}$  (measures of stretching or compression of the skin in response to a given applied force). Such analysis yields derivative information about the elastic properties of the skin. Analysis of the phase lag between force and displacement responses yields derivative information about the viscous properties of the skin.

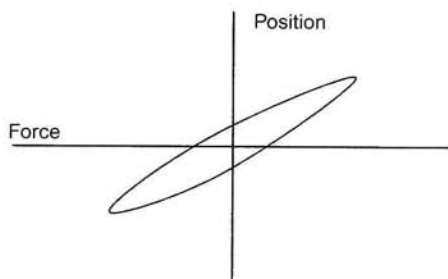


**FIGURE 8.1** Equipment used in a GBE workstation: (a) GBE probe, (b) storage oscilloscope, (c) function generator, (d) signal conditioner, (e) air compressor. (From Matts, P.J. and Goodyer, E., *J. Cosmet. Sci.*, 49, 321, 1998. With permission.)

More than 20 years of experience with the GBE within the author's laboratories has led to the belief that the GBE measurement principle is still among the best available for measuring changes in the mechanical properties of the human stratum corneum *in vivo*. Subtle but important changes in skin mechanics in response to the application of moisturizing formulas (dubbed "softness" by Maes et al.<sup>3</sup>) have been measured, as have changes in skin "tightness" due to surfactant damage. The

author's experience has, however, also highlighted the drawbacks of employing the original Hargens GBE instrument in a modern laboratory. These are as follows:

1. Importantly, the instrument employs an "open-loop" method of control; i.e., during calibration of the instrument, and in subsequent routine operation, one assumes that an applied current equals a given force. As the GBE is calibrated on one point only (3 g), linearity is not guaranteed over the whole measurement range of the GBE. In addition, calibration drift over time is certain.



**FIGURE 8.2** Typical position vs. force hysteresis loop produced by one GBE measurement cycle. (From Matts, P.J. and Goodyer, E., *J. Cosmet. Sci.*, 49, 321, 1998. With permission.)

2. The components needed to run the GBE are bulky and dated (function generator, signal conditioner, storage oscilloscope, compressed gas/air).
3. The probe components are fragile and, in the author's experience, break easily and require excessive servicing when used routinely (for example, the fine copper wires connecting the armature to the body of the probe).
4. The air bearing employed in the probe design is inherently susceptible to misalignment, soiling, and malfunction.

In recent years, the cost of precision has improved greatly. It is now possible to achieve using conventional technology what was achieved previously only through Hargens<sup>1</sup> considerable ingenuity. A new instrument has been designed and built that retains and builds on all the principles of the original GBE, but contains *none* of the components. This instrument, designated the Linear Skin Rheometer (LSR<sup>6</sup>), is described in the following sections.

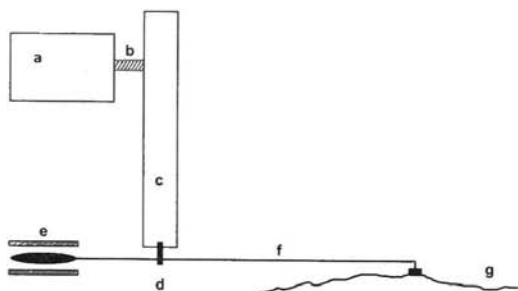
## HARDWARE

### INSTRUMENT HARDWARE AND CONTROL

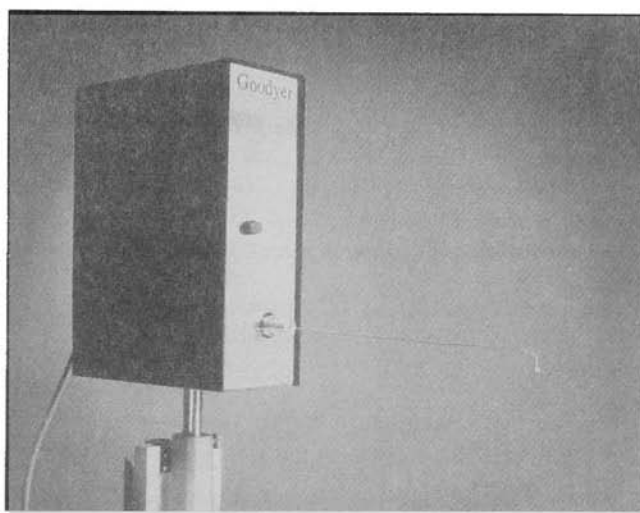
A schematic diagram of the new instrument is shown in Figure 8.3. A force-controlled miniature DC servo [Maxon Type 106328 (0.75 W, 9 V) by Maxon UK], gearing, and lead screw now replace the GBE solenoid arrangement, and drive the LSR probe. The original Schaevitz 050 HR LVDT in the GBE has been replaced with a unit of linearity 0.3% (15  $\mu\text{m}$ ) and sensitivity 0.01% (0.5  $\mu\text{m}$ ) (Type DFg5 by Solartron Metrology Ltd, U.K.). The force exerted on the probe is now measured directly by a calibrated load beam (Type F301 by Novatech Ltd, U.K., rated 100 g) with an overall repeatability of  $\pm 0.03\%$  ( $\pm 30$  mg). The load beam is mounted vertically within the instrument casing and acts horizontally in the direction of motion.

All components fit into one casing measuring  $20.0 \times 14.8 \times 6.9$  cm and the whole unit weighs 1.7 kg. The probe housing itself is a lightweight machined perspex chuck mounted on a low-friction swivel assembly allowing  $360^\circ$  movement (analogous to the GBE). This is protected from damage during routine usage by a metal collar. The chuck contains wire grips to allow the wire probes to be inserted or withdrawn by a simple, firm push or pull. A single lead connects the unit to a PC via a 25-pin D-type connector. Power for the LSR unit is taken from the PC via the connector. The unit can be seen in Figure 8.4.

An IBM (or compatible) PC is used to control the movement of the probe and to log force and displacement data. Both force and displacement are monitored continuously at a rate of 1 kHz using a 12-bit ADC plug-in card (National Instruments MIO16). The motor is controlled with an analog output signal also generated by the PC. The desired force/time cycle, which is normally a single sinusoid, is calculated initially and then stored in memory as a table of values. The actual force applied to the probe is compared with the desired value in the table 1000 times a second. A feedback loop is used to control the motor, which moves the load cell in a way that minimizes any discrepancy. The force applied thus follows the desired force/time cycle extremely closely. The control loop uses an algorithm with proportional and integral terms, whose relative weighting can be varied.



**FIGURE 8.3** Schematic diagram of the LSR sensing head: (a) miniature motor, (b) lead screw, (c) load cell, (d) load cell sensing head, (e) LVDT, (f) probe, (g) skin surface. (From Matts, P.J. and Goodyer, E., *J. Cosmet. Sci.*, 49, 321, 1998. With permission.)

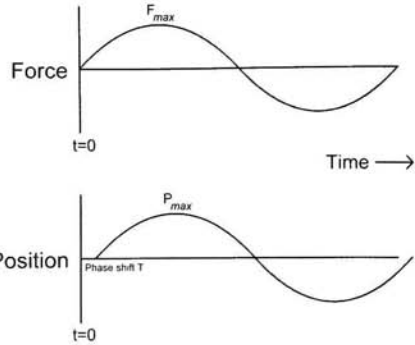


**FIGURE 8.4** The Linear Skin Rheometer. (From Matts, P.J. and Goodyer, E., *J. Cosmet. Sci.*, 49, 321, 1998. With permission.)

The PC logs all the force and displacement values over a complete measurement cycle, which is usually set at 0.33 Hz, thus generating 3000 pairs of points over a 3-s cycle. Two waveform plots are then obtained (Figure 8.5). Three parameters may be obtained from these curves:

- $F_{\max}$  = the peak force that is applied to the skin surface
- $P_{\max}$  = the peak displacement occurring as a result of that force
- $T$  = the phase shift between the two signals

The DSR of the stratum corneum is given simply by the formula  $F_{\max}/P_{\max}$ . Derivatives are calculated and expressed as g/mm, mm/N, and  $\mu\text{m/g}$ .



**FIGURE 8.5** Waveform plots demonstrating a complete LSR measurement cycle. (From Matts, P.J. and Goodyer, E., *J. Cosmet. Sci.*, 49, 321, 1998. With permission.)

The viscous component of the stratum corneum is often inferred by calculating the area of the ellipse shown in Figure 8.2. A more rigorous approach is to perform a regression on the original sinusoidal data in order to solve the equations:

$$F = F_{\max} \sin(t) \quad (8.1)$$

$$P = P_{\max} \sin(t + T) \quad (8.2)$$

where

$F$  = instantaneous force,  $F_{\max}$  = peak force,  $t$  = time for one complete cycle in seconds

$P$  = instantaneous displacement,  $P_{\max}$  = peak displacement,  $T$  = phase shift in radians

Having solved for these equations, it is then a straightforward problem to solve the integral over one cycle that represents the area of the ellipse:

$$\int_0^{2\pi} F_{\max} \sin(t) P_{\max} \cos(t + T) \quad (8.3)$$

The LSR software solves the above equations for both elastic and viscous components of the data. These are subsequently displayed, directly after measurement.

*Note:* Units of  $\mu\text{m/g}$  (1/DSR, a measure of stretching or compression of the stratum corneum in response to a given applied force) will be used as a convenient expression of skin softness in the rest of this chapter.

### CALIBRATION OF THE LSR

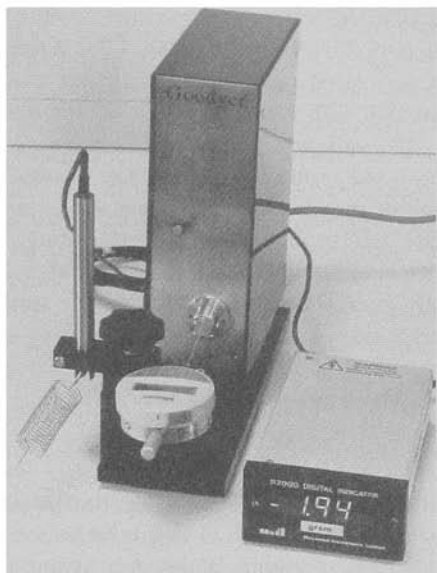
A simple calibration jig has been designed and built that allows rapid, absolute calibration of *actual* force and displacement (Figure 8.6). Displacement is measured by a 10  $\mu\text{m}$  resolution Digimatic Indicator [Mitutoyo (UK) Ltd, Warwick, U.K.] traceable to NAMAS calibration standards. Force is measured by a 10 g load beam (Maywood Load Beam type 49034, Maywood Instruments Ltd, Basingstoke, U.K.) with <10 mg accuracy, also traceable to NAMAS calibration standards.

The calibration factors are expressed in terms of ADC input units to achieve 1 g force, and 1 mm displacement. This method means that the calibration factors take account of the signal conditioning and data acquisition electronics as well as the precision transducer characteristics.

## SOFTWARE

The LSR software runs on a standard IBM (or compatible) PC of at least 386 33 MHz speed, and is sourced in C programming language. The closed-loop control employed by the LSR is achieved as follows. Because the LSR control loop is a sampled data system, it is essential that a fast real-time clock be generated that triggers the measurement of data samples and updates the control signal output. All IBM PCs have as standard a user interrupt (on interrupt vector 0x1c) called the TIMER TICK, which is available for programmers to use as a regular timing source. This timing signal is generated from the 4.192 MHz system clock via an Intel 8253 programmable interval timer. The BIOS presets this timer to its full scale of 65536 and, therefore, the TIMER TICK interrupt is normally 18.188 Hz. This is far too slow for a sampled data system.

This problem is overcome by reprogramming the 8253 divider to give the desired frequency during the measurement cycle, in this case 1 kHz. In order, however, not to disrupt important internal functions such as monitoring disk drive heads, the timing of interrupt 0x8 (the interrupt number actually triggered by the 8253 output) must be restored. This may be achieved by not using interrupt 0x1c, but replacing the BIOS interrupt function at 0x8 with the control program itself. The original timing is derived within the new interrupt 0x8 by installing a simple counter and calling the BIOS interrupt at the correct interval. In this way, a fast timer is generated that allows data sampling at 1 kHz but which does not harm other internal PC operations.



**FIGURE 8.6** LSR calibration jig. (From Matts, P.J. and Goodyer, E., *J. Cosmet. Sci.*, 49, 321, 1998. With permission.)

## TAKING AND INTERPRETING LSR MEASUREMENTS

### REPRODUCIBILITY AND MEASUREMENT SITE

For direct comparison with the GBE reproducibility data obtained by Maes et al.,<sup>3</sup> the reproducibility of the LSR was estimated by the same method. In the study,

40 consecutive identical measurements were performed on the back of the hand of a female volunteer. The resulting coefficient of variation for this measurement set was only 2.9% ( $n = 40$ ; mean = 281.8  $\mu\text{m/g}$ ; SEM = 1.3  $\mu\text{m/g}$ ). This demonstrates the very good reproducibility of the measurement technique and compares very favorably with the value of 3% obtained by Maes et al.<sup>3</sup> for the GBE.

The variation measured is almost certainly due to movement of the subject during the probe cycle. This has always been the main source of error in these types of sensitive measurements, and various means have been employed to minimize subject movement during readings (e.g., use of a pre-cast plaster mold by Maes et al.<sup>3</sup>). However, like Cooper et al.,<sup>4</sup> the author has found that the use of no restraint is preferable and employs a simple sloping table on which subjects rest their hands.

## LSR MEASUREMENT CASE STUDY

### Study Protocols

To determine the ability of the LSR to measure sensitive changes in stratum corneum mechanics in response to simple hydration, the following study was performed. Two moisturizing formulas of differing hydration performance (products A and B; hydration performance was determined by impedance measurements using a Nova Dermal Phase Meter 9003, see below) were applied to the back of the hands of 13 female subjects (aged 18 to 35). The dorsal surface of the hand was chosen for mechanical measurements (1) to conform to previous measurement sites using the GBE<sup>3</sup> and (2) because it is relatively simple to immobilize the hand effectively. The study was performed in a controlled-environment chamber (temperature  $20 \pm 1^\circ\text{C}$ ; relative humidity  $45 \pm 5\%$ ). The plastic stub on the end of the LSR wire probe was attached to skin on the back of the hand via a circular piece of double-sided tape (5 mm diameter). LSR measurements were then performed in triplicate. Baseline measurements were performed before product application. Test products were then applied at a rate of  $2 \mu\text{l}/\text{cm}^2$  to the entire back of the hand according to a predetermined randomization schedule. LSR measurements were performed at 1, 3, and 6 h after product application. As the whole dorsal surface of each hand was used for product treatment, inclusion of an untreated control was not possible. Results were, therefore, expressed as mean difference from initial pretreatment baseline.

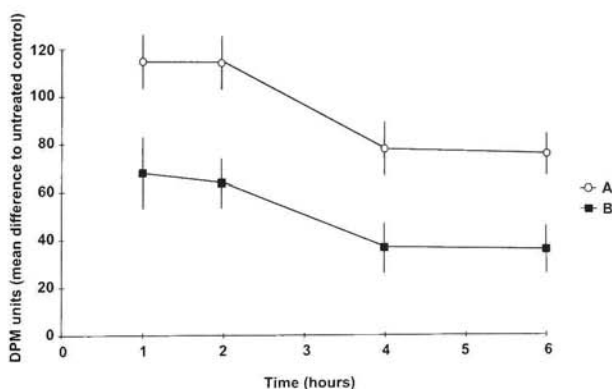
Hydration performance of products A and B was assessed by randomized application at the same rate as above ( $2 \mu\text{l}/\text{cm}^2$ ) to  $5 \times 5 \text{ cm}$  sites on the volar forearms of 12 female subjects (aged 18 to 35); the volar forearm was chosen as the site for hydration measurements because of its smooth, hairless morphology and its utility as a standard in this type of testing.<sup>7</sup> Each forearm also contained an untreated  $5 \times 5 \text{ cm}$  control site. The study was performed within a controlled-environment chamber (temperature  $20 \pm 1^\circ\text{C}$ ; relative humidity  $45 \pm 5\%$ ). Impedance measurements were performed using a Nova Dermal Phase Meter 9003 with the standard measuring probe DPM 9103 (Nova Instruments) at 1, 2, 4, and 6 h after application, and results expressed as mean difference from untreated control.



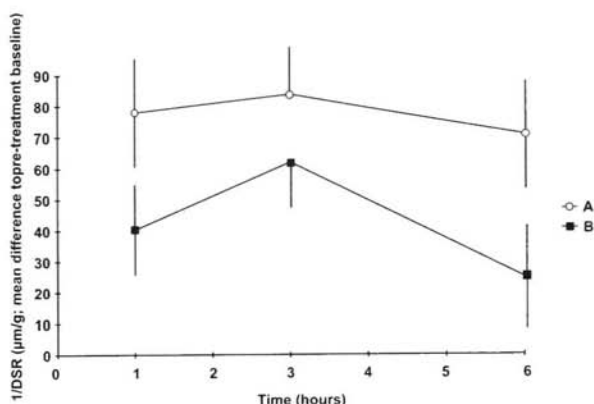
## Results and Interpretation

The results of the study using the Nova DPM 9003 to measure the hydration efficacy of products A and B can be seen in Figure 8.7. Both products induced significant increases ( $p < 0.05$ ; paired t-test vs. untreated control) in apparent stratum corneum hydration (as measured by impedance changes) up to, and including, 6 h after application. Moreover, product A increased stratum corneum hydration significantly more ( $p < 0.05$ ; paired t-test) than product B at all time points up to and including 6 h after application. Water exerts considerable influence on the mechanical properties of the human stratum corneum because of its complex interactions with keratin.<sup>8,9</sup> This plasticization of the stratum corneum, an essentially viscoelastic material, has been described as skin "softening."<sup>2,3</sup> In the case of topical application of a moisturizing formula, the extent of this softening effect is directly related to the ability of the product to deliver and maintain increased water concentrations within the stratum corneum. This is usually achieved by the delivery of humectant compounds such as glycerol and/or use of occlusive lipidic films. Indeed, in the case of products A and B, product A might be expected to leverage greater increase in stratum corneum hydration as a result of its higher glycerol content (4% w/w glycerol in A, in contrast to 3% w/w in B) and formulation (gel network, in contrast to a simple oil-in-water emulsion in B). For products A and B, therefore, one would expect to be able to measure (1) absolute significant increases in softness for both treatments and (2) differing relative changes in skin softness for both treatments in accordance with their apparent hydration performance.

Results of the study using the LSR to measure the effects of products A and B on stratum corneum mechanics are presented in Figure 8.8. Both products induced significant increases ( $p < 0.05$ ; paired t-test vs. pretreatment baseline) in skin softness at all time points up to and including 6 h after application. Moreover, product A induced greater increases in skin softness than product B throughout the time



**FIGURE 8.7** Relative hydration performance of products A and B (as measured by impedance). (From Matts, P.J. and Goodyer, E., *J. Cosmet. Sci.*, 49, 321, 1998. With permission.)



**FIGURE 8.8** Relative performance of products A and B as measured by LSR. (From Matts, P.J. and Goodyer, E., *J. Cosmet. Sci.*, 49, 321, 1998. With permission.)

course, significantly so ( $p < 0.05$ ; paired t-test) at 6 h after application. These results compare favorably with the relative hydration profiles of the two products (Figure 8.7). The LSR is, thus, able to measure subtle changes in stratum corneum mechanics in response to hydration and to distinguish between the effect of topical application of moisturizing products with differing relative hydration performance.

## DISCUSSION

The control system used for the LSR provides the instrument with an inherently more accurate and reliable measurement capability because it employs closed-loop (feedback) control. The GBE, in contrast, uses an open-loop method of control where a predetermined current is applied to the solenoid and assumed to be transformed into the desired force. Because no determination of the actual force generated is made at the time of measurement, it is difficult to know with certainty the true force applied to the skin. While open-loop techniques can be used successfully in perfectly stable environments, no account can be taken of instantaneous fluctuations in such a system (notably, in this case, subject movement). With the LSR closed-loop system, the true force applied to the skin is measured at a rate of 1 kHz and corrective action taken within 1 ms to restore that measured force to the required value. This system helps ensure that the test sequence is reliable, repeatable, and can dynamically adjust for the inevitable variations that occur during *in vivo* testing. Put another way, because this system allows instantaneous compensation of error resulting from the conversion of an electrical signal to a mechanical force, the need for the friction-free gas-bearing arrangement of the GBE is eliminated. This allows the deployment of a compact, efficient, and flexible new instrument.

## ACKNOWLEDGMENTS

The author wishes to thank Mr. Eric Goodyer (E & C Consultancy, Hathern, Leicestershire, U.K.) and Dr. Paul Stevens (Paul Stevens Mechanical Design, Tunbridge Wells, Kent, U.K.) for their significant skill and expertise in the design of the LSR software and hardware. Much of the material included in this chapter is taken from a paper published originally within the *Journal of Cosmetic Science* (Matts, P.J. and Goodyer, E., A new instrument to measure the mechanical properties of human stratum corneum *in vivo*, *J. Cosmet. Sci.*, 49, 321, 1998) to whom the author is grateful for permission to reproduce relevant text and graphical material.

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# 9 Hardware and Measuring Principles: The Dermaflex A

*Jørgen Serup*

## CONTENTS

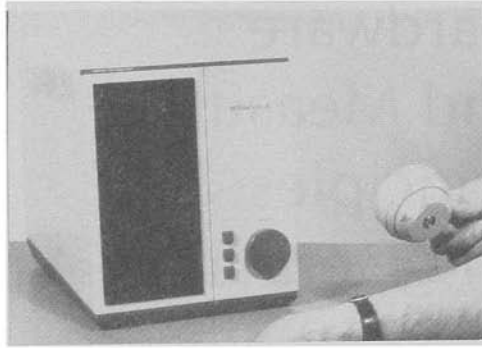
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## INTRODUCTION

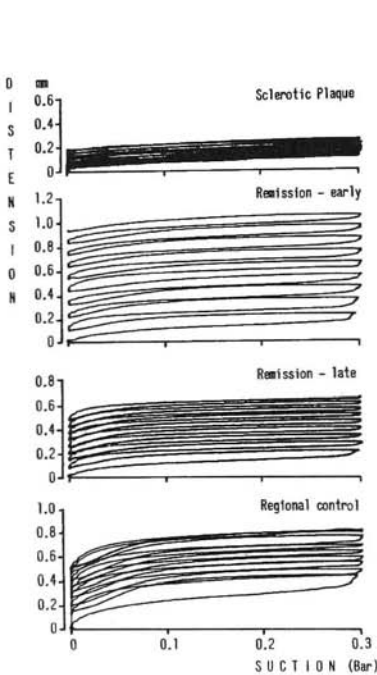
The Dermaflex A (Figure 9.1) was originally developed as a prototype by the Department of Dermatology, Rigshospital, Copenhagen, Denmark and the Institute of Technical Engineering (ATV), Glostrup, Denmark. Its purpose is to measure objectively the stiffness of the skin in scleroderma (Figure 9.2) in concert with other methods for measurement of skin thickening and change of color in this disease.<sup>1,2</sup> It soon became applied to assessment of psoriasis and histamine wheals exemplifying edematous states (Figure 9.3).<sup>3</sup>

## MEASURING PRINCIPLE AND HARDWARE

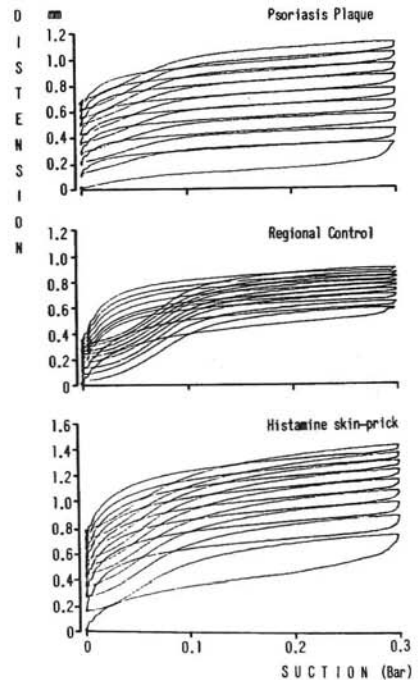
The Dermaflex is a suction chamber device. The circular aperture of the chamber is 10 mm in diameter, constructed with two sharp, concentric rings to avoid creeping of skin during negative pressure and a surrounding flat bases prepared for the application of a double-sided adhesive ring sealing the probe to the skin. A concave electrode with an outlet tube to the suction system is located in the top of the chamber. This electrode and the surface of the skin exposed in the suction chamber constitute a capacitance system with the distance between skin surface and top electrode the



**FIGURE 9.1** The Dermaflex A. (Courtesy of Cortex Technology, Hadsund, Denmark.)



**FIGURE 9.2** Stress-strain curves in sclerotic plaque of morphea vs. regional control of clinically uninvolved skin. The distensibility (strain after first suction) is decreased in all stages of the disease. In early remission, the hysteresis or creeping is increased due to some mucinous edema.



**FIGURE 9.3** Stress-strain curves in psoriasis vs. regional control of clinically uninvolved skin. Increased hysteresis of a histamine wheal raised in uninvolved skin illustrates the influence of tissue water on distensibility, particularly reflected in the hysteresis.

variable of the system. This is measured in millimeters with high precision on the order of magnitude of about 0.05 mm. The suction outlet is connected to a negative-pressure reservoir or tank, controlled by a vacuum pump. Because of the reservoir, a preset negative pressure is immediately effected at the initiation of recording in the suction chamber. There is some low resistance in the tube between the reservoir and the probe chamber.

The negative pressure, the duration of suction, and the number of repetitions of suction and release of pressure cycles can be selected. Suction pressure greater than 300 mbar may be unpleasant or painful. The electrical constants of the capacitive measuring system were chosen so that the measured distance and elevation are not dependent on the skin surface hydration state.

The circular opening of the chamber was chosen to standardize the start of recording and to eliminate the influence of Langer line orientation on baseline recording, albeit the elevated skin will show some ellipsoid deformation, which, however, does not disturb the result and reproducibility. The Dermaflex automatically sets the zero elevation immediately at the initiation of negative pressure.

## PRECONDITIONING OF INDIVIDUALS AND MEASUREMENT

Individuals should be placed comfortably in a position defined in the study protocol. It is particularly important that the joint positioning be specified, and the measured site located precisely within a few millimeters. Lanugo hairs do not interfere with measurement, but terminal hairs may be a problem. It is important that the probe at the initiation of measurement be positioned neutrally and vertically over the measured site, and that the probe is not supported but remains in position as a result of its own weight. The reason is that the recorded elevation is a delta value, i.e., the difference between the zero surface state and the same surface elevated under the influence of suction.

## THE PARAMETERS EXPRESSED BY THE DEVICE

The parameters expressed by the Dermaflex A are as follows:

- Distensibility, i.e., elevation in mm after the first suction. Resilient distensibility (not displayed) is the elevation in mm following the first suction, after the skin has retracted toward its original state.
- Elasticity, i.e., percentage retraction after one suction; 100% is full recovery to zero state.
- Hysteresis or creeping, i.e., the delta distension after repeated suction cycles.

The Dermaflex A appears quite independent of subcutaneous binding. With constant suction, the probe can be elevated millimeters or centimeters without disturbing the distensibility reading. With no suction or a weak suction, even small maneuvers

of the probe exert major variation of the displayed strain values, illustrating the important and vulnerable zero state situation, which in the measurement requires much attention and insight to standardize properly.

## APPLICATIONS AND INTERPRETATION

The principle is that of a stress-strain exercise. Reduced distensibility is easily understood as skin stiffening exemplified by scleroderma, and increased distensibility as softening exemplified by edematous skin conditions such as inflammation. Poor elasticity percentage is understood as poor turgor, as exemplified by dehydrated dermis, and/or reduced ability of the skin to recover to normal state following a deformation, as exemplified by aged skin.

The reproducibility of the method, body site variations, and findings in scleroderma, Pierini atrophy of morphea, psoriasis, and histamine wheals are described in the original publications.<sup>1-4</sup> Anatomical site differences in 22 sites, comparison of genders, and the influence of gravity and diurnal changes were studied in various studies that provide detailed information.<sup>5-7</sup> Skin elasticity following tissue expansion with expansion of the subcutaneous space was studied in relation to breast cancer surgery.<sup>8</sup> Dr. G.B.E. Jemec and co-workers conducted systematic studies on the Dermaflex A, its precision and variables, the effects of superficial hydration and care products, and finally the use of the Dermaflex A in plastic surgery.<sup>8-15</sup> (Also see Chapter 17 of this book.)

It is noteworthy that there is a high degree of correlation between the different elasticity parameters, and it appears that all essential information is given in the distensibility and the elasticity percentage describing the essential clinical traits of the skin, namely, the ability to stretch and retract to the original state. It should be borne in mind that the first suction comes closest to illustrating the original skin mechanics, and repeated suction starts with a zero drift because of the incomplete recovery from the previous strain, i.e., the creeping dependent on the hydration state of the viscoelastic skin tissue. Gniadecka and Serup<sup>16</sup> have reviewed the Dermaflex A in a recent book chapter.

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# 10 Hardware and Measuring Principles: The DermaLab

*Jørgen Serup*

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## INTRODUCTION

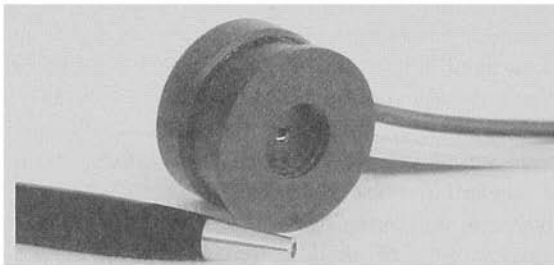
The DermaLab (Figure 10.1) is a new suction chamber method for measurement of skin elasticity developed by Cortex Technology, Hadsund, Denmark. The system can be mounted with special probes to measure transepidermal water loss and skin hydration as well. The elastometer device has been developed especially to overcome the problem of baseline setting normally creating startup noise in the recording. The system is designed to simplify and preset factors normally somewhat difficult to measure with high precision and to measure factors that can be sensed technically with high precision and to nominate the latter as measuring end points. Skin elevation or distensibility is a fixed delta value of 1.5 mm, and the applied vacuum is also fixed; however, the vacuum is not applied immediately but, rather, gradually built up to a plateau over some 30 s. The DermaLab operates with controlled pretension load before baseline setting followed by the 1.5 mm stress-strain exposure under the influence of a standard pressure as described above. The device is mounted with an especially lightweight measuring probe. The results are expressed by the manufacturer as an empirical Young's modulus termed *elast* and as the time to achieve the fixed skin elevation of 1.5 mm.



**FIGURE 10.1** The DermaLab skin elasticity measurer. The complete DermaLab system also includes systems and probes for measurement of transepidermal water loss and epidermal hydration. (Courtesy of Manufacturer Cortex Technology, Hadsund, Denmark.)

### MEASURING PRINCIPLE AND EQUIPMENT

The probe consists of a polyethylene cylindrical suction chamber with height of 3.8 mm and a circular aperture of diameter 10 mm (Figure 10.2). The probe has a flat 7.5-mm concentric base that is sealed on the skin surface with double-sided adhesive tape. Diodes and a circular lens system for optical monitoring of skin elevation are mounted in the probe cylinder wall at two fixed positions: level 1 at



**FIGURE 10.2** The DermaLab suction chamber probe. The probe is especially lightweight, 10 g. The outer dimensions are height 15 mm and diameter 25 mm. The cylindrical suction chamber is 10 mm in diameter and 3.8 mm in height, with optical sensors mounted in the chamber 1.0 and 2.5 mm above the opening toward the skin.

1.0 mm and level 2 at 2.5 mm above the base of the probe. The lens system focus is in the middle of the axis of the cylindrical chamber. A continuous skin surface elevation curve during suction is, thus, not measured. The main body of the equipment includes a base and a display for settings of a number of repeated suction and relaxations. The suction period is displayed as a result, whereas the relaxation time is a preset variable. Suction time read out as a result may in practice vary between a few seconds in very soft skin and 1 to 5 min in stiff and sclerotic skin.

Results may be printed out or loaded into a computer. The display will show the end vacuum pressure RES1 in pascals and, of course, the main result, the “elast” in megapascals (MPa). In its manual the manufacturer provides the following explanation of the parameters displayed:

- ELAST. The calculated elasticity modulus for the actual measurement sequence based on the first measurement cycle.
- RES1. Indicates the differential vacuum necessary to elevate the skin from detection level 1 to detection level 2 in the first suction cycle. The unit is Pa.
- N (upper in display). Indicates the differential vacuum necessary to elevate the skin from detection level 1 to level 2 in the last actual suction cycle. The unit is Pa.
- TIM1. The elevation time corresponding to the first suction cycle (RES1).
- N (lower in display). The elevation time corresponding to the last actual suction cycle.

The device is specially constructed with resistance in the tube system to apply the vacuum slowly over a period of perhaps 30 to 60 s until a plateau vacuum in the chamber is maintained in equilibrium with the capacity of the pump. The negative-pressure curve in the chamber is not known exactly and is supposed to be nonlinear. The DermaLab has no vacuum tank and no barometric control of the buildup of negative pressure. The pretension control bringing the skin from biological baseline (in principle, there is no touching and no probe held against the surface) to experimental baseline at level 1 at 1.0 mm above the probe base is thought to unfold microanatomical foldings and to harmonize the orientation of the dermal fiber networks at a level of negative pressure believed to be subclinical.

Skin elasticity  $E$  displayed as elast in MPa is, according to the manufacturer, a calculated Young's modulus where

$$\Delta X = \Psi \cdot p = \frac{r^4}{E \cdot S^3}$$

$\Delta X$  = deviation middle of surface,  $\Psi$  = elasticity constant for measured object estimated from civil engineering,  $p$  = negative pressure,  $r$  = radius of surface measured,  $s$  = thickness of object measured.

Constant  $\Psi$  is set by manufacturer to 0.5;  $r$ , defined by the chamber geometry, is 5 mm;  $s$  is set by manufacturer to standard skin thickness 1.0 mm. This leads to

$$E = 0.3125 \frac{\Delta p}{\Delta X}$$

The Young's modulus originates from engineering of solid and isotropic materials of some measurable thickness with well-defined mechanical properties, and the modulus is normally not considered applicable to anisotropic materials such as skin. Skin is a complex viscoelastic material with layers of different mechanical resistance. The actual  $\Psi$  and the actual thickness of the skin are not known and are not entered as variables. Thus, the modulus given by the DermaLab is an empirical modulus in conflict with prerequisites known in engineering.

### MEASURING WITH THE DERMALAB

An advantage of the probe is its light weight. It is important that the probe be fixed gently to the skin surface by double-sided adhesive tape and left undisturbed during recording. As with any other elasticity method, the positioning of the test individual must be carefully standardized with respect to joint position, etc. After a variable suction period needed for the skin to elevate the fixed distance of 1.5 mm, the equipment automatically stops recording and reads out the  $E$  and the time for elevation to occur. Results may be printed or loaded into a computer. The equipment is easy to operate, and the procedure is described in detail in manufacturer's manual.

*Range of operation:* There is little experience with applications in cosmetology and dermatology, and no publications have yet appeared. Obviously, very soft skin will swiftly elevate, and stiff and sclerotic skin may never reach the elevation of 1.5 mm unless suction is applied for several minutes, which may lead to prominent edema and even subepidermal blister formation. Thus, the DermaLab appears applicable only to relatively normal skin within a reasonable average range so that measurement can be concluded in about 30 s or less.

Obviously, a lengthy vacuum period results in water accumulation in the measured skin, seen as a wheal-like circular elevation above the surrounding skin, and thus a major measurement artifact may be introduced; see below.

### RESULTS AND THEIR INTERPRETATIONS

The manufacturer outlines the following measuring end points:

- *The empirical modulus E as end point.* The higher the modulus, the stiffer is the skin; see equations. The limitations of this calculated modulus were discussed above.
- *Suction time as end point.* This may work well if the suction period is relatively short. The longer the suction time, the stiffer is the skin. It shall be borne in mind that the vacuum is built up in the chamber slowly until

a plateau is reached, following an unknown curve; linearity cannot be expected. It should also be considered that water and edema will accumulate in the skin under suction, thicken the skin, and contribute to its elevation especially in stiffer skin requiring a longer time to reach the fixed elevation of 1.5 mm. This is expected to influence mechanical skin properties during suction and recording and to create an artifactual situation where the measured object undergoes a significant change as a result of the recording procedure. This disturbance will influence all end points registered with the DermaLab, as it will with other systems with longer suction periods. To overcome the problems of prolonged suction in sclerotic and stiff skin, the DermaLab may be delivered with a special probe with reduced height between level 1 and level 2.

- *Vacuum needed to elevate (RES1)*. This might only be meaningful with very short suction times since after perhaps 30 s the RES1 will be constant and will simply illustrate the suction capacity of the pump. The manometer is mounted close to the pump, and not in the chamber.

Optional end point interpretation and nomenclature (proposed by the author of this chapter):

- *“Stiffness” expressed as E and given in arbitrary units*. The value is higher in sclerotic and stiff skin, which reaches the elevation of 1.5 mm only following a higher vacuum and a longer suction period unless the optional probe is used. It should not be called a modulus, and results should be simply given in arbitrary units. The essential limitations are discussed above.
- *“Softness” expressed as reciprocal E (1/E) and expressed in arbitrary units*. The reciprocal *E* should be higher in soft skin; see above. This end point might be especially interesting for uses in cosmetology. Units are arbitrary.

Further studies on instrument validation, comparison with other instruments, usefulness, and applications to practical situations should be conducted to finally establish the value of the DermaLab in experimental and clinical research. The DermaLab appears especially suited for the measurement of smoothing and softening effects of cosmetic products on skin.





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# 11 Hardware and Measuring Principles: The Dermagraph in Patients with Systemic Sclerosis and in Healthy Volunteers

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Burkhard Seifert, and Beat Michel*

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## SUMMARY

This chapter describes the testing of a novel device, the Dermagraph<sup>®</sup>, for measuring the distensibility of normal and diseased skin by applying a vacuum onto the skin at 22 defined body areas. *Intrarater* testing resulted in an average weight of the vacuum device of approximately 400 g with a reliability of 0.77 for the distensibility of normal skin. *Interrater* reliability for the distensibility of normal skin in nearly 100 healthy volunteers at 22 body locations was 0.55 and therefore comparable with the value of the earlier used Sclerimeter<sup>®</sup> (0.57). The average *intrarater* reliability of the Dermagraph in healthy volunteers was 0.71 and therefore better than with the earlier used prototype Sclerimeter with a mean value of 0.61.<sup>1</sup> There were statistically significant differences between the values of distensibility among both genders, showing higher values at 7 of 22 skin locations in women with the Dermagraph. The *interrater* reliability in relevant skin locations in ten patients with systemic sclerosis (hand, feet, and face at an early or intermediate stage) showed a mean value of 0.81. The mean *intrarater* reliability of these three relevant skin locations in patients was 0.84, much better than the correspondent value of 0.33 with the Sclerimeter.

The Dermagraph has a standardized and validated weight of the vacuum probe, is handier, and has the ability to produce a printout, comparable to an electrocardiography device. The Dermagraph is a simple and easy-to-use device for measuring parameters of skin elasticity and can therefore be used for longitudinal measurements in patients with systemic sclerosis. With respect to practicability and reliability the Dermagraph can be compared with the Cutometer, except that the Cutometer measures much smaller areas of skin<sup>16</sup> and to the authors' knowledge has never been validated in patients with early and intermediate stages of systemic sclerosis.

## BACKGROUND

### MEASURING MECHANICAL SKIN PROPERTIES IN HEALTH AND DISEASE

The thickening of skin combined with its decreased distensibility and tethering are hallmarks of systemic sclerosis. Several skin parameters such as area of diseased skin and decreased tethering, seem to correlate well with morbidity (risk of internal organ disease) and rapid deterioration of the disease process and therefore can be used as representative parameters<sup>2-7a</sup> of disease activity and outcome in systemic sclerosis.<sup>7b</sup>

To date, the most often used clinical techniques for measuring skin tethering or distensibility are manually performed skin scores, e.g., modified Rodnan total skin thickness score. In various studies their variability was approximately 20%, even if the examiners were carefully instructed on how to perform the manual skin measurements. As a consequence, easier-to-use manual scores were suggested.<sup>8</sup>

Measuring of skin elasticity goes back to the 1960s, when the first reports on skin measurements by devices were published. But thus far no method or device has been introduced in routine clinical practice for patients with systemic sclerosis, mostly because the techniques were too complicated to use in a day-to-day setting and no comparative trials with the manual scores or validation process of the device itself had been undertaken.<sup>9-29</sup>

Recently, devices that measure skin distensibility by applying a vacuum, comparable to manual skin testing, have been introduced in normal and diseased skin and have also been validated with respect to reliability (*interrater* reliability; several examiners measure the same patient) and precision (*intrarater* reliability; same examiner, repeated measurements in same patient). Together with the Rüetschi AG, a company manufacturing medical high-precision products, the authors developed a prototype of a device for measuring skin distensibility at the Department of Rheumatology and Physical Medicine at the University Hospital in Zurich and called it the Sclerimeter.<sup>1</sup> Former studies of comparative testing against some published manual skin scores of Harrison,<sup>47</sup> Brennan,<sup>43</sup> Pope,<sup>48</sup> and Silman<sup>8</sup> showed better values for *intrarater* as well as *interrater* reliability. In comparison with the published devices with the highest reliabilities, such as the SEM 474 Cutometer<sup>®</sup>,<sup>46</sup> the Sclerimeter showed similar values. These facts stimulated further improvements in the handiness and reliability of the first prototype "Sclerimeter," which led to the "Dermagraph," a device that can easily be used in an inpatient (research) as well as an outpatient setting (Dermatologist and Rheumatologist/Internist) in clinical routine.

Therefore, the objectives for this study were threefold:

1. Exploration of the most appropriate weight of the vacuum device in normal and diseased (systemic sclerosis) skin with respect to measuring precision by determination of the *intrarater* reliability.
2. Measuring the *intra-* and *interrater* reliability of the measuring process in patients with systemic sclerosis by using the most appropriate weight of the vacuum probe.
3. Finally, acquiring reference values for skin distensibility and relaxation in a population of normal healthy people of both genders and different ages.

## SYSTEMIC SCLEROSIS

Systemic sclerosis is a disease that affects the connective tissue of the locomotor system and of internal organs. As a consequence, skin, joints, tendons, and internal organs such as lungs, intestines (e.g., esophagus), heart, and kidneys can be damaged. Pathogenetically, the disease process leads to a generalized fibrosis and sclerosis of the connective tissue, mediated by an increased synthesis of normal and abnormal components of the connective tissue, mostly of collagen type I and III.

To date, systemic sclerosis has been classified according to manual measurement of the area of diseased skin and other organ involvement (see classification criteria of the American College of Rheumatology, ACR, 1980).<sup>34</sup> Only recently, workers have tried to use other parameters of the disease process to classify systemic sclerosis using other clinical, serologic, and genetic markers.<sup>33</sup> There are published reports

suggesting to classify patients with various disease severity and location into subgroups, mainly in the form of limited vs. diffuse disease with significantly different prognoses.<sup>7a,36</sup>

Other research groups differentiate the disease according to the amount of abnormal skin into a limited form (mostly sclerosis of the fingers), an "intermediate" form (skin of proximal extremities is involved), and a "diffuse" form (extension of skin involvement to the torso).<sup>37-40</sup> The classification of Clements et al.<sup>2</sup> with a semiquantitative Skin-Score uses not only the area of affected skin but also its semiquantitative grading of severity. All body areas are treated equally in terms of severity and are summarized into a total skin score with a maximal score of 30.

### MANUAL GRADING OF SKIN ELASTICITY IN PATIENTS WITH SYSTEMIC SCLEROSIS

Two fingers of the examiners are used to evaluate the degree of tethering of the skin by elevating the skin from its surface. According to the different authors the scale ranges from zero (normal tethering) to three or four (maximally reduced tethering). The examination is performed at defined areas of the skin (e.g., ten body areas used by Clements) by adding the local score number to a total skin score.<sup>2,41-44</sup>

### GRADING OF SKIN ELASTICITY USING DIFFERENT MEASURING DEVICES

This has been reviewed earlier by the authors' group, and the reader is referred to Reference 1. Basically, there are methods to aspirate the skin from its surface<sup>9-18</sup> to compress the skin toward the underlying resistance,<sup>19,20</sup> or to extend the skin.<sup>21-29</sup>

## METHODS

### THE DERMAGRAPH

The Dermagraph device (Figure 11.1) is a further development of the first prototype, the Sclerimeter.<sup>1</sup> There are no fundamental differences between the two devices; an easier-to-handle vacuum probe (Figure 11.2) was manufactured, and a dot plot printer was installed. The distensibility of the skin is measured by applying a constant vacuum. The amount of aspirated skin is measured in millimeters with a measuring device, which is situated within the aspirating probe. The measuring curve of the distended and relaxed skin over time is printed on a 55-mm-wide paper strip. The initiation of the vacuum is automatically induced as soon as the vacuum probe is in tight contact with the skin, producing a vacuum. There is no need for a pedal as in the Sclerimeter. The diameter of the vacuum probe is 20 mm. Because the precision of the 5-mm vacuum probe for the skin of the fingers was suboptimal, further evaluation of the 5-mm vacuum probe was halted.

### MEASURING SKIN DISTENSIBILITY AND RELAXATION WITH THE DERMAGRAPH

The measuring process lasts for 10 seconds (s). During 6 s a constant vacuum, which is shown on the printout, is applied followed by 4 s of skin relaxation (Figure 11.3).

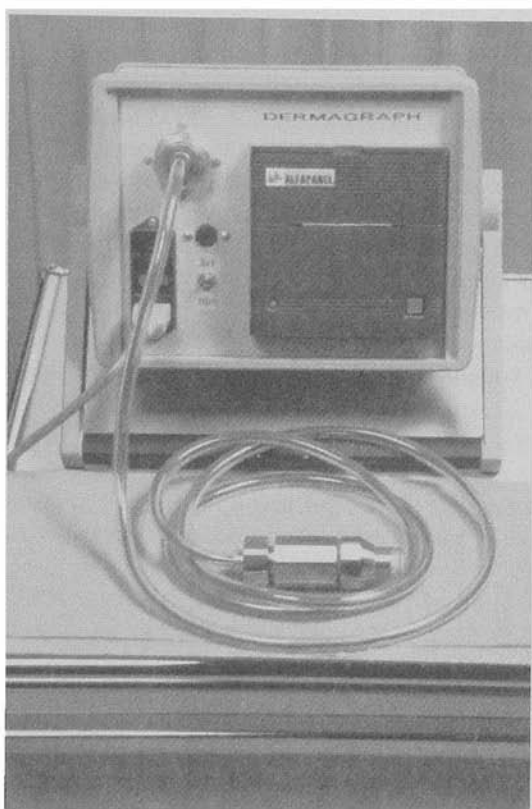


FIGURE 11.1 Dermagraph with vacuum probe in front.

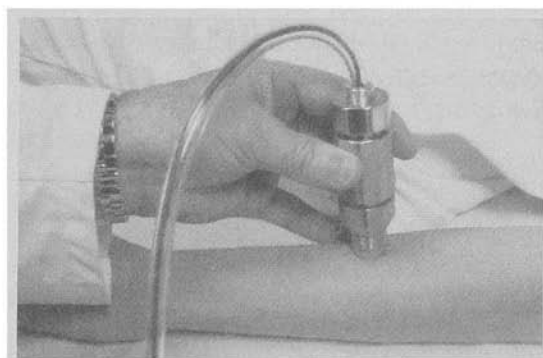
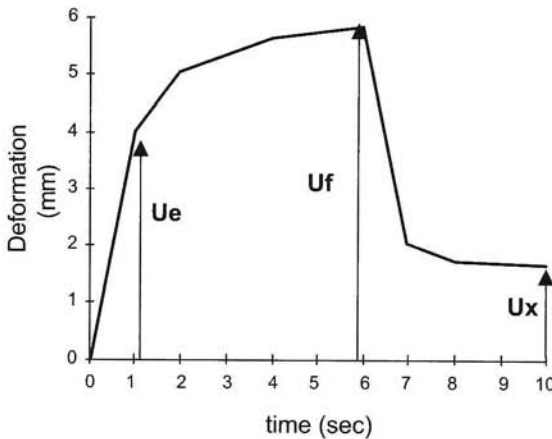


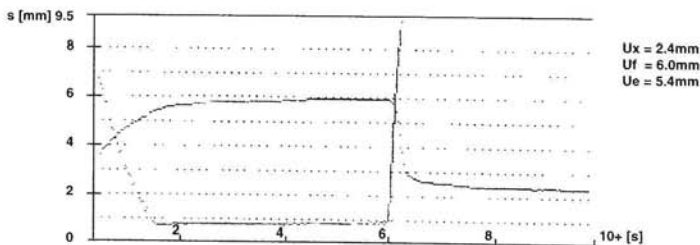
FIGURE 11.2 Vacuum probe applied perpendicularly onto the ventral lower arm of a healthy volunteer.

The aspiration or tethering of the skin over time is not constant but, because of the plasticity of the skin, it follows the mathematical equation of a hyperbole. After 6 s, the vacuum is stopped, resulting in an initial phase of fast relaxation followed by a slow phase (elastic retraction). The relaxation period has been set to 4 s.

The whole process (distention and relaxation process as well as vacuum over time) is printed onto a paper strip (Figure 11.4). The following measuring parameters have been taken from an earlier publication of Agache et al.<sup>45</sup> and are shown in units of millimeters with a precision of a tenth of a millimeter (see Figure 11.3). The skin distensibility after maximal vacuum ( $U_e$ ), the distention at a maximal vacuum for 6 s ( $U_f$ ), and the residual distention, 4 s after stopping the vacuum ( $U_x$ ). The three measuring parameters are printed immediately after the curve. Several body areas can be measured without any delay, as the parameters are stored. As soon as the



**FIGURE 11.3** Schematic representation of measuring process with the Dermagraph. The parameters initial skin distensibility  $U_e$ , maximal distensibility  $U_f$ , and residual distensibility  $U_x$  are defined and marked by arrows.



**FIGURE 11.4** The applied vacuum and skin distensibility over time are printed on a paper strip. The absolute values of initial skin distensibility  $U_e$ , maximal distensibility  $U_f$ , and residual distensibility  $U_x$  are printed onto the paper strip in millimeters with the precision of a tenth of a millimeter.

machine sends two beeps, the measuring process must be terminated and the next skin area can be measured without delay.

According to the earlier publication<sup>1</sup> the precise localizations of the 20 measured body areas are in concordance with the manually measured skin tethering published by Clements et al.<sup>2</sup> They represent face, torso, abdomen, upper back, upper and lower arms, hands, thighs, calves, and feet. The exact definition of the localizations and the positioning of the patient have been published elsewhere.<sup>1</sup>

#### **DETERMINATION OF VACUUM PROBE IN HEALTHY VOLUNTEERS AND PATIENTS WITH SYSTEMIC SCLEROSIS**

To evaluate the most appropriate weight of the device in terms of optimal precision of the measuring process, the *intrarater* reliability of this device was tested in ten patients with systemic sclerosis at the Department of Rheumatology and Physical Medicine in Zurich (eight women and two men, 37 to 74 years old), as well as in ten healthy volunteers (six women and four men, 16 to 81 years old).

Five different weights of the vacuum probe were chosen to measure each of the 22 defined skin locations (see below): 88, 176, 225, 442, and 619 grams (g). With the exception of the temperature, no other parameter was controlled for. All measurements were done at an ambient temperature between 19 and 23°C. The usual parameters at all 22 body areas as mentioned above were measured with respect to *intrarater* reliability of the five different weights. In addition, all parameters were calculated for the three most relevant measured body areas in patients with systemic sclerosis (hand, foot, and face). After these tests were performed and the best, e.g., most reliable, weight of the vacuum probe was defined, all following examinations were performed with this single best vacuum probe.

#### **INTRATER RELIABILITY IN PATIENTS WITH SYSTEMIC SCLEROSIS**

Three raters measured ten patients in groups of three at all 22 body areas. The selection of the raters with respect to their order of measuring the patients was randomized. Two raters were experienced with the handling of the Dermagraph; for the third rater the device was new except for a 15-minute training program before the test. The vacuum probe used has been chosen according to the best results of *intrarater* variability testing (442 g).

#### **REFERENCE VALUES IN HEALTHY VOLUNTEERS**

In 96 healthy volunteers (51 men, 45 women, 16 to 81 years of age), the same skin parameters of distensibility, relaxation, and elasticity as mentioned above were measured at all 22 body areas with the definitive vacuum probe of 442 g. Mean values and standard deviation were calculated. *P* values were calculated for significant differences between volunteers and patients with systemic sclerosis as well as for differences between the genders of the healthy volunteers.

## RESULTS

### MEAN *INTRATER* RELIABILITY WITH DIFFERENT WEIGHTS OF VACUUM PROBE

With respect to different weights of the vacuum probe of the Dermagraph, examinations of *intrater* reliability showed very good values for the maximal ( $U_f$ ) and initial ( $U_i$ ) distensibility irrespective of the weight. The mean value of the *intrater* reliability for  $U_f$  of all measured body areas in ten patients with systemic sclerosis was between 0.847 (with a vacuum probe weighing 225 g) and 0.745 (with 619 g). The mean value for the three most relevant body areas in this disease, hand, feet, and face, was between 0.872 (with 225 g) and 0.807 (with 619 g). With regard to the ten healthy volunteers, the reliability was lower. The mean value of all 22 measured body areas was between 0.729 (with 619 g) and 0.609 (with 176 g); the mean value of *intrater* reliability of the three body areas (hand, feet, and face) was between 0.654 (with 619 g) and 0.510 (with 176 g).

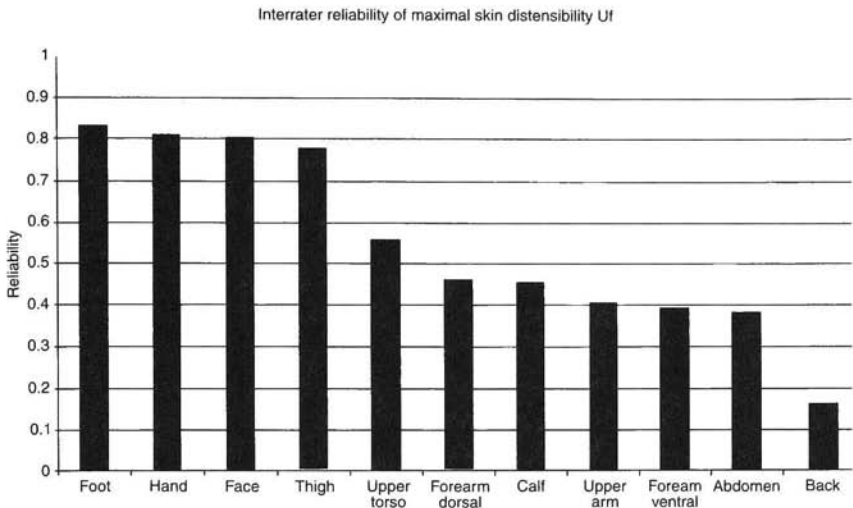
Values of *intrater* reliability of  $U_x$  (residual distention 4 s after stopping the vacuum) showed a much higher dependency on the weight of the vacuum probe, because reliability clearly dropped when using a probe weighing only 88 g. In patients with systemic sclerosis, the mean value for *intrater* reliability of all 22 body areas was between 0.837 (using 442 g) and 0.638 (with 88 g). The corresponding values for the three most relevant body areas were between 0.720 (with 442 g) and 0.312 (with 88 g). Even lower mean values could be shown in the ten healthy volunteers: between 0.696 (with 225 g) and 0.369 (with 88 g) for all 22 body areas and between 0.479 (with 619 g) and 0.239 (with 88 g) if only the three most relevant areas were measured.

The corresponding mean reliability values for the different weights with respect to the skin parameters "relaxation" ( $U_f - U_x$ ) and "elasticity" according to the definition of Agache ( $U_f/U_f - U_x$ ) were between the excellent values for maximal skin distension ( $U_f$ ) and the lowest values for  $U_x$  (data not shown). To eventually define the most appropriate, e.g., most reliable, weight of the vacuum probe, all values were subject to a ranking order considering all mean reliability values of  $U_f$  and  $U_x$  of all 22 body areas and the most relevant three body areas, hand, feet, and face. This resulted in four different ranking orders of the five weights. Summarizing the ranking orders, the weight of 442 g was clearly positioned best followed by 225 g of the vacuum probe. Three out of four times the weight of 442 g ranked first.

### *INTRATER* RELIABILITY OF MAXIMAL SKIN DISTENSIBILITY IN PATIENTS WITH SYSTEMIC SCLEROSIS

*Interrater* reliability for maximal skin distension  $U_f$  in patients with systemic sclerosis showed better results if considering only the two experienced raters. Values from all three raters were between 0.882 (right hand) and 0.033 (back left side) (Figure 11.5). Of the 22 reliability values, 11 were over 0.5, 9 of them over 0.6, and the rest lower than 0.5. Considering only the two raters familiar with the Dermagraph,





**FIGURE 11.5** Interrater reliabilities of maximal skin distensibility  $U_f$  at 11 body areas in patients with systemic sclerosis (three raters) are shown in rank order.

*interrater* reliability was between 0.830 (right foot) and 0.170 (back, right side). Of the 22 values, 19 were over 0.5, 14 over 0.6, the rest below 0.5.

The best *interrater* reliability values in patients with systemic sclerosis were calculated from measurements at the three most relevant body areas, hands, feet, and face. The corresponding excellent values were (all three raters) between 0.882 (right hand) and 0.741 (left hand). Four of the six values were over 0.8. Interestingly, the familiarity of the rater with the Dermagraph was less important at these three relevant body areas, because the variability values of the two experienced raters were very similar to all three raters (between 0.888 and 0.690), and four out of the six values were above 0.5.

### REFERENCE VALUES IN HEALTHY MALE AND FEMALE VOLUNTEERS

The highest mean reference values for maximal skin distensibility  $U_f$  (between right and left side of the body) in healthy volunteers of both genders were between 6.06 mm (abdomen in men) and 6.38 mm (upper arms in women); values are shown in Table 11.1. Mean standard deviation (between right and left side of the body) was between 0.38 mm (calves in men) and 1.34 mm (hands in women) (Table 11.1). There were significant differences ( $P$  value < 0.05) for maximal skin distensibility in 12 of 22 body areas between the two genders (Table 11.1).

Mean reference values from healthy volunteers of both genders in terms of the parameter relaxation ( $U_f - U_x$ ) were between 2.19 mm (feet in men) and 4.64 mm (abdomen in women); values are shown in Table 11.2. It was only possible to show significant differences between the two genders at four skin locations, always showing higher values in women than in men.

**TABLE 11.1**  
**Reference Values of Maximal Skin Distensibility  $U_f$  in 96 Healthy Volunteers**

Body Areas	Men	Women	Mean Diff.	P Value
Face right	5.24 ± 0.89	5.04 ± 0.80	+0.20	0.2629
Face left	5.05 ± 0.94	5.06 ± 0.96	-0.01	0.9802
Upper arm right	5.79 ± 0.96	6.50 ± 1.24	-0.71	<b>0.0023</b>
Upper arm left	5.58 ± 1.06	6.25 ± 1.11	-0.67	<b>0.0033</b>
Lower arm ventral right	4.59 ± 0.69	5.45 ± 0.88	-0.86	<b>&lt;0.0001</b>
Lower arm ventral left	4.50 ± 0.49	5.18 ± 0.77	-0.68	<b>&lt;0.0001</b>
Lower arm dorsal right	4.77 ± 0.43	5.13 ± 0.58	-0.36	<b>0.0008</b>
Lower arm dorsal left	4.79 ± 0.54	5.37 ± 0.75	-0.59	<b>&lt;0.0001</b>
Hand right	4.22 ± 0.98	4.84 ± 1.32	-0.62	<b>0.0095</b>
Hand left	4.51 ± 1.03	4.79 ± 1.37	-0.28	0.2502
Upper torso right	5.66 ± 0.61	6.26 ± 0.93	-0.60	<b>0.0003</b>
Upper torso left	5.50 ± 0.56	5.85 ± 0.64	-0.35	<b>0.0059</b>
Abdomen right	6.12 ± 0.76	6.27 ± 0.83	-0.15	0.3610
Abdomen left	6.01 ± 0.60	6.12 ± 0.81	-0.11	0.4481
Thigh right	4.63 ± 0.58	4.64 ± 0.43	-0.01	0.9197
Thigh left	4.61 ± 0.58	4.63 ± 0.44	-0.02	0.8889
Foot right	4.51 ± 0.70	4.63 ± 1.06	-0.12	0.5072
Foot left	4.26 ± 0.60	4.64 ± 0.99	-0.38	<b>0.0233</b>
Calf right	4.61 ± 0.39	4.69 ± 0.43	-0.08	0.3581
Calf left	4.48 ± 0.37	4.54 ± 0.33	-0.07	0.3601
Back right	4.83 ± 0.54	5.12 ± 0.50	-0.29	<b>0.0079</b>
Back left	4.84 ± 0.55	5.10 ± 0.52	-0.26	<b>0.0211</b>

Mean references values for the parameter “elasticity” according to the definition of Agache ( $U_f/U_f - U_s$ ) in healthy volunteers were between 1.37 (abdomen in women) and 2.14 (foot in women). Mean low values, e.g., high elasticity (lower than 1.6) were measured at the abdomen in women (1.44), at the back in men (1.50), and at the back in women (1.52). High values, e.g., low elasticity, were measured at the extremities (Table 11.3). Significant differences between the two genders were seen at eight body areas. Importantly, all measurements with regard to maximal skin distensibility, relaxation, and elasticity did not show any significant age dependency.

## DISCUSSION

The Dermagraph seems to be very reliable for measuring skin distensibility, relaxation, and elasticity at body areas that are relevant for patients with systemic sclerosis, namely, the face, hands, and feet, irrespective of being familiar with or especially trained for this device, a fact that underlines the easy handling of the Dermagraph. The reliability tests demonstrate relevant differences between the reliability values of maximal skin distension between patients and healthy volunteers. One possible explanation for this could be that the underlying area is neither homogeneous because of extensor tendons nor exactly horizontal to allow easy positioning of the apparatus

**TABLE 11.2**  
**Reference Values for Skin Relaxation  $U_f - U_x$  in 96 Healthy Volunteers**

Body Areas	Men	Women	Mean Diff.	P Value
Face right	3.02 ± 0.75	2.93 ± 0.95	+0.08	0.6275
Face left	3.01 ± 0.86	3.02 ± 0.97	-0.01	0.9385
Upper arm right	3.20 ± 0.98	3.63 ± 1.44	-0.43	0.0889
Upper arm left	3.09 ± 1.10	3.35 ± 1.10	-0.26	0.2561
Lower arm ventral right	2.53 ± 0.52	2.88 ± 0.81	-0.35	<b>0.0136</b>
Lower arm ventral left	2.38 ± 0.41	2.53 ± 0.61	-0.15	0.1663
Lower arm dorsal right	2.48 ± 0.44	2.65 ± 0.61	-0.17	0.1261
Lower arm dorsal left	2.54 ± 0.61	2.91 ± 0.89	-0.36	<b>0.0206</b>
Hand right	2.15 ± 0.83	2.98 ± 1.28	-0.83	<b>0.0002</b>
Hand left	2.51 ± 0.95	2.94 ± 1.30	-0.43	0.0639
Upper torso right	3.47 ± 0.85	4.03 ± 1.07	-0.56	<b>0.0052</b>
Upper torso left	3.20 ± 0.84	3.65 ± 0.90	-0.44	<b>0.0148</b>
Abdomen right	4.34 ± 0.96	4.72 ± 1.16	-0.38	0.0831
Abdomen left	4.28 ± 0.76	4.56 ± 1.07	-0.29	0.1328
Thigh right	2.90 ± 0.59	2.68 ± 0.57	+0.21	0.0778
Thigh left	2.86 ± 0.60	2.66 ± 0.58	+0.20	0.1010
Foot right	2.23 ± 0.58	2.33 ± 0.97	-0.11	0.5146
Foot left	2.17 ± 0.71	2.35 ± 0.84	-0.19	0.2417
Calf right	2.86 ± 0.36	2.97 ± 0.61	-0.11	0.2672
Calf left	2.73 ± 0.37	2.80 ± 0.43	-0.07	0.3910
Back right	3.31 ± 0.60	3.45 ± 0.62	-0.14	0.2697
Back left	3.27 ± 0.60	3.45 ± 1.90	-0.18	0.1581

in a perpendicular direction. In addition, patients sometimes have difficulties relaxing their periorbital muscles when the Dermagraph is measuring skin distensibility at the face. Because of the sclerosis of the skin, some of these difficulties are less pronounced in patients with systemic sclerosis, which affects mostly both hands, the face, and the feet. According to the reliability results it seems to be important to provide precise instructions to examiners who are measuring normal or little-affected skin.

With respect to gender differences, the values of maximal distensibility  $U_f$  were again higher in women with normal skin, as already shown in the earlier study testing the first prototype Sclerimeter.<sup>1</sup> The same tendency could be shown for the parameter relaxation  $U_f - U_x$ . In contrast, the parameter elasticity  $U_f/U_f - U_x$  did not show a gender specific difference but a significant difference with respect to skin localization in both genders, e.g., high elasticity at the torso and low elasticity at the extremities.

Surprisingly, a significant age dependency of measured skin parameters could not be demonstrated with the Dermagraph in almost 100 healthy volunteers 16 to 81 years of age.

Comparing the actual data with the earlier published values of the Sclerimeter, a clearly better average (of all 22 body areas) *intrarater* reliability of the Dermagraph (0.71 vs. 0.61) is demonstrated. The mean *interrater* reliability was about the same

**TABLE 11.3**  
**Reference Values for Elasticity According to the Definition of Agache**  
 $U_f/U_f - U_x$  in 96 Healthy Volunteers

Body Areas	Men	Women	Mean Diff.	P Value
Face right	1.79 ± 0.32	1.83 ± 0.44	-0.04	0.6176
Face left	1.76 ± 0.33	1.80 ± 0.50	-0.05	0.5787
Upper arm right	1.91 ± 0.39	1.95 ± 0.46	-0.04	0.6538
Upper arm left	1.90 ± 0.37	1.97 ± 0.39	-0.07	0.3635
Lower arm ventral right	1.85 ± 0.24	1.96 ± 0.29	-0.11	<b>0.0410</b>
Lower arm ventral left	1.93 ± 0.27	2.11 ± 0.32	-0.18	<b>0.0043</b>
Lower arm dorsal right	1.96 ± 0.30	1.99 ± 0.29	-0.03	0.6376
Lower arm dorsal left	1.94 ± 0.31	1.94 ± 0.35	+0.01	0.9336
Hand right	2.10 ± 0.48	1.76 ± 0.42	+0.34	<b>0.0004</b>
Hand left	1.94 ± 0.45	1.74 ± 0.37	+0.19	<b>0.0239</b>
Upper torso right	1.69 ± 0.30	1.61 ± 0.24	+0.08	0.1544
Upper torso left	1.79 ± 0.32	1.66 ± 0.28	+0.13	<b>0.0440</b>
Abdomen right	1.45 ± 0.18	1.36 ± 0.22	+0.09	<b>0.0391</b>
Abdomen left	1.43 ± 0.19	1.38 ± 0.19	+0.05	0.2145
Thigh right	1.62 ± 0.19	1.78 ± 0.25	-0.17	<b>0.0004</b>
Thigh left	1.65 ± 0.24	1.78 ± 0.26	-0.14	<b>0.0091</b>
Foot right	2.11 ± 0.43	2.17 ± 0.54	-0.06	0.5392
Foot left	2.11 ± 0.54	2.10 ± 0.48	+0.004	0.9722
Calf right	1.63 ± 0.19	1.61 ± 0.19	+0.02	0.5609
Calf left	1.67 ± 0.20	1.66 ± 0.23	+0.01	0.8037
Back right	1.49 ± 0.21	1.52 ± 0.22	-0.03	0.5264
Back left	1.50 ± 0.18	1.51 ± 0.22	-0.01	0.8606

Note: The lowest possible value of 1 denotes highest elasticity.

(0.55 vs. 0.57), but the average value of 0.81 in the three most relevant body areas in patients with systemic sclerosis, hand, foot, and face, was much higher than with the earlier Sclerimeter (0.47). In summary, the Dermagraph shows a more reliable measuring process of skin distensibility in the most relevant body areas, hand, foot, and face, for patients with systemic sclerosis.

To the authors' knowledge the only comparable device to measure skin distensibility with a vacuum is the SEM 474 Cutometer, which measures immediate and late distensibility as well as immediate and definite retraction of the skin.<sup>46</sup> In 19 patients with a late form of systemic sclerosis Enomoto et al.<sup>46</sup> measured an excellent *intrarater* reliability of 0.94 and an *interrater* reliability of 0.94 for maximal skin distensibility at 74 body areas. The study of Enomoto is not directly comparable to this one because of the different patient population (only consideration of patients with a late stage of systemic sclerosis). The Dermagraph has been developed to examine the skin of patients with systemic sclerosis early on and prospectively over time with the option to correlate early skin disease with disease outcome (potential complications of internal organs). Therefore, of most interest were patients with an early or intermediate stage of systemic sclerosis (examination on *interrater* reliability)

or healthy volunteers (half of people in examinations of *intra-rater* reliability). To compare the two devices directly, an examination with the Cutometer must be undertaken in patients with early and intermediate stages of systemic sclerosis, as well.

The Dermagraph can be used in longitudinal studies in patients with systemic sclerosis with or without testing new therapeutic agents by in-house rheumatologists, dermatologists, and internists (transplantation units) as well as for physicians seeing outpatients with systemic sclerosis and similar skin diseases. Whether the Dermagraph can be helpful in other diseases, such as reflex algodystrophy, still has to be shown. The most relevant and important task ahead is to show whether the Dermagraph and other devices offer an advantage in predicting disease outcome in patients with systemic sclerosis. This must be done in prospective studies comparable to the low vs. high penicillamine trial.<sup>7b</sup>

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# 12 Hardware and Measuring Principles: The Durometer

*Marco Romanelli and Vincent Falanga*

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## INTRODUCTION

The mechanical properties of the human skin are complex; although the skin is readily accessible, it is always a difficult task to identify simple and noninvasive measurement methods suitable for a specific skin parameter. This chapter describes a novel and simple instrument called a durometer, which is now used to assess and quantify the degree of skin hardness. The durometer is an engineering instrument widely employed in industry to measure the hardness of metals, plastic, rubber, and other nonmetallic materials. The instrument has been applied in the last few years in several medical conditions where skin hardness is a clinical feature of the disease and where there is a need for quantification of hardness for prognostic and therapeutic reasons.

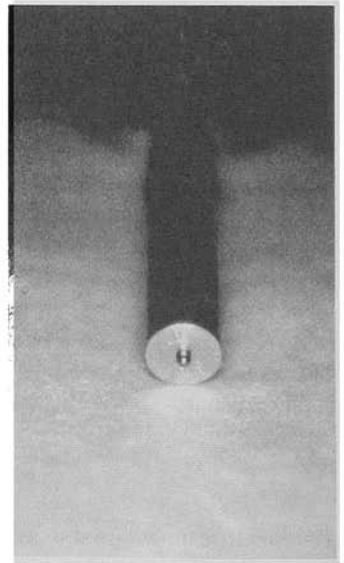
## THE MEASURING SYSTEM

The first instrument used to assess skin hardness was a Rex durometer (model 1700, Rex Gauge Company, Inc., Glenview, IL). This instrument is the international standard for measuring the hardness of rubber, plastic, nonmetallic materials, and soft

tissue such as skin. The durometer is a portable hand-held device, which is provided with a calibrated gauge that registers linearly the relative degree of hardness on a scale of units divided from 0 to 100 (Figure 12.1). This feature is the result of a spring-loaded interior that senses hardness by applying an indentation load on the specimen. The bottom of the durometer has a small, dull indenter which is retractable and is responsible for the measurements registered on the gauge (Figure 12.2). The instrument is rested by gravity against the skin and must be held in a vertical position (Figure 12.3). Initial hardness is defined as that recorded within 1 s of firm contact of the durometer with the skin. For many materials, this initial reading remains unaltered after the first second of measurements (near perfect elasticity). Imperfect elasticity is referred to as plasticity and is observed when continued contact of the durometer with the surface leads to a higher reading. The degree of this plasticity is referred to as creep, and in animal tissue the amount of creep is minimal. The type of durometer used in dermatology to assess skin hardness is Model 0 which is provided with an 822 g springload. To eliminate operator error, the company has improved the first model with a specified amount of weight (400 g), located on top of the instrument, which is used to depress the indenter without any additional pressure. This constant load principle provides a more consistent reading to the operator every time the gauge is applied to the skin. For measurements on the skin, the durometer is used at 25°C and four consecutive readings are usually taken at the same site. Between readings the durometer is reset to 0 and measurements are made with the patient supine, thus avoiding muscle tension or contraction.



**FIGURE 12.1** Durometer model 1700 (Rex Gauge), type 00, with (right) and without (left) constant load weight.



**FIGURE 12.2** Bottom of the durometer with the retractable indenter responsible for detecting the degree of hardness.

**FIGURE 12.3** Durometer rested by gravity over an area of lipodermatosclerosis in a patient with venous insufficiency and a chronic wound.



## ACCURACY AND REPRODUCIBILITY OF THE MEASUREMENTS

Durometer readings obtained with four consecutive determinations at the same site in each subject and in different clinical conditions differed constantly by less than 5%.<sup>1,2</sup> The durometer was tested for interobserver and intraobserver variability in a study<sup>3</sup> where patients with morphea, a localized form of scleroderma, were investigated for skin induration. The durometer was used in combination with a skin scoring system called MSS (Modified Skin Score).<sup>4</sup> The interobserver variability in the durometer score was only 0.5% and was even lower than the interobserver variability of the MSS (0.5 vs. 2.2%). The intraobserver variability, which is the variation in readings obtained by the same observer, was estimated as 0. The correlation between the total MSS and the durometer score was approximately 0.5. Insensitive durometer readings were found in different areas of the skin, such as the forehead and dorsal digit, where subcutaneous tissue is less represented. The hypothesis of underlying bone or tendon structure giving higher readings at these sites was raised as a possible explanation of this failure to discriminate between normal and indurated skin.<sup>1</sup>

## MEDICAL APPLICATIONS

### SCLERODERMA

Sclerodermatous skin is characterized by induration of the lower dermis and directly underlying tissue, which could be affected diffusely as in systemic sclerosis or in a more localized involvement as in morphea. The degree and extent of skin hardness in scleroderma are used as a prognostic value for the disease, and are generally assessed subjectively using a clinical skin scoring system. Objective measurements of skin involvement in scleroderma have included the use of ultrasonography, skin elastometers, transcutaneous oxygen tension measurements, and also such more-sophisticated techniques as magnetic resonance imaging. All these methods were able to provide useful information about the extent of skin involvement but are generally considered not practical for sequential measurements in clinical practice. Falanga and Bucalo<sup>1</sup> were the first to describe the use of a durometer in patients with systemic sclerosis. They investigated six anatomic sites in 12 patients and in 12 control individuals using the durometer in combination with a skin severity score. A direct relationship between the skin severity score and durometer readings was present for all anatomic sites except the forehead: the higher the skin score, the

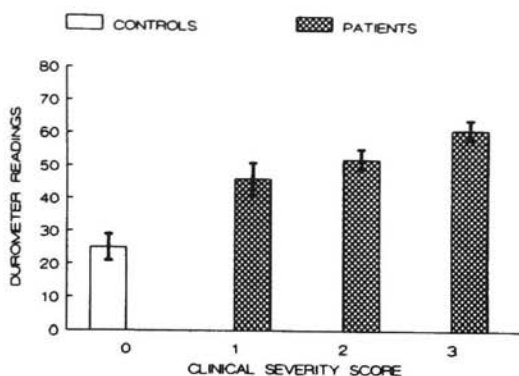
greater the amount of deflection measured with the durometer ( $p = 0.0032$ ,  $p = 0.0002$ , and  $p = 0.0005$  for skin scores of 1, 2, and 3, respectively). Moreover, the durometer was able to differentiate between increased levels of skin hardness (Table 12.1). In this study no statistically significant relationships were found among body weight, skin score, diameter of anatomic sites measured, and durometer readings. The use of the durometer was not associated with any pain or discomfort. Same results of increased skin hardness in morphea were obtained by Aghassi et al.<sup>2</sup> in a study where the durometer was also used in combination with a laser Doppler perfusion imager. In that study the authors found a relationship between age and durometer readings over the ventral aspect of the forearm in normal controls. Skin hardness rises from birth, reaches a constant level by puberty, and then remains steady until age 65 years, when the skin begins to lose its firm quality progressively. Women had lower durometer readings compared with men, and the instrument was able to define contiguous areas of different degrees of sclerosis in morphea lesions.

The efficacy of treatment has been investigated in patients with localized scleroderma by means of durometer readings in two different studies. Seyger et al.<sup>5</sup> evaluated the effect of low-dose methotrexate (15 mg/week) in nine patients with widespread morphea in a 24-week trial using the durometer and other clinical assessments to monitor the therapeutic regimen. A total of seven patients of nine showed a decrease of durometer readings at the end of the trial, with mean values changing from  $101 \pm 13.9$  before treatment, to  $89.7 \pm 10.3$  after treatment ( $p = 0.07$ ). The greatest improvement in durometer score among the sites examined was in the arm region ( $p = 0.03$ ). In another study, Karrer et al.<sup>6</sup> evaluated the efficacy of topical photodynamic therapy by means of durometer readings and clinical score in five patients with progressive localized scleroderma who had failed to respond to other therapies. In all patients the therapy was highly effective as measured by durometer score, which showed a mean reduction of 20% after a treatment period of 6 months.

## LIPODERMATOSCLEROSIS

Chronic lipodermatosclerosis is characterized by hyperpigmented indurated skin on the medial aspect of the leg and is common in patients with venous insufficiency. The severity of induration of lipodermatosclerosis has been associated with poor ulcer healing. Nemeth et al.<sup>7</sup> reported a correlation between the degree of skin induration in lipodermatosclerosis and ulcer healing. They used a clinical score to assess skin induration and found that the lipodermatosclerosis was less severe in patients who had ulcers that healed than in those who did not. Durometer testing of skin hardness was performed in a group of patients with lipodermatosclerosis with and without venous ulcers.<sup>8</sup> A clinical scoring for hardness by a blinded observer was used in combination with durometer measurements at a skin site midway between the upper and lower margin of lipodermatosclerosis. Measurements of transcutaneous oxygen pressure (TcPO<sub>2</sub>) at the same site were also performed. Compared with normal skin in control subjects, increased skin severity scores were associated with higher durometer readings ( $p < 0.01$ ). This direct correlation between clinical scores and durometer readings was linear ( $r = 0.9621$ ). The durometer was

**TABLE 12.1**  
**Durometer Readings in Patients with Lipodermatosclerosis and Venous Ulcers Who Had Different Skin Scores**



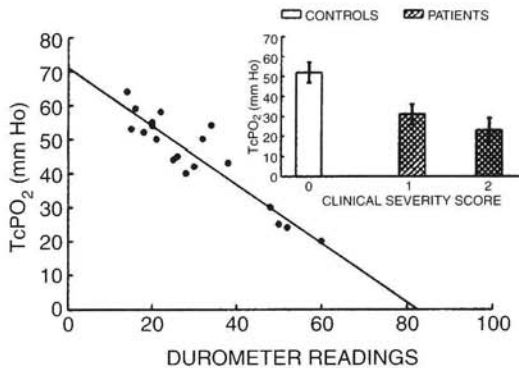
Source: Romanelli, M. and Falanga, V., *J. Am. Acad. Dermatol.*, 32, 188, 1995. With permission.

able to differentiate between increased levels of skin hardness. Thus, a skin severity score of 2 reflected a higher durometer reading than that of a skin score of 1 ( $p = 0.0016$ ). An inverse and statistically significant relationship ( $r = 0.431$ ;  $p = 0.0079$ ) between  $TcpO_2$  measurements and durometer readings was found in both patients and control subjects (Table 12.2). The correlation between  $TcpO_2$  measurements and durometer readings found in that study confirms the hypothesis of poor oxygen diffusion through dense and thickened skin as occurs in lipodermatosclerosis. LeBlanc et al.<sup>9</sup> used the durometer to assess the area of lipodermatosclerosis around venous ulcers and to obtain a map of skin induration. Their hypothesis was that maximum skin induration correlated with the presence of ulcers. The authors found that venous ulcers are located in skin that is most affected by lipodermatosclerosis. Durometer measurements showed a progressive and linear decrease from the top of the ulcer's edge to the knee ( $r = 0.925$ ). In the same study, the authors tested 14 patients with pitting edema and 8 controls without edema. There were no significant differences in durometer readings in patients with minimal or more severe edema ( $p > 0.05$ ) regardless of anatomic location.

## NEUROPATHIC FOOT

Patients with diabetes with peripheral polyneuropathy are at increased risk for foot ulceration. One of the key events in the pathogenetic pathway to neuropathic ulceration is hyperkeratosis, which develops in areas of increased pressure. Nonenzymatic glycosilation and autonomic dyhidrosis have been implicated in the pathogenesis of skin hardening. Piaggese et al.<sup>10</sup> measured skin hardness at three different sites on the foot of a selected group of patients with diabetes, avoiding areas with bony prominences. Skin hardness was more pronounced in neuropathic patients than in non-neuropathic patients and controls ( $p < 0.01$ ). Among neuropathic patients, those

**TABLE 12.2**  
**Relation between  $TcPO_2$  Measurements and Durometer Readings (scattergram) or Clinical Severity Score (inset) in Patients with Lipodermatosclerosis**



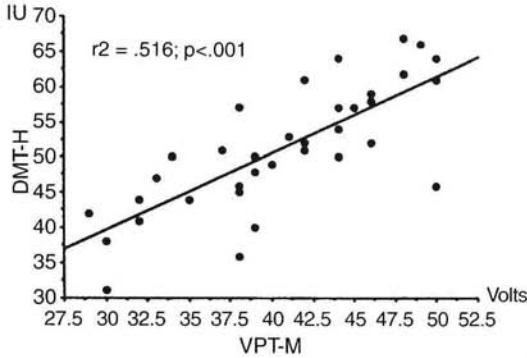
Source: Romanelli, M. and Falanga, V., *J. Am. Acad. Dermatol.*, 32, 188, 1995. With permission.

with metatarsal hyperkeratosis had significantly higher durometer readings compared with those without hyperkeratosis ( $p < 0.001$ ). Subjects were also evaluated for neuropathy by determining the vibration perception threshold (VPT) with a biothesiometer. This instrument is an electrical device provided with a vibrating probe, which is applied to the test site and to which an increasing vibrating intensity is applied. The lowest of three intensities of vibration defines the VPT. In that study, a significant positive correlation was found between durometer readings and VPT at the malleolus ( $r = 0.516$ ) and at the allux ( $r = 0.624$ ) in neuropathic patients (Table 12.3).

## CONCLUSIONS

Durometry is a technique for measuring skin hardness. The method takes advantage of the ability of the durometer to sense and record hardness on a linear scale, and it is unique in its simplicity and ease of use. Measurements with the durometer are highly reproducible in the same subject and in persons with the same degree of skin induration. Data obtained indicate that the durometer may be insensitive when used in areas of skin where the subcutaneous tissue is not well represented. At this stage the instrument is used as a standard noninvasive tool to measure skin hardness in systemic sclerosis. The authors believe that durometry could be applied in other dermatologic diseases to assess skin involvement and to monitor the efficacy of treatment.

**TABLE 12.3**  
**Relation between Vibration Perception Threshold at Malleolus (VPT-M) and Skin Hardness Measurement at Heel (DMT-H) in Patients with Neuropathic Diabetes**



Source: Piaggese, A. et al., *J. Diabet. Complications*, 13, 129, 1999. With permission.

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# 13 Hardware and Measuring Principles: The Ballistometer

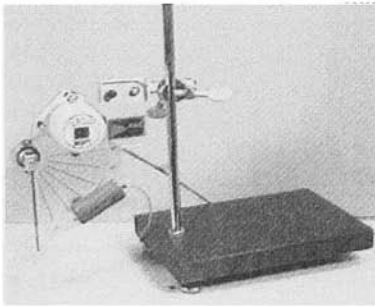
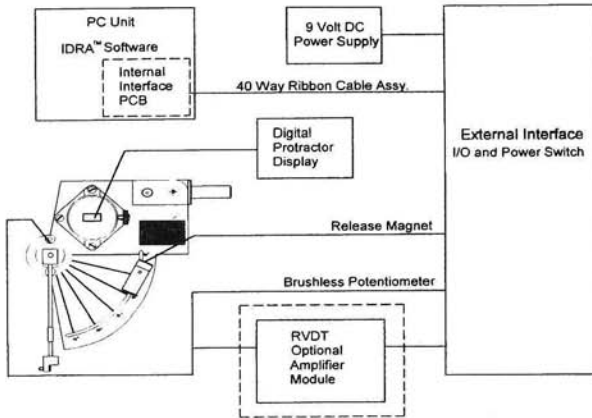
*Peter T. Pugliese and John R. Potts*

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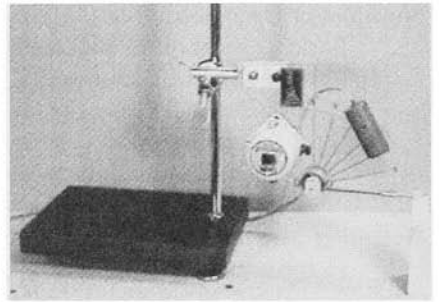
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## DESCRIPTION OF THE INSTRUMENT

The IDRA<sup>®</sup> (Integrated Dynamic Rebound Analyzer) ballistometer consists of ten main parts: an external interface unit, a 9-v DC power supply, an internal PC interface card, an interconnecting cable, a holding magnet, a rotary transducer, a ballistic hammer, a multipositional mounting plate, a fixed stand, and IDRA control and data processing software (Figure 13.1).



(A)



(B)

**FIGURE 13.1** Transducer mounting plate; (A) horizontal; (B) vertical. Illustration of the relationship of the parts on the IDRA mounting plate assembly. Shown is a lightweight ballistic hammer, rotary transducer, multipositional mounting plate, magnet for holding and releasing the ballistic hammer at a fixed angle, and a rigid support stand. Also shown is an optional attachment and a digital protractor system, which is used for accurately and conveniently calibrating the angular displacement of the hammer to within  $0.1^\circ$ . Alternatively, calibration of the angular displacement may be done by using the numbered angle markings on the mounting plate, which are spaced at  $15^\circ$  intervals over a quadrant.

## PRINCIPLES OF OPERATION

IDRA is a PC-based ballistometer and employs a dynamic technique for assessing intrinsic viscoelastic properties of skin. That is, it is an instrument for determining physical properties that do not depend on the method of measurement. For relatively soft materials, such as skin, the measurement technique involves a lightweight hammer, anchored at one end, that free-falls onto the test surface under gravitational force. The resulting hammer oscillatory displacement–time data are recorded and analyzed, and characteristic physical parameters are determined. Ballistometry is a method of choice for characterizing the viscoelasticity of skin, since it is nondestructive, noninvasive, fast, and easy to use.

## BASIC CONCEPT OF THE MEASUREMENT

The IDRA ballistometer system accepts two types of suitable rotary transducers: RVDTs (Rotary Variable Differential Transformers) and Brushless Potentiometers (Hallpot<sup>®</sup> transducers). Both RVDT and Hallpot transducers give highly reproducible DC analogs, with excellent linearity, over a wide range of angular displacement. The Hallpot used in an IDRA system is custom-made for third-party research and development by Elweco, Inc., and incorporates several superior, critical design features such as miniature, ultralow-friction bearings with nonviscous lubricant, very wide sensor bandwidth, and excellent reproducibility and linearity for up to 60° angular displacement.

An RVDT model R30A transducer, manufactured by Lucas, was employed for the studies discussed in this chapter. This transducer has miniature, ultralow-friction bearings and has sufficient bandwidth to permit accurate recording of the dynamic angular displacement–time response of the ballistic hammer, as it contacts and rebounds from the surface of the skin. RVDTs are essentially bipolar devices with four linear regions (in which the output voltage is proportional to the angular displacement) and two null points. A properly calibrated RVDT, in combination with its AC–DC amplifier, produces a DC signal that is directly proportional to the angular displacement of the transducer shaft and attached ballistic hammer. The IDRA system design permits facile alignment of the RVDT optimal null point, the long axis of the hammer, and the angular markings on the mounting plate. The highest precision is achieved by nulling the RVDT at the midpoint of the full angular displacement range.

As shown in Figure 13.1A, the mounting plate is positioned for horizontal impact with a test surface. Vertical impact with a test surface is achieved by simply rotating the mounting plate 90° counterclockwise, as shown in Figure 13.1B. The accuracy, reproducibility, and relevancy of characteristic parameters, determined by ballistometry, depend markedly on the skin elasticity, design of the ballistic hammer, testing and data processing techniques, dynamic measurement range, and the test quadrant selected. Significant surface movement during a measurement cannot be tolerated. A 95% measurement success rate is easily achieved with proper measurement technique. Unacceptable surface movement is automatically detected and flagged in IDRA software by comparing the baseline readings just before the hammer is released to those at steady state.

## BASIC PHYSICS OF BALLISTOMETRY

The hammer is a rigid body that rotates about a noncentroidal axis and the basic scalar equation needed to represent the motion is

$$\sum M_o = I_o \alpha \quad (13.1)$$

where  $\sum M_o$  is the algebraic sum of the moments of the external forces about the axis of rotation ( $o$ ),  $I_o$  is the moment of inertia of the hammer about the axis of

rotation, and  $\alpha$  is the angular acceleration of the hammer. This is a second-order nonlinear differential equation and has no closed-form solution.

For either vertical or horizontal contact with the skin, the potential energy of the hammer can be calculated from the mass of the hammer, the distance from the center of rotation to the hammer's center of gravity, and the angular displacement of the hammer, with respect to the test surface. The horizontal or vertical position of the arm is assumed to be  $0^\circ$ , for reference.

#### **Potential Energy of the Hammer for Horizontal Impact**

$$\text{P.E.} = \text{mass} \times \text{distance} \times (1 - \cos(\text{angular displacement})) \quad (13.2)$$

#### **Potential Energy of the Hammer for Vertical Impact**

$$\text{P.E.} = \text{mass} \times \text{distance} \times \sin(\text{angular displacement}) \quad (13.3)$$

These formulae represent a simplified instrument model. They assume that the relative potential energy of the hammer is zero at the horizontal or vertical position, and that the angle of the hammer in contact with the surface at steady state, i.e., the contact angle, is  $0^\circ$ . In practice, it is more convenient to allow for some measurement-to-measurement variation in the actual contact angle, which is recorded and included in accurate estimates of the characteristic parameters.

The angular displacement of the hammer with time is accurately recorded during a measurement, which permits calculation of the angular velocity, and angular acceleration of the hammer, at various times. The angular velocity of the hammer, at the instant of impact with the test surface, can also be calculated from the formula for the kinetic energy of hammer rotation, with the value of kinetic energy set equal to the potential energy of the hammer at a previous peak displacement.

#### **Kinetic Energy of the Rotating Hammer**

$$\text{K.E.} = \frac{1}{2} \times \text{moment of inertia} \times (\text{angular velocity})^2 \quad (13.4)$$

The moment of inertia of the hammer may be accurately determined from its oscillatory period during a free swing experiment, by treating the hammer as a compound pendulum. The value of the moment of inertia determined from a free-swing experiment agrees closely with that calculated for the hammer using formulas for the moments of inertia of symmetrical bodies.

The product of its moment of inertia and angular velocity is defined as the angular momentum of the hammer. The average force of the hammer impact on a test surface can be estimated from the formula for angular impulse, which is the change in angular momentum.

#### **Force of Impact of Hammer with Test Surface**

$$\text{Force} = \frac{\text{moment of inertia} \times (\text{change in angular velocity})}{((\text{distance from hammer tip to center of rotation}) \times (\text{time for arm to stop}))} \quad (13.5)$$

For hammers of sufficient length, to a first approximation, the uniaxial deformation of the test surface can be estimated by multiplying the distance from the hammer tip to the center of rotation and the sine of the maximum angle of deformation.

$$\text{Deformation} = (\text{distance from hammer tip to center of rotation}) \times \sin(\text{maximum angle of deformation}) \quad (13.6)$$

Typical parameter values used for computer calculation of force and deformation, in the IDRA system, include hammer free-swing period = 0.66 s, hammer center of gravity distance = 5.62 cm, hammer mass = 8.75 g, and hammer tip distance = 11.8 cm. All other parameters were determined from program analysis of transducer signals collected with 12 bit A/D conversions under computer interrupt control.

### INTRINSIC PARAMETERS FOR CHARACTERIZING MATERIALS

Figure 13.2 shows the basic response curve for the IDRA ballistometer system. As shown in Figure 13.2, the oscillatory angular displacement of the hammer is recorded with time. The baseline, shown as a line above and parallel to the time axis, is the position of the hammer when it is resting on the test surface. Four major parameters are defined as measures of viscoelasticity (AMP, COR, CAC, and stiffness) and will be discussed in detail below. Angular displacement–time data above the baseline are used to determine AMP, COR, and CAC, whereas that below the baseline is used to determine stiffness.

The AMP is defined as the amplitude or angular displacement measured with respect to the baseline, and is a measure of elasticity. Fthenakis et al.<sup>1</sup> reported the

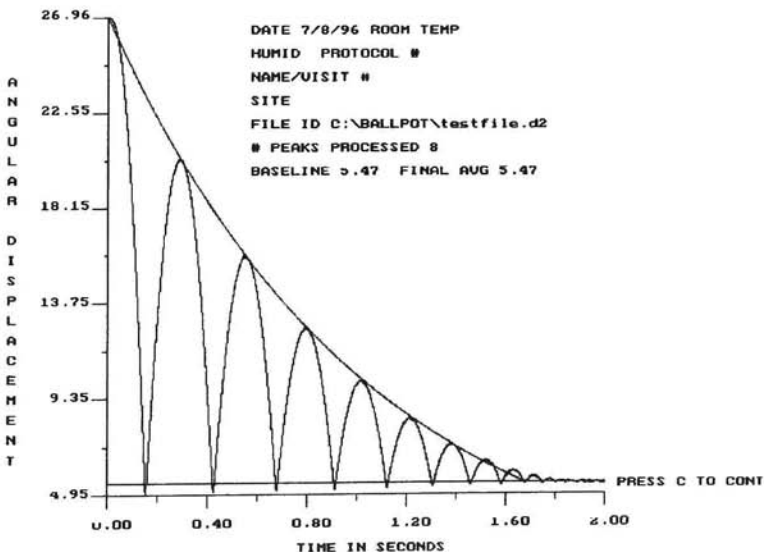


FIGURE 13.2 IDRA basic response curve (test material).

use of AMP to measure changes in elasticity in cosmetic claims studies. The ballistometer employed in these studies was based on principles discussed by Hargens.<sup>2</sup>

The COR, or coefficient of restitution, first applied by Tosti et al.,<sup>3</sup> is a measure of elasticity defined as the ratio of the hammer rebound speed to its speed just before impact. The COR is calculated two ways: (1) as the ratio of rebound and initial hammer speed, and (2) as the square root of the P.E. ratio of two adjacent peaks.

The CAC, or cutaneous absorption coefficient, first applied by Adhoute et. al.,<sup>4</sup> is also a measure of elasticity defined as a dynamic time constant; it presumes that hammer impact energy is lost exponentially with time, and is calculated from peak heights.

Stiffness, first reported by Potts and Pugliese,<sup>5</sup> provides stress–strain information and is defined as the ratio of the hammer impact force to the skin deformation. Stiffness is defined as the force of impact in newtons divided by the deformation in centimeters. Stiffness provides information on the stress–strain behavior of a test material.

For accurate simultaneous determination of COR, CAC, stiffness, and other parameters, an IDRA system employs interrupt-driven, 12 bit A/D data collection, at rates of up to 8000 data points/s, coupled with optimal parameter calculation techniques. The instrument bandwidth is adequate to permit accurate free-fall, contact, and rebound angular displacement measurements to  $\pm 0.05^\circ$  with nonlinearity of  $0.5^\circ$  over a range of  $60^\circ$

## Determination of Coefficient of Restitution

### From Hammer Speed

$$\text{COR}_W = W_R/W_I \quad (13.7)$$

where  $W_R$  and  $W_I$  are the rebound and impact angular speeds.

### From Peak Amplitudes

Vertical impact with skin

$$\text{COR} = \text{SQRT} [\sin(\text{AMP}_R) / \sin(\text{AMP}_I)] \quad (13.8)$$

where  $\text{AMP}_R$  and  $\text{AMP}_I$  are the rebound and impact peak amplitude.

Horizontal impact with skin

$$\text{COR} = \text{SQRT} [(1 - \cos(\text{AMP}_R)) / (1 - \cos(\text{AMP}_I))] \quad (13.9)$$

where  $\text{AMP}_R$  and  $\text{AMP}_I$  are the rebound and impact peak amplitude.

## Determination of Cutaneous Absorption Coefficient

$$(\text{AMP}_n + \text{BL}) = (\text{AMP}_0 + \text{BL}) * \exp(-Kt_n) \quad (13.10)$$

*Copyrighted Material*

where  $K$  is the cutaneous absorption coefficient,  $t_n$  is the time at the  $n$ th peak, AMP refers to the angular displacement vs. the baseline at the peaks, and BL the baseline displacement from the horizontal or vertical.  $K$  is determined as a one-parameter fit of the exponential equation, above.  $K$  is also calculated for peak amplitudes, assuming exponential behavior, using the following formula:

$$K = - (1/t_n) * \log ((AMP_n + BL)/(AMP_0 + BL)) \quad (13.11)$$

where  $t_n$  is the time at the  $n$ th peak.

### Determination of Stiffness

As already stated, stiffness is defined as the force of impact in newtons divided by the deformation in centimeters. It is the slope of the hammer impact force vs. surface deformation curve, which is shown in Figure 13.3.

The amplitude, impact force, stiffness, CAC, surface deformation, COR calculated from peak amplitudes, and COR calculated from angular speeds are tabulated for sequential rebounds in IDRA as shown in Figure 13.4. These processed data are automatically stored on disk in an IDRA system as an ASCII file, which may be easily imported into commercial spreadsheets for further data processing and study. Raw data for each study are also stored on disk in ASCII format.

The COR and CAC place less demand on instrumentation, since they are generally determined from peak values of angular displacement. CORs can be determined with a precision of 1% and CACs to within 1 to 2%. In contrast, stiffness, which is defined as the force of impact of the ballistic hammer divided by the

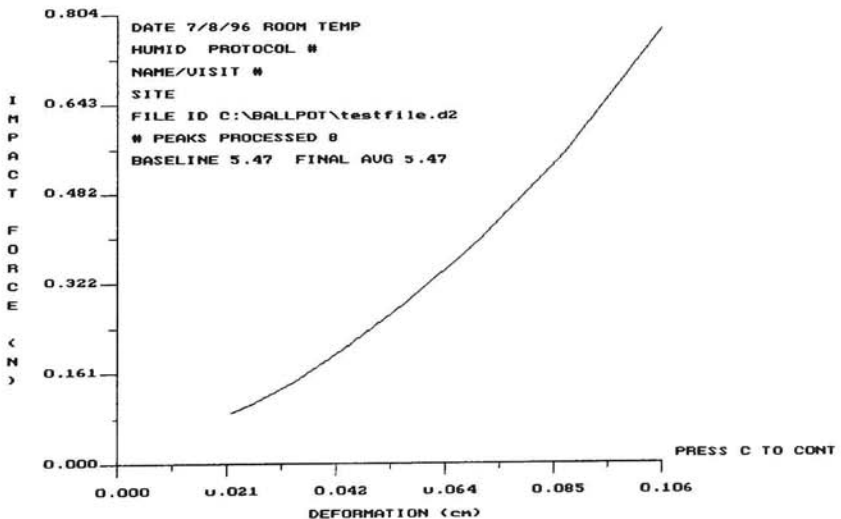


FIGURE 13.3 Impact force vs. surface deformation.

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DATE 7/8/96 ROOM TEMP
HUMID PROTOCOL #
NAME/VISIT #
SITE
FILE ID C:\BALLPOT\testfile.d2
# PEAKS PROCESSED = 8
BASELINE 5.47 FINAL AUG 5.47
AUG FIT M = -0.95+/-0.02 B =27.0
AVERAGE CAC = 0.95 STD DEV = 0.02

AMP F(N) STIFF CAC DEFORM COR CORU
14.95 0.804 7.59 0.97 0.106 0.75 0.72
10.47 0.565 6.51 0.96 0.087 0.76 0.77
7.15 0.397 5.67 0.96 0.070 0.76 0.77
4.71 0.276 4.96 0.96 0.056 0.76 0.72
2.96 0.189 4.33 0.96 0.044 0.75 0.75
1.78 0.128 3.75 0.95 0.034 0.74 0.74
1.05 0.088 3.29 0.93 0.027 0.75 0.68
0.56 0.070 3.18 0.92 0.022 0.71 0.61

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PRESS C TO CONT

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FIGURE 13.4 Tabulated data for sequential rebounds.

associated uniaxial surface deformation, requires instrumentation with wide bandwidth and high angular resolution. The data used to determine stiffness is below the baseline with displacements ranging only a few degrees over a time period of milliseconds. Stiffness can be determined with a precision of 5 to 6% for skin, given an instrument calibration technique that is optimal for the simultaneous measurement of all three parameters. With more optimal calibration conditions set for the determination of stiffness, measurement precision can be significantly improved for this parameter.

## MEASURING WITH THE BALLISTOMETER

The instrument described above was used in a clinical evaluation of viscoelastic properties of the forearm in 70 female subjects.

### METHODS AND MATERIALS

An IDRA ballistometer was used in this study. The study group consisted of 70 female subjects, in good health, and they were instructed not to use skin care products or soap on their forearms for 10 days prior to the test day. All subjects signed an informed consent document before entering the study. Table 13.1 shows the age distribution of the test subjects.

### PROCEDURE

The volar surface of the right forearm was used as the test site. Subjects were seated in a comfortable though rigid chair and their right forearm was extended onto a table. Placement of the arm in relation to the ballistometer is critical to obtaining reproducible results. Relaxation of the subject is essential for an accurate measurement. Prior



**TABLE 13.1**  
**Age Distribution of Subjects (years)**

35–39	40–44	45–49	50–54	55–65
CB	LF	MT	DK	JK
DH	CA	DP	SE	SS
DC	DW	CZ	GS	PP
ED	AF	BS	LP	DV
RF	PB	KE	BM	PL
VC	MM	PK	LC	BW
CB	LW	PJP	RE	PH
CA	VC	LR	MC	MD
MY	SW	SE	RT	PW
DW	LS	BM		YG
VZ	AN	GS		JC
	PB	LB		RR
	PR	DF		GW
	CG	LF		PP
	CR	SS		SN
	KR	JR		
	PB			
	KH			
	KO			

to making the measurement, the subject is instructed in all aspects of the procedure to help achieve relaxation. The zero position of the ballistometer arm is calibrated by placing the hammer against the skin, and the instrument is adjusted to zero following the instructions supplied by the manufacturer. This zero point is taken as the baseline of the graph that will be generated in the computer. The measurement is made by releasing the hammer from the magnetic holder electronically.

## RESULTS

The following parameters were generated by the computer program from the input data for each subject: amplitude, stiffness, cutaneous absorption coefficient, and coefficient of restitution.

### AMPLITUDE

The amplitude is a measure of elasticity as it relates to the rebound energy of the skin. The amplitude decreases as the subject's age increases as shown in Figure 13.5.

### STIFFNESS

Skin stiffness relates to "skin hardness" and is a function of deformation of the skin on impact. It is expressed as a ratio of the impact force to the skin deformation and

thus represents a true stress-strain parameter. This is a new measurement value obtained from the ballistometer, first reported by Potts and Pugliese.<sup>5</sup> The stiffness value has an inverse relationship to age until the fourth to fifth decade, after which it increases sharply with age in females. This relationship is shown in Figure 13.6.

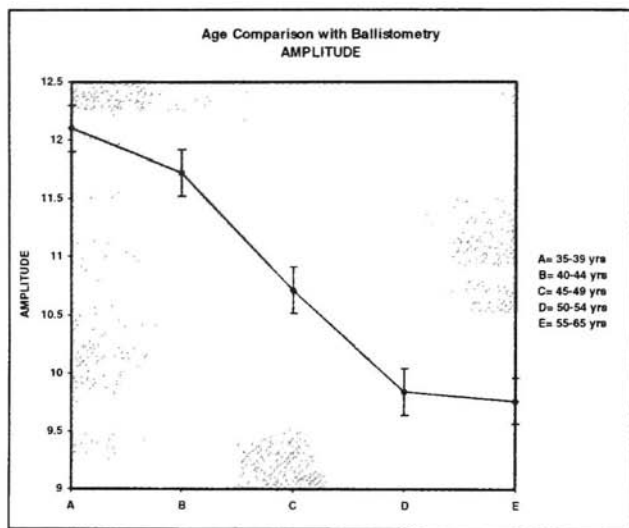


FIGURE 13.5 Amplitude.

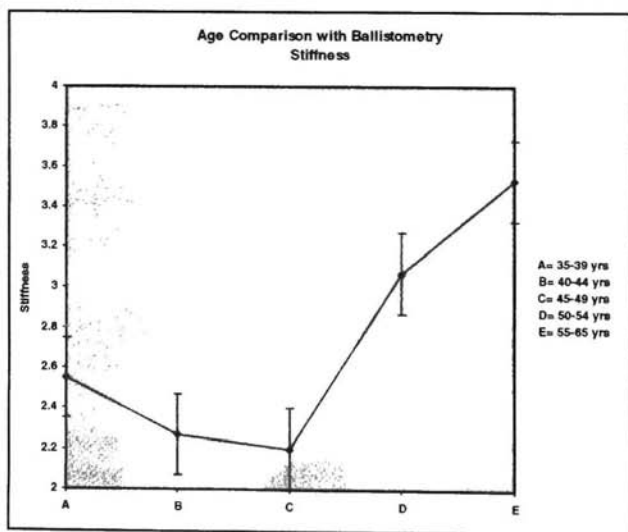


FIGURE 13.6 Stiffness.

### CUTANEOUS ABSORPTION COEFFICIENT

The CAC is a measure of the elasticity defined as a dynamic time constant and presumes that the hammer impact energy is lost exponentially with time. In this study the CAC increases with age, as shown in Figure 13.7.

### COEFFICIENT OF RESTITUTION

The COR represents the ratio between the hammer rebound speed to the hammer speed just before the impact on the skin. The COR increases directly with age as is shown in Figure 13.8.

## DISCUSSION

The three basic parameters reported by previous investigators, amplitude, CAC, and COR, are confirmed in this study. Amplitude and COR decrease with age, while COR increases with age. These three parameters move in the direction one would expect as the subject's age increases. The stiffness parameter, however, shows a biphasic curve when plotted as the subject's age increases.

This phenomenon might be explained if one considers first that all the subjects were female, and second that the ages of the subjects ranged from 35 to 49 years during the period that the stiffness decreased; a period of life for females representing the maximum effect of estrogen on connective tissue. It is well known that estrogen stimulates collagenase production by fibroblasts, a mechanism responsible for endometrial sloughing in the menstrual cycle; however, this action of collagenase

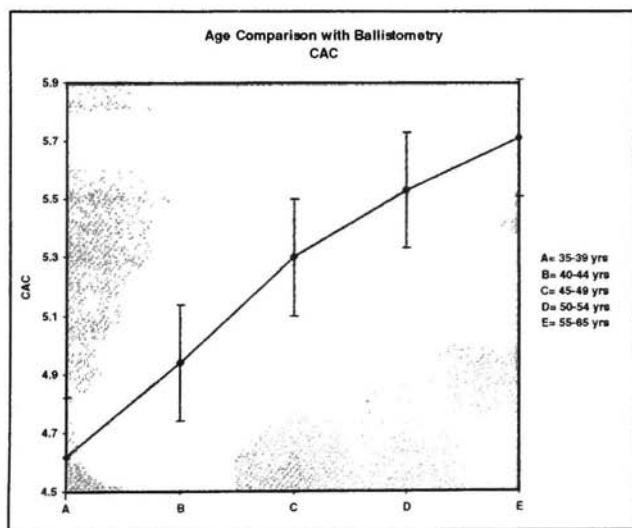


FIGURE 13.7 CAC.

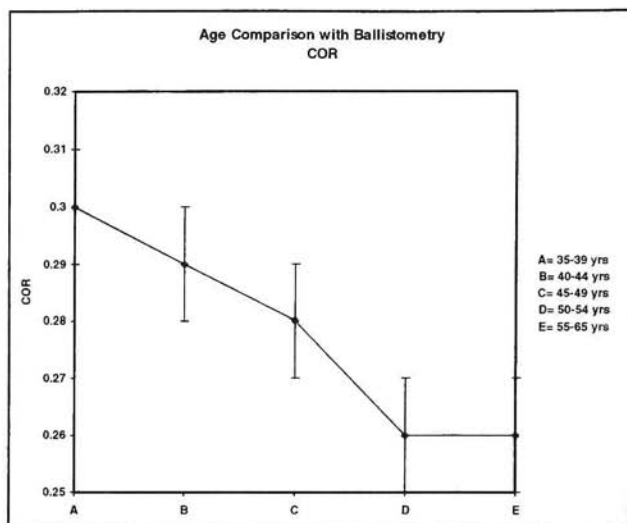


FIGURE 13.8 COR.

is decreased, but does not diminish entirely.<sup>6</sup> Cross-linking of collagen and lack of production of new collagen would contribute to overall stiffness.

## CONCLUSIONS

The IDRA ballistometer is described in detail and clinical data presented using this instrument to evaluate viscoelastic properties of the skin of 70 female subjects. The ballistometer is a sensitive and accurate means of determining viscoelastic properties of skin. It is noninvasive, offers a quick and easy evaluation, and has a wide dynamic measurement range. It measures four parameters: amplitude, stiffness, cutaneous absorption coefficient, and coefficient of restitution, three of which have been previously reported. Stiffness is reported in this chapter as an additional parameter. The data obtained in the clinical study on 70 female subjects show a decrease in the values with age for amplitude and the coefficient of restitution, while the cutaneous absorption coefficient shows a direct increase with age (Figure 13.9). Stiffness follows a biphasic curve decreasing to age 50 and increasing sharply after age 50.

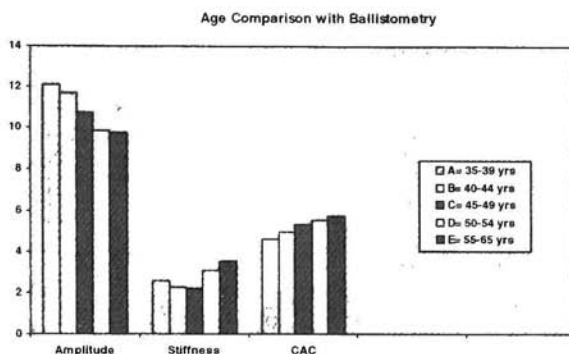


FIGURE 13.9 Age comparison with ballistometry.

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# 14 Hardware and Measuring Principles: The Microindentometer

*Christopher J. Graves and C. Edwards*

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## INTRODUCTION

The stratum corneum provides an important physical barrier that protects the body from desiccation, infection, and minor traumata. The “competence” of the stratum corneum in providing physical protection against injury depends on its biomechanical properties. This protective property is often thought of as “hardness” but is better described as increased stiffness, tensile strength, and mass.

While impairment of this barrier often leads to dermatitis, many endogenous skin disorders actually reduce the competence of the skin in providing this barrier. The aim of this instrumental technique is to measure the mechanical properties of the stratum corneum in isolation from its underlying structures. This will be of major benefit in studying the causes and treatment of many skin disorders and dermatoses such as atopic dermatitis or ichthyosis where abnormal keratinization is a feature of the disorder.

This chapter describes just one instrumental approach adopted to obtain mechanical information from this layer using dynamic microindentation. A prototype computer-controlled indentometer has been developed that uses a 1-mm-diameter flat-tipped needle to indent the stratum corneum by a preset distance of 20  $\mu\text{m}$ . A piezoactuator is used with a response time of 1 ms. Dynamic indentation serves to isolate the stratum corneum surface response from that of the slower underlying tissues, but produces considerable inertial artifacts. To measure the true mechanical resistance of the skin surface, matched force transducers and then an impedance head were used as a means of canceling out these artifacts. The precise positioning of the indentometer tip to the skin surface and its subsequent indentation is automated by the computer program ensuring both reproducibility and ease of use.

Measurement of changes in the reaction force to indentation will enable characterization of the mechanical properties of the stratum corneum. Thus, changes due to disease or its treatment, and to application of topical agents such as emollients, can be quantified.

## STRATUM CORNEUM MECHANICAL COMPETENCE

### INTRODUCTION

One of the primary functions of the stratum corneum is to provide a physical barrier protecting against mechanical insult and trauma.<sup>1</sup> Apart from an exceptional ability of the skin to repair itself, the *competence* of the stratum corneum at providing protection against mechanical injury is related to its strength, flexibility, stiffness, and hardness. The *hardness* of a material is defined as resistance to wear, indentation, and scratching,<sup>2</sup> although what is perceived as increase in hardness of the stratum corneum may in fact be a combination of increased stiffness, strength, and mass, as well as true hardness. However, tensile strength, stiffness, and hardness are interrelated properties.<sup>3</sup>

Thus, measurement of stratum corneum hardness is one way that the mechanical competence of stratum corneum can be assessed. In classical engineering, the measurement of hardness is usually carried out by indenting the surface of the material being tested, and this practice has been used for the testing of skin. Schade<sup>4</sup> was the first to use the technique on skin and since then it has regularly been advanced as a technique by other researchers. By measuring the forces involved in the point indentation of stratum corneum, it is believed that one or more parameters relating to strength, stiffness, and hardness can be obtained. This would then provide a measure of stratum corneum mechanical competence.



Biomechanical characterization of the stratum corneum could do much to improve clinical decision making and therapy. Impairment of this physical barrier invariably results in some form of dermatitis.<sup>5,6</sup> Conversely, many endogenous skin disorders reduce the mechanical competence of the skin in providing this barrier.<sup>7</sup> In many disorders, abnormal keratinization or desquamation results in the stratum corneum becoming thickened and stiff, often leading to brittleness and fissuring.<sup>8</sup> In some disorders, severe mechanical fragility can result.<sup>9</sup> It is also likely that it is altered after prolonged occlusion of the skin leading to an increased susceptibility to mechanical (and possibly chemical) trauma. Indeed, changes found in stratum corneum compliance after glove patch occlusion<sup>10</sup> have raised the question whether this is indicative of a less mechanically protective stratum corneum, as perhaps would be expected. To address these problems, a microindentometer device was constructed, based on the principles of an earlier instrument.<sup>11</sup>

This chapter describes the development of a research instrument to characterize the mechanical response of the stratum corneum *in vivo* to microindentations to assess stratum corneum mechanical competence.

## REVIEW OF INDENTATION RESEARCH

Many researchers have used indentation as a way to study the mechanical properties of skin. However, very few have used the technique to investigate stratum corneum properties. Rather, the dermis, whole skin, and even muscle have been the focus of attention. Schade<sup>4</sup> used a spherical ball on the end of a pivoted arm. The force for indentation was provided by a 50-g mass. The depth of indentation produced was of the order of millimeters. Schade's method and design has been used by a number of investigators.<sup>12-14</sup> Most later workers have used smaller indentors. A flat disk was first used by Vlasblom<sup>15</sup> and then by Dikstein and Hartzstark,<sup>16</sup> who continued to use weights to provide the indentation force. A different approach was adopted by Barbenel et al.,<sup>17</sup> who compressed a fold of skin with a predetermined constant deformation and measured the force that was required to do this. Some authors have employed commercially available hardness testers used in the rubber industry. Peck and Glick<sup>18</sup> used one such device called a durometer to carry out *in vitro* measurements on keratin specimens. Falanga and Bucalo<sup>19</sup> and Romanelli and Falanga<sup>20</sup> used a similar durometer device to assess skin hardness in patients with scleroderma. Measurements were taken by resting the device under gravity against the skin of finger pads, forearms, and thighs, and taking four consecutive readings as the skin exhibits creep. Good correlation was found between durometer readings and clinical severity score. A different technique was described by Prall,<sup>21</sup> based on the lowest load able to cause a stylus to visibly scratch the skin. A scratch was distinguished by its ability to scatter light.

A number of authors have published work on measuring the hardness of muscle tissue. Honda<sup>22</sup> used a spherical indenter of 5 mm radius and compared measured values with a theoretical spring and dashpot model. Horikawa et al.<sup>23</sup> devised a hand-held instrument for evaluating muscle hardness consisting of a 1-cm<sup>2</sup> pressure disk attached to a load cell. A separate optical displacement transducer was fixed to the side of the instrument. In operation, pressure is applied manually. The indentation

produced and the force required to produce it is continually recorded. Other authors have developed large-scale *in vivo* indentation systems for the investigation of pressure sores,<sup>24</sup> and for the biomechanical characterization of limb tissues in rehabilitation engineering.<sup>25-27</sup>

On a scale that could prove useful for future *in vitro* studies of stratum corneum, a cell-indentation apparatus (cytoindenter) has recently been developed to obtain intrinsic material properties of individual cells attached to a rigid substrate.<sup>28</sup> Meanwhile, researchers investigating the dermal anchoring of skin equivalents have used a spherical indenter in a quasi-static test of tensile properties.<sup>29</sup>

Only one indentation device has been constructed specifically to investigate the pliability and hardness of stratum corneum.<sup>30-32</sup> The device consists of an interchangeable needle mounted on a moving coil vibrator, which was electronically controlled,<sup>33</sup> to give a single indentation movement of variable travel to a maximum of 100  $\mu\text{m}$ , lasting 4 ms. The needle was manually positioned above the skin using a modified microscope translation stage. Needles used had tip diameters of 1, 10, and 20  $\mu\text{m}$ . The original version used a linear variable displacement transducer; however, this was removed at a later stage as it was found to be a source of artifact.<sup>11</sup> *In vitro* samples of thigh skin that had been differentially hydrated were indented. A decreasing resistance to indentation was found with increasing levels of hydration.<sup>32</sup> Successive removal of the stratum corneum using skin surface biopsies<sup>34</sup> produced a reduction in the indentation force registered.<sup>31</sup> The effects of delipidization and hydration on the forearm skin indentation were measured.<sup>11</sup> Delipidization with diethyl ether was found to cause an increase in resistance to indentation; however, the effect had almost disappeared 20 min later. Hydration of forearm skin was found to reduce resistance to indentation.

## MEASUREMENT PRINCIPLES

### INTRODUCTION

The microindentometer is based on the principle that indentation of the stratum corneum by a needle is opposed by the extensible horny membrane. Hendley et al.<sup>11</sup> stated:

As the skin is a viscoelastic structure the faster the [indenting] needle moves the smaller is the time available for skin surface elongation to relieve the indenting force and the greater the viscous drag. Therefore, the force registered on initial impact will depend mainly on the properties of the horny layer.

Although the theory is still poorly developed, it is known that viscous effects are proportional to velocity, so if the stratum corneum is viscoelastic, then the force registered by a rapidly moving needle will depend on stratum corneum viscosity as well as stiffness. If the underlying epidermis deforms only a little due to stratum corneum viscosity, then one can consider that the reaction force depends mainly on stratum corneum properties. However, it is possible that a stiffer stratum corneum would cause depression of the epidermis under an area of stratum corneum.

The success of the device depends on its ability to rapidly indent the stratum corneum by an amount that is of an equivalent order of magnitude to its thickness (10 to 15  $\mu\text{m}$ ). Impedance measurements of human finger pulp<sup>35</sup> based on the mechanical model attributed to Voigt and Kelvin give a minimum mechanical impedance of around 250 Hz with characteristic stiffening at higher frequencies. This indicates that the needle must be able to move at a velocity greater than  $5 \times 10^3 \text{ ms}^{-1}$  (10  $\mu\text{m}$  in 2 ms) in order for the skin to present itself as a stiff system.

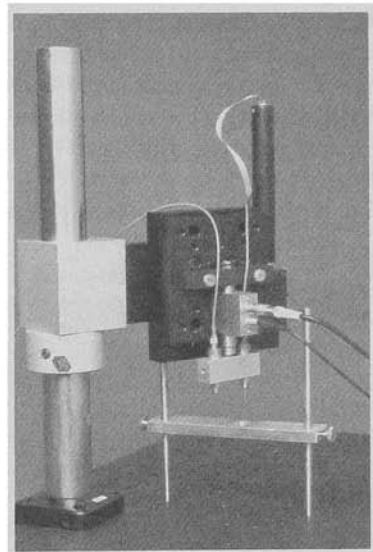
The authors have chosen to implement an impact response approach to the extraction of stratum corneum properties. This maximizes the possibility of separating the mechanical responses of underlying tissues in the time domain, since it would be expected that some time delay in the response of tissues would be proportional to the distance from the indenting tip. Furthermore, input from a step function by definition imparts a range of frequencies into the skin and enables analysis of the response in the frequency domain. Methods of extracting useful frequency responses from step or point function excitation are well developed.

## HARDWARE

A microindentometer device was designed and constructed. In part it was based on the original indentometer device of Guibarra, Nicholls, Hendley, and co-workers, reviewed above. Their device used a moving coil vibrator, incorporating a linear variable displacement transducer (LVDT). It was clear that a far more reliable instrument could be produced by utilizing some of the recent advances made in the field of laser and optics technology. The component parts and operation of the new indentometer shown in Figure 14.1 are described below.

### Indentometer Actuator and Needle

The instrument works by rapidly indenting the stratum corneum to a maximum depth of 20  $\mu\text{m}$  and monitoring the force of reaction. A piezoelectric actuator and controller (Photon Control/Melles Griot NGS20ZC and NDA501-75Fc) were used. The actuator can move a component, such as a lens, mirror, laser, or in this case a force transducer and "needle," by distances of up to 20  $\mu\text{m}$  at a speed of 10  $\mu\text{m}$  in 1 ms. This type of actuator will perform the operation repeatedly and without error. Needles of 1 mm diameter and smaller were used (Figure 14.2).



**FIGURE 14.1** The indentometer device without arm rest or pressure cuff.

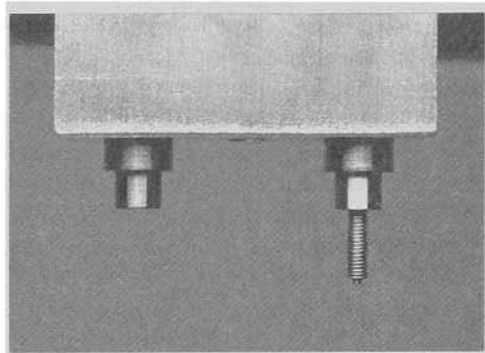


FIGURE 14.2 Close-up view of 1-mm indentometer “needle” mounted in force transducer.

### Positioning System

One of the major technical problems with stratum corneum indentometry is accurately positioning the indentometer needle above the stratum corneum before commencement of indentation. This is because it is difficult to measure precisely the location of the part of the skin surface to be indented, in relation to the position of the needle. The indentometer resolved this problem by using an automated probing and indentation action as shown in Figure 14.3. The automated procedure that was used is described as follows:

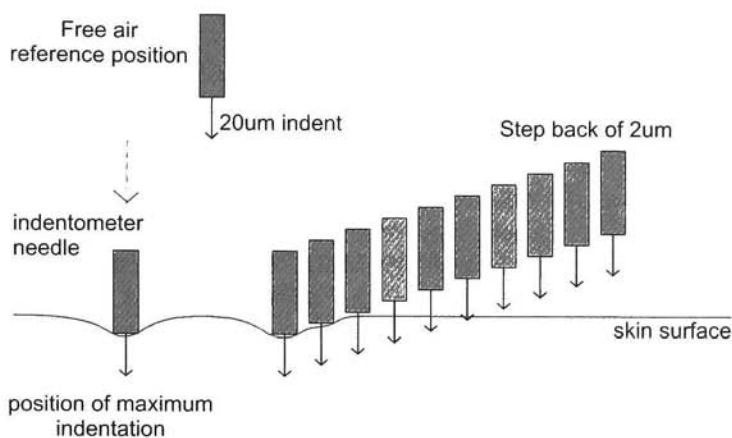
1. The indentometer moved toward the skin in  $10\ \mu\text{m}$  steps performing a  $20\text{-}\mu\text{m}$  indentation “jab” after each maneuver.
2. When a predetermined, sufficiently large reaction force was registered,\* the needle had reached a position of maximum indentation and the stepping forward ceased.
3. The indentometer moved back  $50\ \mu\text{m}$  and made a reference measurement, indenting “free air.”
4. Then the indentometer returned to the position of maximum indentation and repeated the previous “jab.”
5. Finally, the indentometer stepped back  $2\ \mu\text{m}$ , made a  $20\ \mu\text{m}$  indentation, and repeated this maneuver 20 times.

All vertical movement was computer controlled and provided by an encoder-driven motorized positioner (37-1104 Ealing Electro-Optics plc).

### Mounting Components

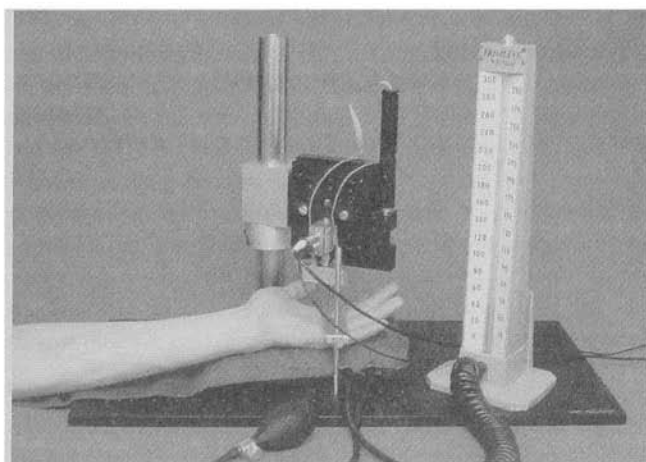
The whole device was attached to a damped column (Ealing Optics) shown in Figure 14.1, which was in turn bolted to an aluminum “bread board” (Newport).

\* This is calculated from previous measurements to ensure that in the final part of the procedure (step 5), some of the indentations commence with the needle in contact with the skin and some commence clear of it.



**FIGURE 14.3** Schematic diagram of indentometer movement control.

This was mounted on a vibration-isolated concrete slab to minimize the effects of extraneous vibrations on measurements. An arm rest was constructed for immobilizing the forearm in position. A metal stop bar with a 12-mm-diameter hole in it was clamped down over the skin to prevent any movement. To immobilize hands for measurement, a blood pressure cuff was used in place of the arm rest. By inflating the cuff under the hand, the area of skin to be measured was pressed against the hole in the metal bar (Figure 14.4). Sufficient pressure was used to keep the hands still; however, measurements had to be completed within a maximum of 5 min because of the discomfort from blanching.



**FIGURE 14.4** Indentometer device in use with hand immobilization provided by an inflated blood pressure cuff.

## Force Measurement

The reaction force to rapid indentation was measured using two piezoelectric force transducers. On indentation of skin, the force transducer into which the needle is mounted registers not only a resistance force from the skin but also a large inertial force contribution due to the acceleration and deceleration of the transducer. The signal from the second transducer and balanced charge amplifier was used to cancel out this inertial force component by putting the two signals through a differential amplifier (Figure 14.5). The resultant signal was low-pass-filtered.

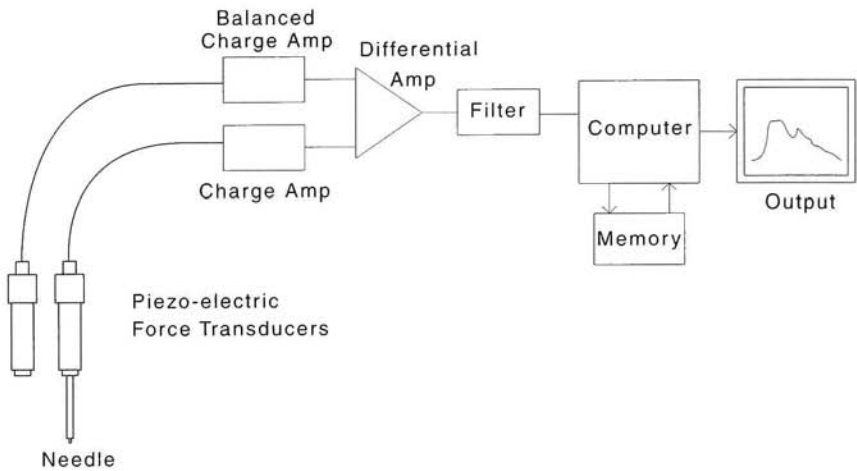
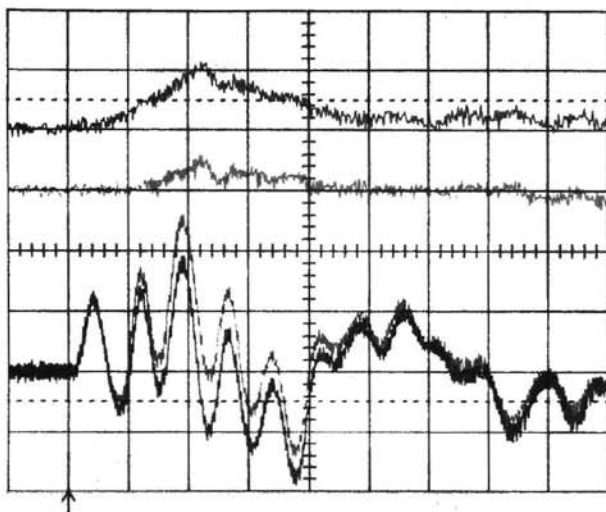


FIGURE 14.5 Differential force measurement to cancel the inertial force contribution.

As it was not possible to balance the two force transducers completely, a further cancellation of residual artifacts was achieved by using the recorded response from indenting free air and subtracting this from each indentation signal measured. The resultant signal was taken as the reaction force measurement. Figure 14.6 shows this further cancellation. The bottom trace is the filtered signal placed in computer memory after indentation of free air and includes residual inertial artifacts. The second-to-bottom trace is the filtered signal from indentation of skin with the same artifacts. The top trace is the indentation signal with the artifacts canceled. The second-to-top trace is the resultant indentation signal (with artifacts canceled) from a previous measurement when the skin was indented by a lesser amount.

## Computer Control

An IBM-compatible PC computer was used. The piezoelectric actuator/controller system was controlled using an IEEE PC card (Brain Boxes Ltd.). The motorized positioner was controlled using a DCX controller card and DCX-MC110 DC servo module (Precision Micro Control Corp.). The PC interface and the DCX-PC100 motion controller drivers were used for software control. Data acquisition was



**FIGURE 14.6** Skin indentation force signals. Bottom trace: free-air reference signal in memory; second to the bottom trace: signal from indentation of skin; top trace: resultant force signal after subtraction of artifacts; second to the top trace: resultant force signal from a previous measurement.

achieved using a PCI20091W 89 kHz analog input board (Burr Brown), in DMA mode. Integrated software was written in Microsoft QuickBasic v4.5.

## TAKING AND INTERPRETING MEASUREMENTS

Two experiments were carried out using the device.

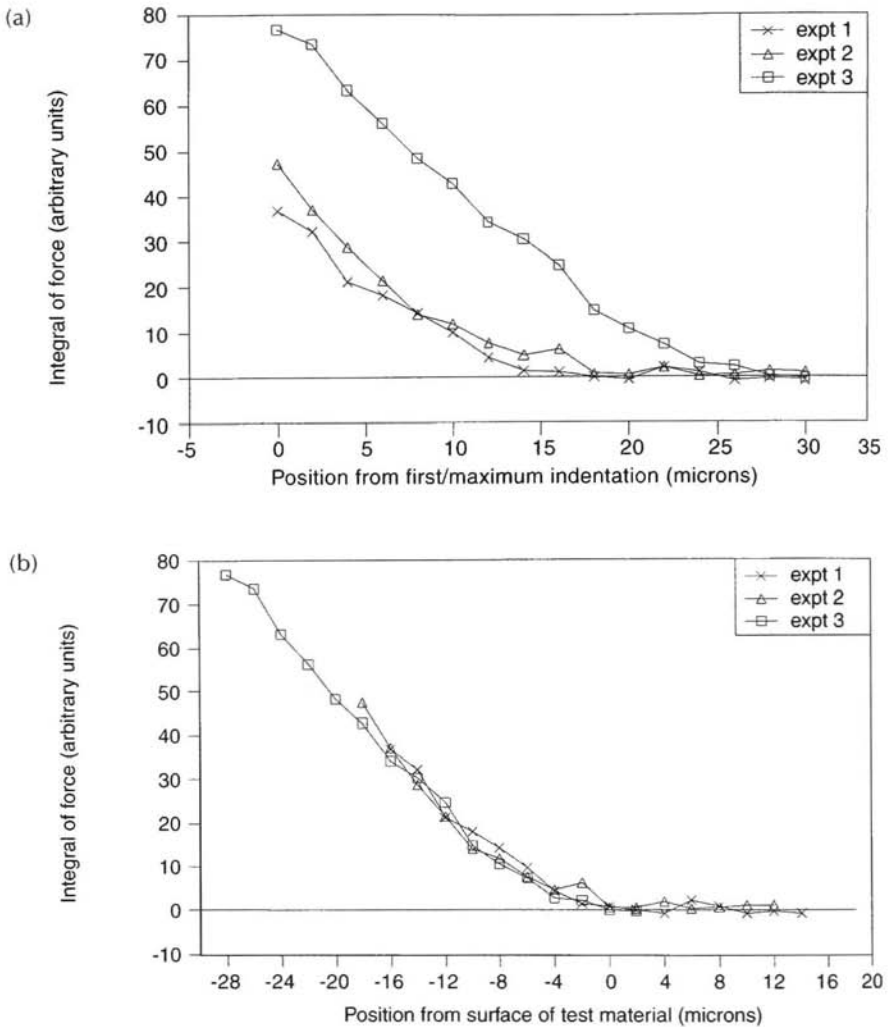
### POSITION TESTING OF NEEDLE RELATIVE TO SURFACE

Measurements were made of an *in vitro* test surface (insulating tape), in order to test the automated probing and indentation action. Three successive runs were made using the same surface, but moving the indenter laterally by a millimeter between runs, so as not to indent any spot more than once.

Figure 14.7a shows the results of the first three series of indentations. The position of maximum indentation is marked as 0  $\mu\text{m}$ . As the indenter stepped away from the material, it eventually cleared the surface and no indentation signal was detected. From this, the position of the surface was deduced and the data replotted relative to the surface. The result of transforming the data in this way is shown in Figure 14.7b. The force reading representing a full 20  $\mu\text{m}$  indent from a starting position just touching the surface is shown at -20  $\mu\text{m}$  on the graph.

### INDENTATION OF HUMAN STRATUM CORNEUM

Measurements were carried out on the palms of two volunteers. Sites at the base of the fingers where calluses had formed and sites on the thenar eminence were measured.



**FIGURE 14.7** Indentation of an *in vitro* test material (insulating tape). Testing the automated probing and indentation action for determining position of the needle relative to a surface. (a) Position relative to first (maximum) indentation; (b) position relative to surface of test material.

In both experiments the integral of the force signal was used to represent the resistance to indentation, rather than the peak force. Computer calculation of the peak indentation force is complicated by the fact that the signals still contain some noise ripple. Averaging the signal is problematic: the time overheads are large for a reliable and accurate determination of peak force. Calculating the area under the force curve is a much quicker and simpler way of assessing the magnitude of the resistance to indentation. Analysis of some data from this experiment was carried out using both the force integral and a manual analysis of peak force.



A sample force trace from a 20  $\mu\text{m}$  indentation of the thenar eminence is shown in Figure 14.8. Peak indentation was achieved in about 1 ms. Figure 14.9 provides a comparison of the peak and integral force methods of representing the resistance to indentation. It can be seen that the two traces virtually superimpose.

Data from the indentation of callus and thenar eminence skin are shown in Figures 14.10 and 14.11. Each set of plotted data was the average of two measurement cycles. The callus measured from volunteer "CE" gave a greater resistance force to 20  $\mu\text{m}$  indentation than the callus from volunteer "RH." The response of the thenar stratum corneum of both volunteers was similar, the resistance force to 20  $\mu\text{m}$  indentation being almost identical.

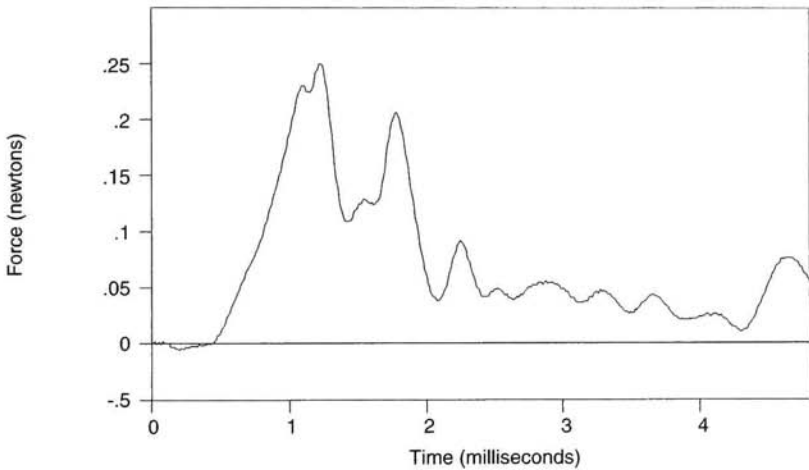


FIGURE 14.8 A sample indentometer force trace from a 20  $\mu\text{m}$  indentation of stratum corneum from the thenar eminence *in vivo*.

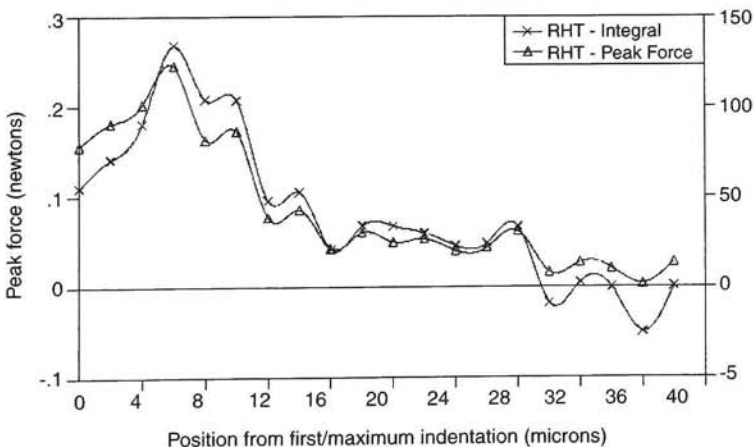
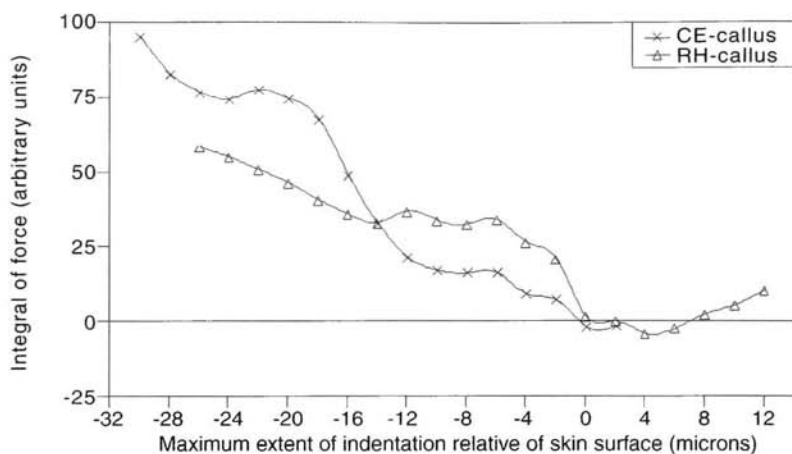
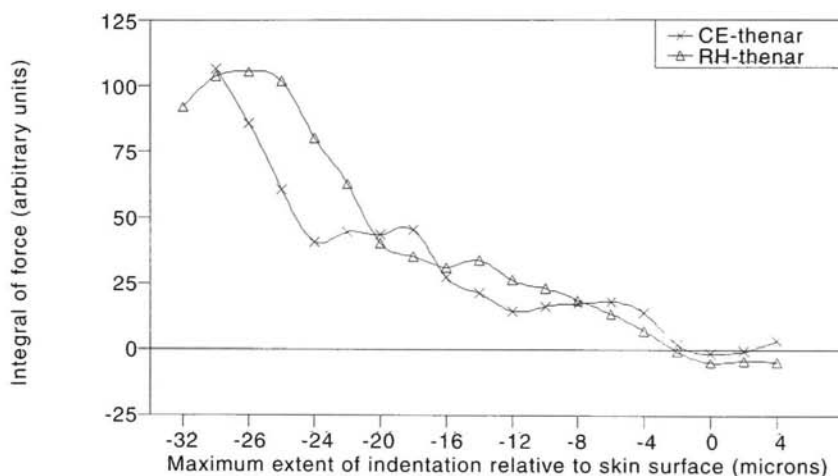


FIGURE 14.9 A 20  $\mu\text{m}$  indentation of human stratum corneum *in vivo*. Comparison of "peak force" and "integral of force."



**FIGURE 14.10** A 20  $\mu\text{m}$  indentation of human callus stratum corneum *in vivo*. Moving average data from two indentation cycles.



**FIGURE 14.11** A 20  $\mu\text{m}$  indentation of human thenar stratum corneum *in vivo*. Moving average data from two indentation cycles.

## DISCUSSION AND PITFALLS

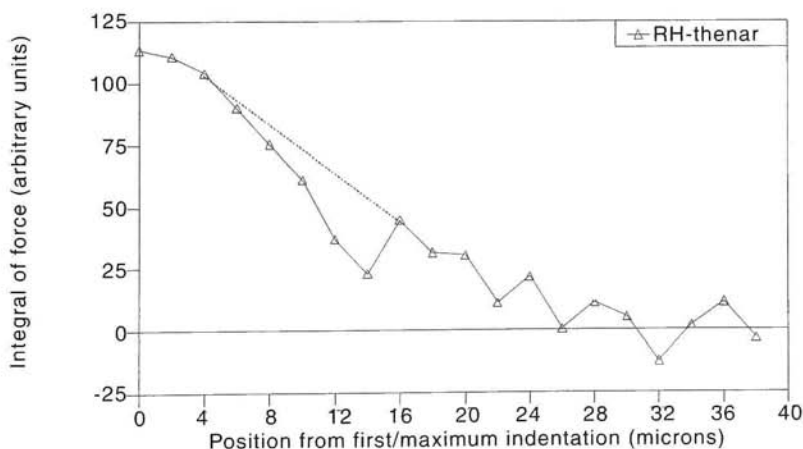
The results from indenting an *in vitro* test material demonstrate that the automated probing and indentation routine works well. After transformation, a clear correlation was observed between each trace (Figure 14.7b), indicating that the position of the test surface had been deduced correctly. It can be seen that for experiment 1 (-x-), the predetermined reaction force for maximum indentation (20  $\mu\text{m}$ ) was insufficient and was only just sufficient for experiment 2. It was modified for experiment 3.

The superposition of the traces in Figure 14.9 demonstrates the validity of using the area under the force curve (integral) in place of the peak force, to represent the magnitude of the resistance to indentation. A peak force of 0.2 N was approximately equivalent to 100 arbitrary units (force  $\times$  time).

In both Figures 14.10 and 14.11, at the point when the indentometer no longer indents the skin there is a clear drop in the force readings. The response from the callus of volunteer "CE" appears to be stiffer than that from volunteer "RH." Clearly, the resistance to 20- $\mu\text{m}$  indentation is greater. However, the same was not observed for measurements taken from the thenar eminence. The similar response of the thenar stratum corneum is as expected as both volunteers were male, in their 30s, and in the same type of occupation.

From Figure 14.11 it would appear that once greater than full indentation occurs, there is a rapid increase in the reaction force. However, more data should be collected to gain a greater understanding of how the skin surface responds to the indentation cycle. This would also enable optimization of the stepping and indentation cycle, improving its efficiency in obtaining a prompt reading. The 4  $\mu\text{m}$  delay in the rise of trace from volunteer "CE" (-x-) may be because noise or artifacts resulted in an incorrect deduction of the skin surface position. However, it is also possible that the measurements were affected by a trough in the skin surface. The surface of the stratum corneum consists of many relatively flat plateaus separated by a network of troughs that crisscross the skin surface. If the indenting needle straddles a trough of similar magnitude to its diameter, then the resistance to indentation is likely to be reduced in some way. Consideration was given as to the size of these plateaus. A series of pictures of increasing magnification were taken of positive skin replicas using an electron microscope. From these, it was possible to relate both the size of the plateaus and individual corneocytes to the topography of the skin.

Immobilizing the hand reliably and allowing for no movement or vibration of the instrument is vital for successful measurements. Figure 14.12 illustrates this



**FIGURE 14.12** Repeated 20  $\mu\text{m}$  indentation of human stratum corneum *in vivo*, demonstrating the effect of a temporary drop in supporting cuff pressure.

point well. It shows data from the repeated indentation of the stratum corneum of one volunteer. In this case, the pressure in the supporting cuff was inadvertently allowed to drop, so that the skin surface slowly moved away from its original position. This was realized halfway through the procedure, so when the pressure was returned to its original level, the skin surface moved back to its original position, producing a slight increase in the force measured. The dashed line indicates the trace that would have been obtained had the pressure drop not occurred.

The question arises whether the indentation cycle involving multiple indentations affects the measurement by initially damaging the skin. While it remains a possibility, it is not likely because the speed of indentation ( $\sim 0.01 \text{ ms}^{-1}$ ), although fast, probably does not pierce the stratum corneum. However, this needs to be tested in future experiments. Nicholls<sup>32</sup> used a stereomicroscope to examine skin that he had indented by  $90 \mu\text{m}$  at a speed of approx  $4.5 \times 10^{-2} \text{ ms}^{-1}$ . However, no signs of surface damage were found.

Mention should be made of the elimination of inertial forces by differential measurement. No mention is made in any of the published work on the original indentometer (reviewed above) of accounting for any inertial force contribution. There is no doubt that inertial forces would have affected the measurements made. With this in mind, the validity of the data is in doubt. Some of the trends reported are convincing and it is possible that a harder, stiffer stratum corneum would produce a significantly greater deceleration of the indenting needle and thus a greater inertial contribution. If this is the case, then the original device measured hardness in terms of increased deceleration of the indenting needle, rather than increased resistance to its penetration.

## FURTHER DEVELOPMENT

Dynamic indentation, although helping to isolate the stratum corneum surface response from that of softer underlying tissues, produces considerable inertial artifacts, which the above design has difficulty in eliminating.

An impedance head (PCB Piezotronics), which incorporates a load cell and an accelerometer in a single compact package, has been used to replace the matched force transducer arrangement described above. It measures the force of resistance offered by the stratum corneum to indentation and enables cancellation of the inertial forces generated by the acceleration/deceleration of the mass of the indentation head and needle assembly. Initially, inertial mass cancellation was carried out in the time domain using

$$F_s = F_m - m_i a$$

where  $F_s$  is the sensed force,  $F_m$  is the measured force,  $m_i$  is the inertial mass, and  $a$  the acceleration. Although with filtering and calibration for free-air "null" indentation representative data have been obtained, it cannot be consistently captured. This is because the dynamic characteristics of the transducers and the overall system are frequency dependent. What is required is a frequency-dependent transfer function

to describe the dynamic response of the system. The transfer function for the indentometer impedance head without skin contact is

$$H_I = A/F_I = 1/M_M$$

where  $A$  is the acceleration,  $F_I$  the indicated input force, and  $M_M$  the inertial mass. Figure 14.13 shows the frequency response function (transfer function) for the impedance head obtained using a two-channel digital signal analyzer (Diagnostic Instrumentation D2200). The measured transfer function with the indentometer in contact with the skin is

$$H_M = A/F_M$$

where  $F_M$  is the measured force. Figure 14.14 is the frequency response function obtained from 10  $\mu\text{m}$  indentation of palmar skin. The force applied to the skin is  $F_S = (F_M - F_I)$ . It is now possible to substitute the two frequency-dependent transfer functions using the equations above, to obtain the corrected indentation force. This can be done using fast Fourier transforms and their inverse.

## DISCUSSION AND CONCLUSION

Although reasonable inertial compensation was achieved in the arrangement of matched force transducers described above, the matching was not exact and a repeated differential with a free-air indentation was necessary to recover a signal from skin. Furthermore, the arrangement was a little bulky and placed restrictions on which skin site could be indented. The use of an impedance head is more compact

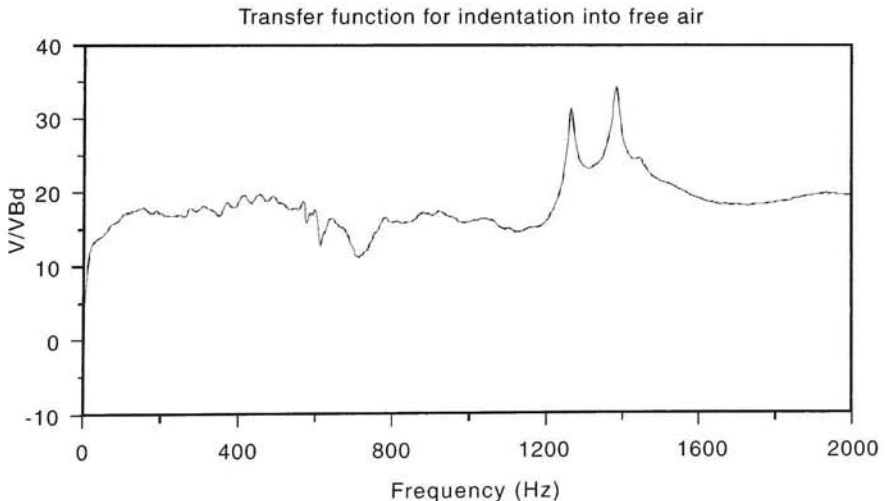
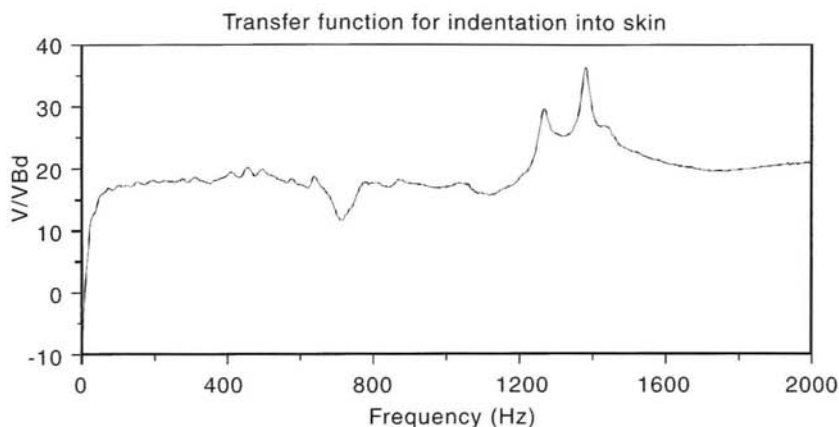


FIGURE 14.13 Transfer function free air.



**FIGURE 14.14** Transfer function 10  $\mu\text{m}$  indentation of palmar skin.

and should eventually allow dispensing with the free-air measurement immediately prior to skin indentation.

Dynamic point indentation currently rests on the theory expounded by Hendley et al.<sup>11</sup> The current assumption is that a velocity of  $0.01 \text{ ms}^{-1}$  is sufficient for the viscous properties of stratum corneum to be significant. If it is found that faster indentation is required, then the inertial compensation technique adopted will be even more pivotal to the success of the device.

In conclusion, the ability to measure the reaction force from the precise indentation of the stratum corneum has been demonstrated. Inertial forces have successfully been eliminated using differential measurement. The point of contact with the skin surface can be found with relative ease using the automated stepping and indentation technique.

By measuring changes in the reaction force to indentation, it will be possible to characterize the mechanical properties of stratum corneum and to assess its mechanical competence in disease and treatment.

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# 15 Standardization of Skin Biomechanical Measurements

*R. Randall Wickett*

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## INTRODUCTION

Standardization of measurement methods has been a goal of many researchers working on noninvasive measurement of skin function. For example, Pierard<sup>1</sup> stated, “optimization of noninvasive biophysical measurements should benefit from strict standardization of measurements and frequent calibration of devices.” While no absolute standards for skin measurements have been published, helpful guidelines have been published for measurement of transepidermal water loss (TEWL)<sup>2</sup> and the electrical properties of skin for assessment of skin hydration. Cook<sup>4</sup> called for standardization of mechanical measurements 20 years ago, and recently the EEMCO group has begun a series of papers discussing guidelines for skin mechanical measurements.<sup>5,6</sup> Rodrigues<sup>6</sup> illustrates the difficulty in standardizing biomechanical

measurements of the skin by pointing out that that estimates of Young's modulus of elasticity for skin *in vivo* vary by four orders of magnitude.

There are at least two factors that make standardization of mechanical measurements difficult. As anyone reading this book will realize, there are several commonly used devices for determining the mechanical properties of skin that work by quite different principles. For example, the dermal torque meter will obviously require different standards than the ballistometer. The other problem is that different workers are trying to obtain fundamentally different classes of information from the measurements. Experiments designed to test the efficacy of a moisturizer are likely to require significant differences in procedure from those designed to determine the effects of wound treatments on the mechanical properties of scars or the effects of medical interventions on diseases of the skin. For these reasons, this chapter will not attempt to promulgate standards for each type of measurement under each condition. Instead, the chapter discusses the factors that the author considers important to control as carefully as possible and some principles of standardization that may apply to the general problem of measuring the mechanical properties of skin.

## FORM OF THE DATA

The many different instruments provide data in various formats. The two commonly used, commercially available instruments, with which the author is most familiar, the Cutometer® and the Dermal Torque Meter® (DTM), can both provide an output of the general form shown in Figure 15.1. This output results when the deforming force (vacuum or torque) is applied for a period of time and then released.

- $U_e$  = elastic deformation of the skin due to the application of stress (vacuum or torque) by the instrument
- $U_v$  = viscoelastic creep occurring after the elastic deformation
- $U_f$  = total extensibility of the skin
- $U_r$  = elastic deformation recovery due to stress removal
- $U_a$  = total deformation recovery at the end of the stress-off period
- $R$  = amount of deformation not recovered by the end of the stress-off period
- $U_a/U_f$  = overall elasticity of the skin including creep and creep recovery
- $U_r/U_e$  = pure elasticity ignoring viscoelastic creep
- $U_v/U_e$  = ratio of viscoelastic to elastic extension called the viscoelastic ratio
- $U_r/U_f$  = ratio of elastic recovery to total deformation

## INSTRUMENTAL FACTORS

The majority of instruments for measuring the properties of skin *in vivo* supply a specified deforming force to the skin, and the extent of the resulting deformation is measured. It is not really possible to separate contributions from the various skin layers, but the general principle is to minimize the extent of the deformation when attempting to study effects on the stratum corneum and to use larger deformations

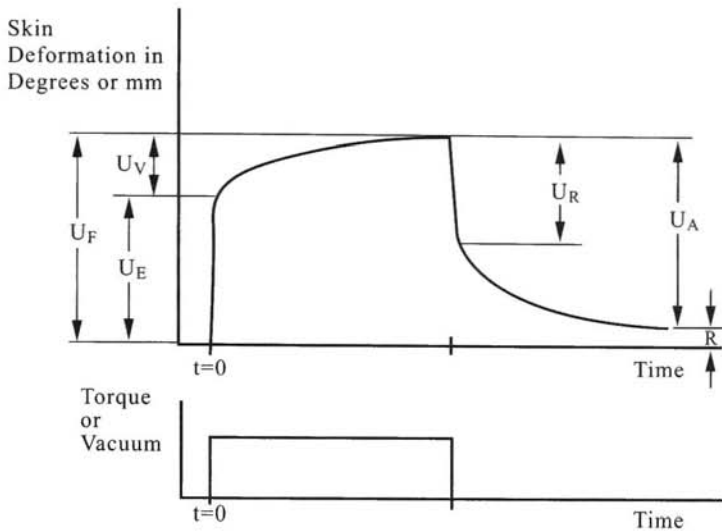


FIGURE 15.1 General form of Cutometer (mode 1) and DTM curves.

when attempting to study the mechanical properties of the dermis. Most studies of the effect of water or moisturizer on skin elasticity with the Cutometer have used the 2-mm-diameter probe.<sup>7-10</sup> The author has found that using a pressure of 200 mbar of negative pressure leads to more sensitivity to moisturizing effects compared with 500 mbar of negative pressure.<sup>11</sup> Pierard et al.<sup>12</sup> performed a systematic study comparing the 2- and 8-mm-diameter Cutometer probes and concluded that the claim that the 2-mm probe is better suited for the study of moisturizers is only justified for pressures of 200 mbar or less. With the DTM the author used the 1-mm ring gap when studying moisturizers<sup>9</sup> or short-term application of water<sup>13</sup> and the 5-mm ring gap when investigating the mechanical properties of scars resulting from treatment of burns with cultured skin substitutes.<sup>14</sup> Although use of lower deformations does lead to more apparent sensitivity of the measurement to effects that should be occurring in the stratum corneum, Diridollou and co-workers<sup>15,16</sup> used a combination of ultrasound and suction measurements to show that both the dermis and even the subcutaneous fat are deformed under 50 mbar of negative pressure with a 3-mm-diameter opening. Thus, it is necessary to keep in mind that at least some contribution to the measurement is coming from lower layers of the skin even when relatively small deformations are used.

## CONTACT PRESSURE OF THE INSTRUMENT ON SKIN

Contact pressure is an important variable with virtually all biophysical measurements that are made with skin contact. The effect is easily verified with the Cutometer by making measurements at different contact pressures on the same site. Table 15.1 shows the effects of contact pressure on some of the Cutometer parameters obtained at the same site on a single subject.

**TABLE 15.1**  
**The Effects of Contact Pressure on Several Cutometer**  
**Parameters Using the Same Site on a Single Subject**

Contact Pressure, g	$U_e$	$U_v$	$U_f$	$U_a$	$U_r$	$R$	$U_v/U_e$
250	0.42	0.27	0.69	0.58	0.46	0.11	0.675
500	0.29	0.22	0.51	0.41	0.30	0.10	0.750

Pressures were varied by placing weights on top of the probe. Pushing the Cutometer probe down just enough to deform the spring to the point that the outer and inner cylinders of the probe are even also results in about 250 g of contact force. Increasing the contact pressure decreased  $U_e$ ,  $U_v$ ,  $U_f$ , and  $U_a$  but did not effect  $R$ . The viscoelastic ratio  $U_v/U_e$  was increased at the higher pressure. The Cutometer spring allows fairly good control of contact pressure, but practice is required and it is very important to make this point when training operators. It is also important that the person performing the measurements be blind to the treatment so that he or she does not unconsciously influence the measurement through contact pressure. Whenever possible, the same operator should perform all measurements in any given study. With the DTM, the weight of the instrument is usually used to control contact pressure. With other instruments the contact pressure should obviously be controlled as carefully as possible.

## PRETENSION

The Cutometer gives the option of applying a brief pretension to the skin. Barel et al.<sup>17</sup> report that using the precondition or pretension mode of the Cutometer can have a significant effect on some of the elastic parameters measured.  $U_r/U_e$  and  $U_f/U_f$  were found to be higher after pretension was applied indicating that preconditioned skin recovers more of its elastic deformation. If preconditioning is used, it should be reported.

## ENVIRONMENTAL FACTORS

The first consideration in performing *in vivo* trials with human subjects is to ensure that the subjects are comfortable and equilibrated to the room conditions. The author's group usually controls temperature at 20 to 22°C and relative humidity at 35 to 45% and allows at least 20 min equilibration time with subjects sitting comfortably in a reclining chair. While mechanical measurements are not as sensitive to skin surface hydration as electrical measurements,<sup>8</sup> they have been shown to have some sensitivity to hydration<sup>7,8,18</sup> so control of relative humidity and equilibration to avoid sweating by the subject are important. If other biophysical measurements are also being made, as they nearly always are, these measurements are usually taken

before mechanical assessments. This is especially important with the DTM because the DTM probe is affixed to the skin with double-sided tape.

## SUBJECT FACTORS

### INFLUENCE OF GENDER

For the most part, studies of the mechanical properties of skin have not found an influence of gender on skin elasticity parameters.<sup>17,19</sup> Pierard et al.<sup>12</sup> investigated the effect of gender on the Cutometer in a study with 100 male and 100 female subjects on forearm skin using both the 2- and 8-mm-diameter probes. The only statistically significant effect of gender was on  $U_f$  with the 2-mm-diameter probe. Auriol et al.<sup>7</sup> saw no difference in baseline forearm data but did see a larger effect of short-term hydration in women when using the Cutometer.

### RACE

There have been relatively few studies of the effect of race on the mechanical properties of skin. Berardesca et al.<sup>20</sup> reported differences in elastic recovery between the volar and dorsal forearm in white subjects that were not seen in blacks and attributed the difference to protection against elasticity changes due to sun exposure in darker skin. Warriar et al.<sup>21</sup> reported significantly higher elastic recovery on facial skin of whites compared with blacks but no significant difference on the skin of lower legs with the same subjects. They also attributed the difference to elasticity changes due to sun exposure.

### BODY SITE

There have been numerous studies demonstrating clear differences in the mechanical properties of skin from different parts of the body,<sup>17,19,22</sup> and it is obvious that this parameter must be controlled.

### AGE

One of the major applications of skin mechanical measurements is to the study of both intrinsic and sun-induced aging of the skin,<sup>19,23–30</sup> so it is not surprising that this factor must be controlled and the age range of the subject should be reported.

### SUBJECT FACTORS AND CONTROL SITES

When conducting studies that involve treatments, it is often feasible to overcome problems with control of subject factors by using each subject as his or her own control. Measurement made at baseline can be compared to treatment on the same subject at the same site. It is also sometimes possible to maintain a contralateral site as an untreated or placebo-treated control.

## CONCLUSIONS

Mechanical measurements of skin function have progressed considerably in the past 20 years. Reliable commercial devices are now available for measuring several different aspects of skin mechanics. With adequate control of instrumental factors, it is possible to obtain valuable data relating to the effects of treatments, disease states, or the natural aging process. Because there are so many different instrumental approaches and different factors to study, it does not seem feasible to set absolute standards. Rather, general guidelines are in order and those practices that are applicable to other bioengineering methods, such as control of instrumental parameters, measurement environment, treatment site, and contact pressure, are also required to achieve good skin biomechanical measurement.

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# 16 Mapping Mechanical Properties of Human Skin

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## INTRODUCTION

The skin performs numerous functions vital to the maintenance of homeostasis. Faced with a variety of extrinsic factors, such as physical trauma from the sun, wind, temperature changes, and the dynamic movements of the body, as well as the intrinsic aging process, its integrity is well preserved by a complex interaction of the three layers: epidermis, dermis, and subcutaneous tissue.

The epidermis, particularly the stratum corneum layer, provides a barrier to permeability. It is tough and resilient as a result of the presence of fibrous keratin. Evidence for stratum corneum elasticity has been described;<sup>1,2</sup> intraepidermal elasticity has also been associated with the presence of sweat.<sup>3</sup> The relatively thick dermis together with the subcutaneous fat gives the skin its toughness and elasticity, an important mechanical property primarily attributable to the intra- and intermolecular cross-links of collagen, elastic, and reticulin fibers embedded in ground substance.<sup>4,5</sup> The extensibility of the skin, however, shows directional variation characterized as anisotropy.<sup>6,7</sup>

The regional variability and age dependency of the elastic properties of human skin *in vivo* has been examined utilizing a noninvasive suction device.<sup>2</sup>

## REGIONAL VARIABILITY OF *IN VIVO* ELASTIC PROPERTIES

Measurements were performed in 33 volunteers on 11 anatomical regions: forehead (center), postauricular, upper arm (inner middle third), volar and dorsal forearm

(center between wrist and elbow), palm (thenar aspect), abdomen (3 cm above umbilicus), thigh (anterior, upper third), ankle (medial malleoli), upper back (scapula), and lower back (at level of L1). Except for measurements of the abdomen where volunteers were recumbent, all measurements were taken with volunteers seated.

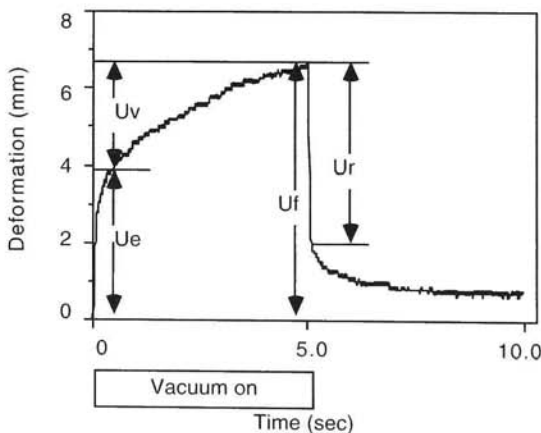
The population was divided into four groups: Group A: 8 young females (age  $25.8 \pm 3.0$ ; mean  $\pm$  SD); Group B: 9 older females (age  $74.7 \pm 5.7$ ); Group C: 8 young males (age  $28.3 \pm 1.2$ ); and Group D: 8 older males (age  $75.1 \pm 4.8$ ). All participants were Caucasians with no signs of apparent skin disease.

Skin elasticity was measured with a commercially available suction instrument (Cutometer SEM 474, Courage & Khazaka, Cologne, Germany). This instrument measures the elastic properties of skin based on the principle of suction/elongation, and is described elsewhere in this book. Because of the small test area (suction chamber  $\approx 3 \text{ mm}^2$ ), skin elongation contributable from the dermo-subepidermal junction is considerably smaller than it is from instruments with larger suction chambers, e.g., the Dermaflex A (suction chamber  $\approx 80 \text{ mm}^2$ ).<sup>8</sup>

In this study the time-strain mode was used with 5-s application of three different loads: 100, 200, and 500 mbar, followed by a 5-s relaxation period. The skin deformation was plotted as a function of time. A typical time-strain recording is illustrated in Figure 16.1. The following parameters were recorded: immediate distension ( $U_e$ ), measured at 0.48 s; delayed distension ( $U_v$ ); immediate retraction ( $U_r$ ); and final distension ( $U_f$ ).<sup>9,10</sup> The deformation curve consists of an initial purely elastic component, followed by a viscoelastic, and a final purely viscous component.<sup>8</sup>

Differences were tested for their statistical significance using Student's t-test for differences between the age groups and by an analysis of variance for regional variation. A  $p$  value less than or equal to 0.05 was considered statistically significant.

Uncorrected results of skin elasticity measurements with respect to anatomical region and age for a load of 200 mbar are summarized in Table 16.1. There are



**FIGURE 16.1** Typical skin deformation plotted as a function of time. The parameters are immediate distension ( $U_e$ ), delayed distension ( $U_v$ ), immediate retraction ( $U_r$ ), and final distension ( $U_f$ ).

tremendous differences between various anatomical sites for all parameters: immediate distension ( $U_e$ ), delayed distension ( $U_r$ ), immediate retraction ( $U_f$ ), and final deformation ( $U_j$ ). All parameters tended to be increased in elderly people at most anatomical regions. These direct elongation parameters are, however, influenced by skin thickness and do not provide immediate information about the elastic properties. Hence, the great difference in the young group between the amount of immediate distension ( $U_e$ ) between the palm with only 0.06 mm and the postauricular region with 0.57 mm can certainly be largely ascribed to parallel differences in skin thickness, and likewise the observed age differences may be partly caused by skin atrophy in the aged group.

However, certain biologically relevant ratios of these parameters are independent of skin thickness and can be compared between subjects and anatomical regions.<sup>6,8,9,11</sup> For each group, two of these relative parameters independent of skin thickness were calculated: First,  $U_r/U_f$  (biological elasticity) was calculated, which measures the ability of skin to regain its initial position after deformation. A value of 1 would indicate 100% elasticity. Decreasing elasticity results in smaller ratios. Second, the viscoelastic proportion of the total distension ( $U_v/U_e$ ). Increasing values of  $U_v/U_e$  indicate an increasing viscoelastic portion of the deformation process, which is controlled by the collagen fibers.

There were significant differences for biological elasticity as well as viscoelastic-to-elastic ratio between anatomical sites and between age groups. Regardless of the load applied, no significant differences (data not shown), however, were noted between the sexes for either ratio for most regions of the body.

The biological elasticity ( $U_r/U_f$ ) tended to increase with increasing loads in both age groups (Table 16.2, Figure 16.2). Biological elasticity was generally higher on the back (abdomen) and proximal extremities (upper arm, thigh) than at distal parts (ankle, palm). This vertical vector of elasticity has also been confirmed by Gniadecka et al.<sup>12</sup> with a different suction device (Dermaflex A); they compared this decreased vertical vector of elasticity (increased stiffness) with the "congenital antigravity suit" of tall animals, e.g., giraffes. Tall animals exhibit stiffer tissue (skin, fascia, veins) in dependent areas to directly compensate for the increased hydrostatic pressure; the finding of a similar vertical vector of skin elasticity provides evidence for a similar antigravity suit in humans.

Biological elasticity ( $U_r/U_f$ ) was significantly decreased in the aged group as compared with the young group at most anatomical sites (Figure 16.2). The effect of aging, i.e., photoaging, can also be seen by comparison of different anatomical sites within one age group. For example, sun-exposed areas (dorsal forearm) showed lower biologic elasticity than areas with low sun exposure (ventral forearm) in both age groups (Figure 16.3). A similar difference in biological elasticity was seen between the lower and the upper back.

The adverse effect of chronic sun exposure as well as of acute ultraviolet-irritation has been described previously by L  v  que et al.<sup>13</sup> and by Berardesca et al.<sup>14</sup>

The effect of aging on skin stiffness has not been fully elucidated. It has been proposed that diminished elasticity in aged skin is due to the damage, disintegration, or changes of the structure of elastic fibers<sup>14-16</sup> that appear both in intrinsic and solar

**TABLE 16.1**  
**Parameters of Skin Elasticity Measurements at 200-mbar Load**

Region	$U_e$		$U_v$		$U_r$		$U_f$	
	Young	Aged	Young	Aged	Young	Aged	Young	Aged
Forehead	0.28 ± 0.05	0.43 ± 0.06*	0.12 ± 0.02	0.23 ± 0.05*	0.29 ± 0.06	0.38 ± 0.07	0.11 ± 0.02	0.28 ± 0.05*
Postauricular	0.57 ± 0.10	0.94 ± 0.17*	0.23 ± 0.03	0.42 ± 0.06*	0.63 ± 0.12	0.93 ± 0.20	0.18 ± 0.03	0.43 ± 0.08*
Upper arm	0.33 ± 0.08	0.61 ± 0.08*	0.10 ± 0.02	0.27 ± 0.03*	0.39 ± 0.09	0.73 ± 0.09*	0.04 ± 0.01	0.14 ± 0.02*
Volar forearm	0.14 ± 0.02	0.47 ± 0.08*	0.05 ± 0.01	0.24 ± 0.04*	0.16 ± 0.02	0.56 ± 0.11*	0.03 ± 0.01	0.16 ± 0.03*
Dorsal forearm	0.11 ± 0.02	0.19 ± 0.04	0.03 ± 0.01	0.11 ± 0.03*	0.11 ± 0.02	0.20 ± 0.06	0.04 ± 0.01	0.11 ± 0.02*
Palm	0.06 ± 0.01	0.08 ± 0.01	0.03 ± 0.00	0.04 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.03 ± 0.00	0.07 ± 0.01*
Abdomen	0.68 ± 0.14	0.30 ± 0.05*	0.17 ± 0.02	0.15 ± 0.04	0.77 ± 0.15	0.39 ± 0.08*	0.07 ± 0.02	0.07 ± 0.02
Thigh	0.16 ± 0.02	0.30 ± 0.04*	0.04 ± 0.00	0.12 ± 0.02*	0.17 ± 0.02	0.32 ± 0.06*	0.03 ± 0.00	0.04 ± 0.00
Ankle	0.09 ± 0.01	0.25 ± 0.01*	0.03 ± 0.01	0.02 ± 0.00	0.09 ± 0.02	0.04 ± 0.01*	0.03 ± 0.00	0.03 ± 0.00
Upper back	0.24 ± 0.02	0.27 ± 0.04	0.09 ± 0.01	0.18 ± 0.04*	0.29 ± 0.03	0.32 ± 0.06	0.05 ± 0.01	0.13 ± 0.03*
Lower back	0.23 ± 0.04	0.35 ± 0.06	0.07 ± 0.01	0.17 ± 0.03*	0.26 ± 0.04	0.40 ± 0.07	0.03 ± 0.00	0.11 ± 0.03*

*Note:* A 5-s load (200 mbar) was applied followed by a 5-s relaxation period.  $U_e$  (immediate distension),  $U_v$  (delayed distension),  $U_r$  (immediate retraction), and  $U_f$  (final deformation). Generally, parameters were noted to be increased in the aged group at all anatomical regions except for the abdomen and ankle. (Mean ± S.E.M.,  $n = 13$  to 16 volunteers.)

\* Statistically significant difference ( $p < 0.05$ ) between the age groups (Student's t-test).

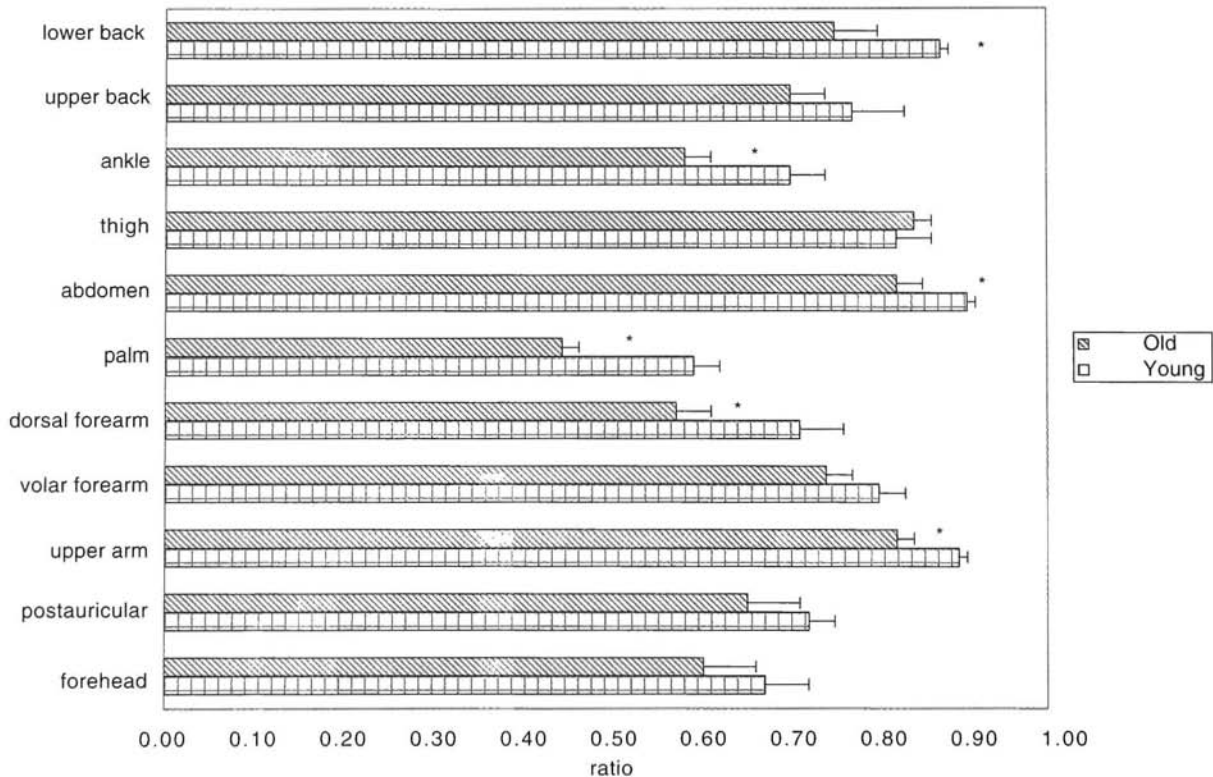
*Source:* Modified from Cua, A.B. et al., *Arch. Dermatol. Res.*, 282, 283–286, 1990. With permission.

**TABLE 16.2**  
**Elasticity ( $U_r/U_f$ ) at Different Loads**

Region	Load (mbar)	Young			Aged		
		Mean	S.D.	S.E.M.	Mean	S.D.	S.E.M.
Forehead	500	0.72	0.17	0.04	0.66	0.21	0.05
	200	0.68	0.17	0.05	0.61	0.25	0.06
	100	0.64	0.15	0.04	0.53	0.25	0.06
Postauricular	500	0.76	0.15	0.04	0.65	0.22	0.06
	200	0.73	0.14	0.03	0.66	0.22	0.06
	100	0.65	0.18	0.05	0.60	0.18	0.05
Upper arm	500	0.92	0.04	0.01	0.84	0.14	0.04
	200	0.90	0.04	0.01	0.83	0.09	0.02
	100	0.85	0.07	0.02	0.78	0.14	0.03
Volar forearm	500	0.88	0.09	0.02	0.77	0.12	0.03
	200	0.81	0.10	0.03	0.75	0.13	0.03
	100	0.72	0.13	0.04	0.67	0.12	0.03
Dorsal forearm	500	0.77	0.19	0.05	0.64	0.17	0.04
	200	0.72	0.20	0.05	0.58	0.15	0.04
	100	0.74	0.13	0.04	0.48	0.15	0.04
Palm	500	0.66	0.09	0.03	0.53	0.08	0.02
	200	0.60	0.09	0.03	0.45	0.09	0.02
	100	0.53	0.11	0.03	0.45	0.09	0.02
Abdomen	500	0.91	0.06	0.02	0.87	0.11	0.03
	200	0.91	0.05	0.01	0.83	0.11	0.03
	100	0.87	0.08	0.02	0.77	0.14	0.03
Thigh	500	0.92	0.05	0.01	0.88	0.10	0.03
	200	0.83	0.15	0.04	0.85	0.09	0.02
	100	0.82	0.06	0.02	0.79	0.10	0.03
Ankle	500	0.78	0.09	0.02	0.62	0.09	0.02
	200	0.71	0.13	0.04	0.59	0.12	0.03
	100	0.65	0.13	0.04	0.52	0.11	0.03
Upper back	500	0.91	0.07	0.02	0.81	0.08	0.02
	200	0.78	0.24	0.06	0.71	0.14	0.04
	100	0.75	0.14	0.04	0.66	0.11	0.03
Lower back	500	0.90	0.08	0.02	0.86	0.14	0.04
	200	0.88	0.05	0.01	0.80	0.19	0.05
	100	0.80	0.10	0.03	0.70	0.14	0.04

Note:  $U_r/U_f$  tended to increase with increasing load in both age groups and was generally lower in the aged than in the young group.

\* Statistically significant difference ( $p < 0.05$ ) between the age groups (Student's t-test); ( $n = 13$  to 16 volunteers).

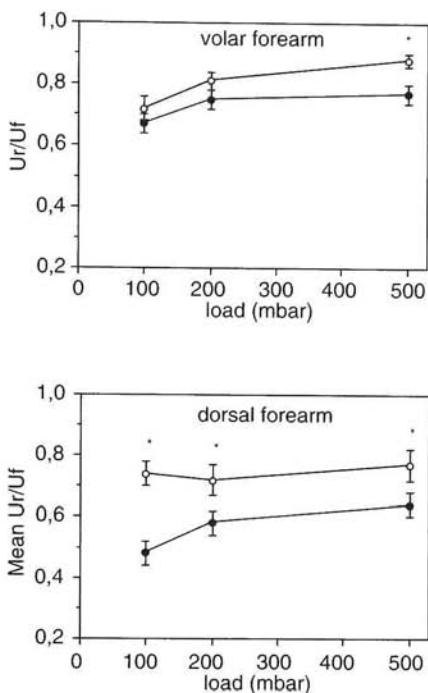


**FIGURE 16.2** Biological elasticity ( $U_r/U_p$ ) after 200 mbar load for 5 s followed by a 5-s relaxation period at 11 different anatomical sites. Means  $\pm$  S.E.M.;  $n = 13$  to 16 volunteers. \*Statistically significantly different ( $p \leq 0.05$ ).

aging. This may be caused by accumulation of glycosaminoglycans in the papillary dermis of the actinically damaged skin interfering with the elastic fiber system located in this region.

It has also been proposed that the viscoelastic properties are dependent on alterations in the equilibrium of the "ground substance" of the dermis,<sup>17</sup> and that the content of glycosaminoglycans or soluble collagen may be related to viscosity, decreasing with maturation and age,<sup>18</sup> whereas the biological elasticity ( $U_r/U_f$ ) should correlate with the function of the elastic fiber network.<sup>8</sup>

In this investigation the viscoelastic-to-elastic ratio ( $U_v/U_e$ ) was increased with increasing loads and tended to be higher in the aged group for almost all anatomical sites. Age differences were especially apparent when high loads were applied (Table 16.3, Figure 16.4). The ratios as a function of load for the dorsal and volar forearm are illustrated in Figure 16.5.



**FIGURE 16.3** Influence of load on  $U_r/U_f$  on the volar and dorsal forearm in young (open circles) and aged (closed circles) volunteers. Means  $\pm$  S.E.M.;  $n = 13$  to 16 volunteers. \*Statistically significantly different ( $p \leq 0.05$ ).

## CONCLUSIONS

To avoid such invasive techniques as biopsy, differences in mechanical properties of the skin at various regions of the human body can be evaluated using the suction device. The mechanical properties of the skin of the human body differ greatly between various anatomical sites. The largest differences are present for the direct elongation parameters, which are mostly due to differences in skin thickness. However, there are also differences in those elasticity parameters independent of skin thickness. Knowledge of these differences and expansion of the database will provide useful material for understanding human skin biology and for planning clinical studies appropriately.

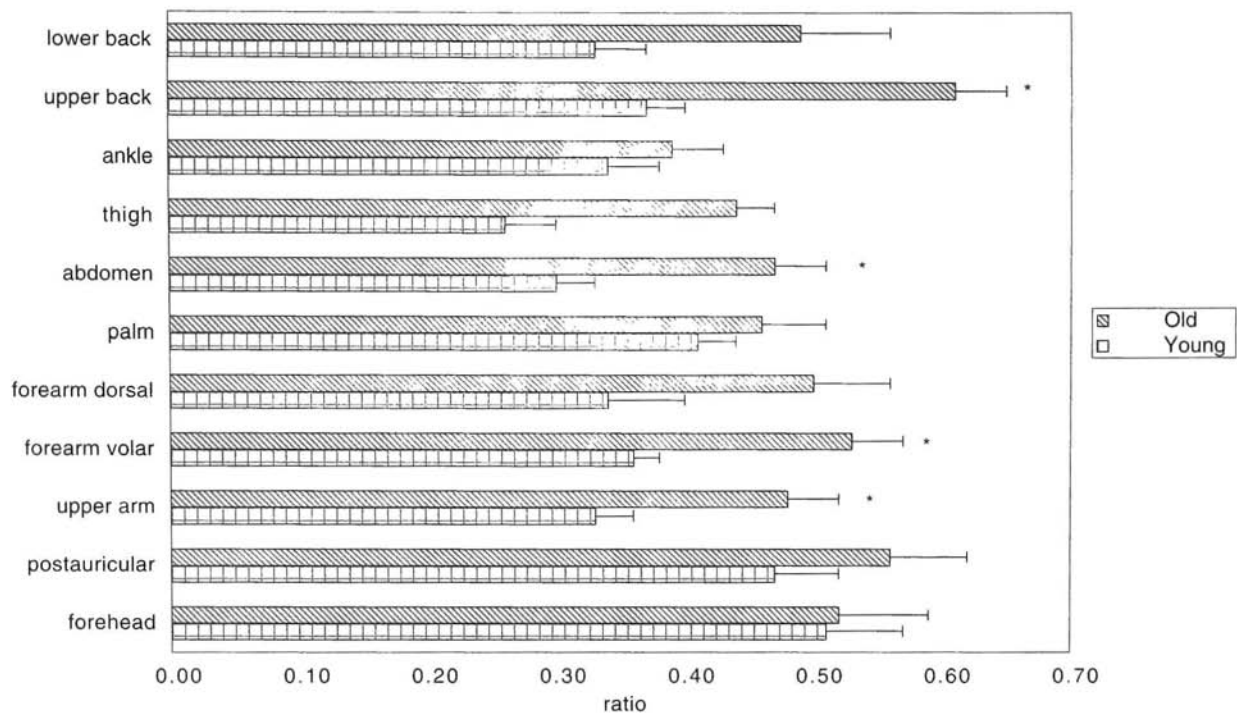
**TABLE 16.3**  
**Viscoelastic Proportion of the Total Distension ( $U_v/U_e$ ) at Different Loads**

Region	Load (mbar)	Young			Aged		
		Mean	S.D.	S.E.M.	Mean	S.D.	S.E.M.
Forehead	500	0.56	0.26	0.07	0.61	0.28	0.07
	200	0.51	0.24	0.06	0.52	0.29	0.07
	100	0.50	0.30	0.08	0.59	0.35	0.08
Postauricular	500	0.49	0.27	0.07	0.46	0.26	0.07
	200	0.47	0.21	0.05	0.56	0.25	0.06
	100	0.49	0.13	0.03	0.60	0.20	0.05
Upper arm	500	0.43	0.18	0.05	0.42	0.18	0.05
	200	0.33	0.11	0.03	0.48	0.15	0.04
	100	0.26	0.09	0.02	0.38	0.20	0.05
Volar forearm	500	0.59	0.07	0.02	0.55	0.20	0.05
	200	0.36	0.09	0.02	0.53	0.14	0.04
	100	0.31	0.14	0.04	0.39	0.15	0.04
Dorsal forearm	500	0.46	0.17	0.04	0.64	0.18	0.05
	200	0.34	0.23	0.06	0.50	0.26	0.06
	100	0.30	0.15	0.04	0.35	0.15	0.04
Palm	500	0.49	0.19	0.05	0.53	0.14	0.04
	200	0.41	0.12	0.03	0.46	0.20	0.05
	100	0.60	0.47	0.13	0.63	0.44	0.11
Abdomen	500	0.27	0.14	0.04	0.49	0.26	0.07
	200	0.30	0.13	0.03	0.47	0.17	0.04
	100	0.26	0.08	0.02	0.33	0.15	0.04
Thigh	500	0.34	0.09	0.02	0.44	0.11	0.03
	200	0.26	0.15	0.04	0.44	0.11	0.03
	100	0.40	0.27	0.08	0.41	0.23	0.06
Ankle	500	0.42	0.15	0.04	0.52	0.18	0.05
	200	0.34	0.13	0.04	0.39	0.16	0.04
	100	0.44	0.11	0.03	0.52	0.19	0.05
Upper back	500	0.50	0.12	0.03	0.65	0.23	0.06
	200	0.37	0.11	0.03	0.61	0.16	0.04
	100	0.32	0.12	0.03	0.41	0.14	0.04
Lower back	500	0.38	0.12	0.03	0.54	0.25	0.06
	200	0.33	0.15	0.04	0.49	0.28	0.07
	100	0.35	0.38	0.11	0.38	0.35	0.09

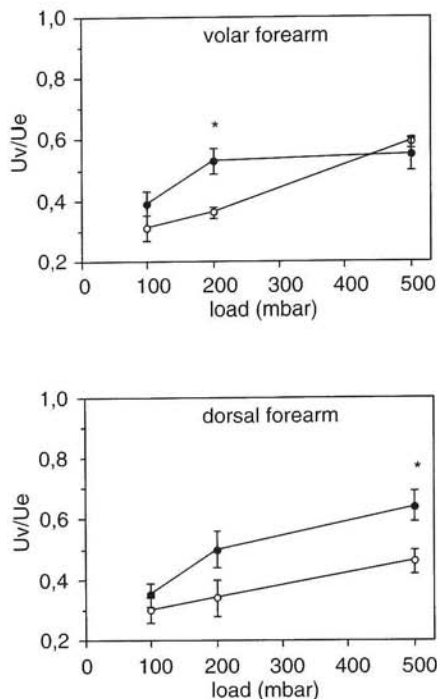
Note:  $U_v/U_e$  increased with increasing loads and tended to be higher in the aged group. Age differences were especially apparent when high loads were applied.

\* Statistically significant difference ( $p < 0.05$ ) between the age groups (Student's t-test); ( $n = 13$  to 16 volunteers).





**FIGURE 16.4** Viscoelastic to elastic ratio ( $U_v/U_e$ ) after 200 mbar load for 5s followed by 5:s relaxation period at 11 different anatomical sites. Means  $\pm$  S.E.M.;  $n = 13$  to 16 volunteers. \* Statistically significantly different ( $p \leq 0.05$ ).



**FIGURE 16.5** Influence of load on viscoelastic-to-elastic ratio ( $U_v/U_e$ ) on the volar and dorsal forearm in young (open circles) and aged (closed circles) volunteers. Means  $\pm$  S.E.M.;  $n = 13$  to 16 volunteers. \*Statistically significantly different ( $p \leq 0.05$ ).

## ACKNOWLEDGMENT

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# 17 Skin Mechanics and Hydration

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## INTRODUCTION

The physical properties of the skin vary with location, age, and sex; but in addition to these endogenous factors, skin hydration is also thought to play a role. Skin consists of two main layers: epidermis (thickness 0.07 to 0.012 mm) and dermis (thickness 1 to 4 mm). Data suggest that both contribute to the overall mechanical properties of the skin, but only the epidermis is available for rapid modification by topical agents either directly or indirectly by, for example, reducing water loss. Topical treatment may also affect the dermis secondarily (e.g., by retinoids), although the timeframe is often much longer for this to occur. Finally, the dermis may be affected by generalized changes in the body. The mechanical effects of skin hydration can therefore involve several different structures.

The water barrier is located to the stratum corneum of the epidermis. Removal of the stratum corneum from human skin results in as much as a 50-fold increase in the rate of water loss from the skin surface.<sup>1</sup> This structure also allows for control of the plastic properties of the corneocytes and of the internal aqueous balance of the body. Forslind<sup>2</sup> describes the skin barrier as composed of two major components: a hydrophilic component, the keratin; and a hydrophobic component. The intercellular lipid material represents the lipophilic/hydrophobic constituent. The lipid phase primarily acts as a barrier against water loss from the body but also prevents free access of water and foreign substances into the body. At the same time, it allows a minute loss of water, which is thought to plasticize the stratum corneum under normal circumstances. This baseline water diffusion (*perspiratio insensibilis* or the unnoticed perspiration) amounts to 2.25 L/m<sup>2</sup>/s and is distinct and separate from

sweat gland secretion. The plasticity of the corneocytes is achieved by hydration of the keratin;<sup>3</sup> i.e., water is a plasticizer of keratin.<sup>4</sup> It is also a clinical impression that overall skin plasticity is dependent on sufficient hydration of the epidermal corneocytes. In skin diseases with reduced plasticity, e.g., chronic eczema or psoriasis, secondary features such as fissures may be related to a stiff, thick, and dry stratum corneum. If the corneocyte keratin is deprived of its water, the material becomes brittle, nonelastic, and breaks easily.

Lipids that can form biological membranes are characterized by a common structure: a hydrophobic component, generally fatty acid hydrocarbon chains, and a more or less hydrophilic head. For thermodynamic reasons the hydrophobic parts of the lipid molecules are segregated to form a separate region, whereas the hydrophilic head group faces the surrounding aqueous face.<sup>5</sup> Specific skin lipids may confer specific barrier properties and plasticity to the skin. In addition, Friberg and Osborne<sup>6</sup> have proposed that a liquid crystalline state of the intercellular lipids is required for optimum barrier function. It may be speculated that the state of the intercellular lipids also influence the mechanical properties of the epidermis. The balance between liquid and solid crystalline phases of the lipids is influenced by hydration, proportion of unsaturated fatty acids, and probably other unknown factors. The skin is constantly influenced by physical and chemical agents, which abrade the epidermal surface mechanically and extract or change the composition of the intercellular lipids. Therefore, a continuous renewal of the lipid structures constituting the water barrier is necessary.<sup>2</sup>

The dermis is traditionally divided into the papillary layer and the reticular layer. The papillary layer is adjacent to the epidermis and living cells are most abundant in this part of the skin.<sup>7</sup> The deeper reticular layer contains the ground substance containing glycosaminoglycans. A major component is hyaluronate, which is hydrophilic and binds most of the tissue fluid.<sup>8</sup> The major determining structure for the overall mechanical properties of the skin is the dermis, and in particular the deeper reticular layer. It consists of collagen, elastin, and reticulin fibers embedded in an amorphous gel-like ground substance. The fibers are thought to be responsible for the highly nonlinear behavior when the tissue is being stretched.<sup>9</sup> The ground substance probably plays a major role when the tissue is under compression. The large molecules of hyaluronate with the bound tissue fluid behave like a gel, which can be regarded as a solid. Some authors are of the opinion that there must be a small amount of free movable fluid in the ground substance that is not bound in the gel or the cells.<sup>10,11</sup> According to Oomens et al.<sup>8</sup> the fiber network embedded in the colloid-rich part of the ground substance can be regarded as some fiber-reinforced solid while the free fluid is considered to be a Newtonian fluid. Oomens et al.<sup>8</sup> compare the bulk material to a sponge. When the sponge is compressed, the fluid will be displaced and the viscosity of the fluid will create a resistance against this flow. Furthermore, the size of the pores of the sponge will decrease when the sponge is depressed. Overall, these components result in a nonlinear time-dependent behavior of the bulk material under compression. Skin hydration affects the mechanical properties of dermis as well since water is bound by both ground substance and collagen fibers.

Several structures that are all susceptible to changes in hydration are therefore potentially involved in determining the overall mechanical properties of human skin *in vivo*. Changes induced by externally applied substances may therefore occur either through a direct action on epidermal structures or through modification of the overall skin homeostasis through, e.g., changes in hydration secondary to changes in water evaporation, or through modification of dermal structures. The time-effect relationship of externally applied plasticizing substances can furthermore offer clues to the nature of involved structures, e.g., the slow action of retinoids affecting epidermal as well as dermal structures, or the near immediate effects of water affecting the stratum corneum.

### THE INFLUENCE OF CHANGES IN OVERALL SKIN HYDRATION ON THE MECHANICAL PROPERTIES OF SKIN

The overall correlation between untreated skin and stratum corneum hydration has been studied using capacitance measurements (Corneometer) and the suction cup technique (Dermaflex).<sup>12</sup> A poor correlation was found, and it was concluded that in the absence of external modifications, such as emollients, skin capacitance was a poor single predictor of its mechanical properties. This conclusion should, however, be interpreted with caution because of the chosen method for measurement of skin hydration, which exhibits a shallow penetration of the epidermis.<sup>13</sup> Hydration of the deeper epidermis was therefore not measured, which may have contributed to the negative results.

A number of experiments describing the consequences of more or less selective active hydration or dehydration of various compartments of the skin, however, strongly suggest that both affect the mechanical properties of the skin. This has been shown using both shear wave propagation and suction cup methods. The viscoelasticity skin analyzer (VESA) is a fast, noninvasive, user-friendly method to evaluate skin viscoelasticity by the speed of elastic shear wave propagation (SWP). This method does not modify the fine structure of the skin.<sup>14-16</sup>

Vexler et al.<sup>17</sup> induced skin edema in rabbit ears by using croton oil as a model for changes restricted to the dermal layers of the skin, i.e., changes in hydration of the deeper dermal layers. Initially, the SWP was similar in the upper and the middle areas on both ears. After treating the upper area, the SWP was significantly ( $p < 0.0001$ ) elevated in both horizontal and vertical directions indicating the increased stiffness of edematous skin. More-pronounced changes were observed along the long axis of the ear, indicating the increase of the skin anisotropy (directional variations in viscoelasticity) in the edematous areas by roughly 15 to 20%. The results are similar to the reduced skin viscoelasticity observed in the patients with postmastectomy lymphedema.<sup>15</sup> By using the Dermaflex machine, similar effects have also been noted in analogous studies of histamine-induced wheals in human skin.<sup>18</sup>

These experiments suggest that volume changes of the dermis affect the overall mechanical properties of the skin adversely. It is thought that this is a consequence

of prestretching the fibers and reducing the possibilities for shifts of the ground substance. These changes cause the skin to lose plasticity, and are in good agreement with crude clinical assessments of overall skin elasticity in edema.

Brazelli et al.<sup>19</sup> made an analogous observation by using hemodialysis as a model to investigate the effects on biophysical properties of the skin induced by removal of fluids and water from the body. Removing water from one compartment to another (from skin to blood) decreases skin thickness after therapy. A significant positive correlation between changes in skin thickness and stratum corneum water content was found. The decrease in the water content of the skin implied an increase in distensibility and a decrease in elasticity. Significant linear correlations were found among stratum corneum water content, skin distensibility, and transepidermal water loss (TEWL).

## MOISTURIZERS AND SKIN PLASTICITY

The mechanism of moisturization is not fully understood, although many details have been described. Querleux et al.<sup>20</sup> have used magnetic resonance imaging as a tool for *in vivo* quantification of water content and water behavior in living tissues.<sup>20</sup> Hydration profiles obtained by this method delineate two different structures of stratum corneum: an outer layer where hydration can be altered by external factors and an inner layer where hydration is not altered. Hydration may be altered by water actively penetrating into the skin, or by water accumulation due to reduced evaporation as the water barrier is improved by moisturizers.

Several *in vivo* mechanical studies of the skin have been carried out to describe the effect of moisturizers or their constituents on the mechanical properties of skin. A number of studies using different techniques have been conducted to suggest that the use of moisturizers affects the water content of the stratum corneum. The techniques use different methodological principles either to quantify skin hydration directly or to assess derived surrogate measures of skin hydration.<sup>16,21</sup>

Changes in skin conductance, impedance, or capacitance are frequently used to study epidermal hydration *in vivo*. These methods correlate mutually and have been shown to correlate to tissue water although the presence of other electrically active molecules may influence the measurements.<sup>16,22</sup> Other aspects of dry skin have also been used as surrogate measures of skin hydration. Scaling has been assessed using D-squame tapes as well as image analysis, and roughness has also been considered as a surrogate measure.<sup>16</sup> It has therefore been of obvious interest to study the influence of externally applied substances on the mechanical properties of skin *in vivo*.

Van Duzee<sup>22</sup> examined the elastic modulus of the skin as a function of water content for untreated stratum corneum and stratum corneum treated with urea and LiBr. The modulus was found to be a function of water content, not water activity. To clarify the role of water, Jemec et al.<sup>23</sup> conducted a simple experiment to study the effect of superficial hydration on the mechanical properties of skin *in vivo* using topically applied tap water. The water was applied to the ventral aspect of the forearm of healthy volunteers for 10 or 20 min. Afterward, the skin distensibility, resilient distensibility, elastic retraction, and hysteresis were measured.



Distensibility is the distension of the skin when negative pressure (suction) is first applied in the suction chamber, and resilient distensibility is any elevation of the skin remaining after the first suction. Elastic retraction is the ability of the skin to return to its original position after suction, and hysteresis is the distance that the skin is stretched beyond the distensibility when the suction is repeated over the same area: the creeping phenomenon. Significant increases in distensibility, resilient distensibility, and hysteresis were noted after 20 min of hydration. Most of these findings were already apparent after 10 min. The parameter that showed the greatest change was hysteresis.

The observations were supported by Auriol et al.,<sup>24</sup> who studied skin elasticity before and after 1, 2, 5, and 10 min of hydration by application of tap water. After hydration there was an increase in all rheological parameters linked to elasticity. These modifications occurred from the first minute and increased thereafter.

These observations were followed by studies of possible effects of some moisturizer components. Olsen and Jemec<sup>25</sup> studied the influence of tap water, paraffin oil, ethanol, and glycerin on skin mechanics, since these substances are common ingredients in moisturizers and emollients. Distensibility and hysteresis showed the most-pronounced changes. Water and paraffin oil application caused significant ( $p < 0.03$ ) increases after only 10 min, persisting for at least 10 min following paraffin oil but less following water application. Glycerin had a slow onset of action, but the changes remained even after cessation of the application. Application of ethanol had a negative effect on distensibility ( $p < 0.03$ ). The rapid onset of action suggests that the outermost layers of the epidermis play an important role in skin mechanics, and the observation that ethanol reduces distensibility suggests that the method used is sensitive to a range of changes.

These results suggested that the mechanical studies of short-term effects were viable, and in continuation of these studies Jemec and Wulff<sup>26</sup> therefore measured skin mechanics (distensibility and hysteresis) and capacitance when using six different types of moisturizers on healthy and atopic skin. Baseline mechanical values were similar in the two groups, but capacitance was significantly lower in atopics ( $p < 0.001$ ). The results were that all moisturizers increased distensibility as well as hysteresis of normal and atopic skin, but that atopic skin was more influenced by moisturizers than was normal skin. Furthermore, high-lipid moisturizers caused significantly greater changes in plasticity of normal skin than low lipid moisturizers while no such effect was observed for atopic skin. A similar study was subsequently conducted in healthy skin and reproduced the findings, suggesting that the amount of lipids in the applied moisturizer was correlated with the changes in the mechanical properties of the skin.<sup>27</sup>

Pedersen and Jemec<sup>4</sup> conducted a study of the plasticizing effect of water and glycerin on hysteresis (change in maximal elevation following repeated suction, the creep phenomenon) and distensibility (maximal distension achieved) on human skin *in vivo* using the Dermaflex machine. Water or glycerin was applied to the flexor side of the forearm, regional untreated skin served as baseline, and readings were made after 3, 6, 9, 12, and 15 min. Both substances caused a significant increase in hysteresis, water after 12 and 15 min of hydration ( $p < 0.01$ ), glycerin after 3 min ( $p < 0.05$ ), and the effect continued to the end of the observation period.

No significant differences were seen in distensibility. Because of the rapid onset of action for both substances, the effects are thought to take place in the outermost layers of epidermis.<sup>22-24,26</sup>

Vexler et al.<sup>17</sup> also examined possible changes in viscoelasticity following local application of hydrating creams (two types) and placebo evaluated by VESA measurements in four volunteer women before and at different time intervals after cream application. The upper, middle, and lower area of the forearm were examined. Both hydrating creams significantly reduced skin stiffness (lowered SWP readings), while the placebo had no significant effect. These changes were found only along the long axis of the forearm and persisted for about 3 h.

## COMMENTS

Plasticity is reduced in dry skin, and emollients have traditionally been used to ameliorate the discomfort caused by skin dryness. The water content of the stratum corneum may play a role in this reduced plasticity, and hydration has therefore been a focal point for several studies, although it is unlikely that a monocausal relationship exists between water and plasticity of the entire skin.<sup>3</sup> Skin hydration can nevertheless affect the mechanical properties of human skin *in vivo*, and is a factor that must be taken into consideration when measuring the mechanical properties of the skin for other purposes.<sup>28</sup> A body of literature exists to suggest that changes occur both in short-term studies and in studies of a longer duration.

The exact underlying mechanisms are not known but are thought primarily to involve epidermal structures because of the responsiveness of the tissue and the presence of the epidermal water barrier. Other substances may have similar effects with a longer lead time — e.g., various lipids and absorbed substances such as retinoids are known to affect a wider variety of skin structures through established biological mechanisms. Because the mechanisms are not known, and because the loss of plasticity is such a prominent feature of dry skin, mechanical measurements may be particularly pertinent to the study of dry skin.

Using the mechanical properties as a functional measure of the effects of skin hydration, however, is not an established technique, and additional methodological work is required to verify and support the methods used in the discussed studies. In particular, the predictive value — both over time and in relation to subjective measures — of the published observations remains to be described, as do the underlying biological mechanisms. Objectively measuring the mechanical properties of human skin in relation to dry skin and hydration may therefore prove even more interesting in the future.

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# 18 Skin Tensile Strength in Scleroderma

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## INTRODUCTION

Assessment of the mechanical properties of skin is useful for evaluation of the severity and therapeutic response of a series of connective tissue disorders including scleroderma.<sup>1</sup> Indeed, a great contrast may exist between the tensile strength of normal and diseased skins. The whole of healthy skin exhibits both flexibility and relative resistance to deformation, thus permitting body movement and allowing temporary compression and distention of a part. Once the deformation ceases, elasticity permits the skin to return spontaneously and progressively to its initial shape. As such, progressive resistance to deformation, flexibility, and elasticity must be adequately balanced to fulfill the ideal tensile strength of the skin. In general, it is reasonable to consider that one is unlikely to be far wrong in interpreting the tensile properties on whole skin as representing the properties of the dermis and subcutaneous tissues. The behavior of the three-dimensional fibrous meshworks is the combination of the response of the components to which the deformation is applied. Such properties represent the functional expression of the structural configuration of the connective tissue from the molecular level to the microscopic level.<sup>1-3</sup>

In reality, the variation in mechanical properties of the skin due to body region, age, and gender outweighs the variability in biochemical composition of skin connective tissues.<sup>1</sup> As a result, the *in vivo* tensile strength of the skin is notoriously complex to assess precisely and may be difficult to interpret, particularly in pathological conditions.<sup>1</sup> This is largely due to the composite structure of the

dermo-hypodermal tissues. The typical mechanical response of each macromolecular component is variable within the wide range of force intensity encountered in life. This obviously adds to the difficulties in interpreting data and unraveling the tensile strength complexity of the skin.

The understanding of the skin mechanical properties in scleroderma is so complex that it is difficult to obtain anything approaching the sort of clean result one obtains from the establishment of the molecular composition of the dermis. Indeed, the correct interpretation of *in vivo* mechanical measurements requires a knowledge of the overall microstructure of the connective tissue, including the arrangement of collagen and elastic fibers, and their relation to other biological components.

## STRUCTURE OF THE CONNECTIVE TISSUE

In general, there is a clear interdependence between the structure and mechanical functions of connective tissues.<sup>1-3</sup> Although the basic properties of the individual fibrous components are quite well identified *in vitro*, the relationship is somewhat complicated *in vivo*. The varying way to stretched presentation of fibers at rest governs part of the mechanical properties. Looseness or compactness of the networks is also important. The situation is further clouded by the presence of physical entanglements between the diverse fibrous structures.

The bulk of the reticular dermis in scleroderma consists of a dense network of collagen fibrils and fibers, the organization of which conditions the mechanical stability of the tissue and its resistance to deformation.<sup>4</sup> The collagen fibrils that are identified by electron microscopy are packed into fiber units visible in the light microscope. Primary and secondary fiber bundles denote assemblies of these fibers. How fibers are packed and held together is important with regard to the mechanical properties of the tissue. Cross-links between collagen molecules are not the primary cause for aggregation of fibrils, but rather the interfibrillar matrix plays an important role here. On a higher hierarchical level, the coarse collagen bundles are connected to each other, and most often closely packed and stretched in superimposed planes grossly parallel to the skin surface.<sup>4</sup> The elastic fibers present in smaller amounts normally serve to restore deformed collagen bundles to a more relaxed and wavy position. This is hardly possible in scleroderma. So-called reticulated fibers are organized in an open network around the bundles of collagen fibers. This multicomponent system of fibers is permeated by a more or less hydrated matrix composed of proteoglycans and glycoproteins in which are located cells of diverse phenotypes. These cells are responsible for maintaining and remodeling the macromolecular matrix. They may exert a contractile activity upon the fibrous networks through the intervention of adhesion molecules.<sup>5,6</sup>

Both the thickness and intimate structure of the dermis play prominent and independent mechanical roles. For example, a major role is sometimes ascribed to the structure, density, and location of the elastic fibers when measuring the tensile strength involved in discrete skin deformations.<sup>3,7</sup> In fact, although it is well acknowledged that these fibers exhibit typical elastic properties, any change in the overall elastic functional properties of the skin cannot be ascribed solely to them. Many

other structures participate in elasticity, and it is practically impossible to disentangle their respective contributions in the tensile response of the skin.<sup>1</sup>

## CLINICAL ASSESSMENT OF SCLERODERMA

Scleroderma is a heterogeneous group of diseases with distinct clinical manifestations. The main types are the localized forms (morphea, monomelic) and the systemic forms. The clinical classification of systemic scleroderma distinguishes three types. Type I is acroscleroderma including a subgroup of the Raynaud's syndrome. Type II is acroscleroderma with progression of sclerosis to proximal areas of the limbs. Type III is diffuse scleroderma usually starting on the trunk with rapid progression to other areas including the extremities.

Skin involvement in scleroderma is characterized by hardness and hidebinding as a result of massive deposition and straightening of collagen bundles. Temporary dermal edema may occur. Skin induration and tethering can be evaluated according to skin severity scoring obtained by clinical palpation. There exists an overlap between the different skin scorings such as the "skin thickness index" and the "skin tethering/hidebound index." The skin thickness/hidebinding is scored in a 4-point scale (0: normal, 1: mild, 2: moderate, 3: severe). It is generally accepted that the sclerotic skin changes correlate with the overall disease activity and prognosis of systemic sclerosis.<sup>8-10</sup> Unfortunately, such assessments remain subjective with low intra- and interobserver reproducibility.<sup>8-16</sup> In addition, they are not free of bias. According to studies, the modified Rodnan skin score has been calculated from 17, 26, or 74 body areas.<sup>8,9,15</sup>

## INSTRUMENTAL ASSESSMENT OF THE SKIN TENSILE STRENGTH

In general, the tensile strength of scleroderma skin has been studied noninvasively by distinct methods applying forces in parallel or perpendicular fashion to the skin surface. Stretching, indentation, elevation, suction, torsion, and vibration devices can afford sound although sometimes distinct or even contradictory information.<sup>1,17</sup> The real value of measuring the tensile strength *in vivo* may be sometimes uncertain because of confounding factors that are not always suspected clinically. These include regional variations in the tensile strength and variability due to body posture, age, gender, and cumulative ultraviolet exposure.<sup>1</sup>

To add complications, tensile strength of the whole skin is normally time dependent. Indeed, when skin is stressed by a load, the overall response of the organ to alter its shape is nonlinear. A rapid elastic extension normally takes place at first to give way to a viscoelastic phase with much less extension. When the load is maintained at a particular level for a period, further extension, known as mechanical creep or viscous extension, gradually takes place. Such phenomena, representing the previous stress history, also occur when a series of stresses are consecutively applied and removed. When the strain is maintained for days and weeks, tissue remodelings progressively occur and are responsible for a biological creep corresponding to a

relaxation distinct from the mechanical creep. Because of the above considerations, time-dependent tensile strength depends to some extent on the rate at which the load is applied, the duration for which it is sustained, and the previous stress history, as well as the preconditioning of the site. In scleroderma, biological creep and mechanical creep are reduced, particularly during the sclerotic stage.

The quantitative assessment of skin toughness in scleroderma may appear of interest for monitoring both the progression of the disease and the effectiveness of therapies. Surprisingly, only a few studies on the mechanical properties of skin in patients with scleroderma have been carried out until now. They were performed using different devices without any standardized protocols. Hence, results are difficult to compare, even if there is overall agreement concerning the basic and specific changes in the viscoelastic properties of skin.

Noninvasive bioengineering techniques such as high-frequency ultrasound<sup>18-22</sup> and possibly nuclear magnetic resonance imaging<sup>23</sup> are well suited to provide reliable and sensitive data. It is beyond doubt that the various tissue thicknesses and volumes affect the overall tensile strength of the skin in scleroderma. However, it is hazardous and probably misleading to use the dermal thickness measured using ultrasound methods as a single severity criterion for scleroderma. Indeed, although the dermis is often thickened, variations in time may be large. When the collagen and elastic fibers are stretched at rest during the induration phase, cutaneous edema subsides and skin thickness may decrease.<sup>22</sup>

Hidebinding is the most impressive and typical change in scleroderma<sup>4,9</sup> and is not directly related to dermal thickening. In fact, it is difficult to pinch the sclerotic skin into a fold. Only a few noninvasive bioengineering methods can adequately assess the deep fixation and induration of the skin.<sup>1,2,4,15,16,24-39</sup> Among them, the suction method is a close imitation of lifting the skin between the fingers to assess hidebinding adequately. Indeed, an important aspect of the global tensile functional properties of cutaneous tissues is the tethering of skin to the fat layer. In scleroderma it limits the free mobility of the dermis.<sup>1,2,40</sup>

The dermis is not a homogeneous structure because it exhibits tremendous differences between its different layers, and also with the variable severity of solar elastosis. In addition, there is ample evidence that the volume of the hypodermis and of the eventual sebaceous lobules is of equal, if not greater, importance than the dermal thickness itself in its influence on the overall tensile functional properties. In fact, the fat-enriched lobules made of either sebocytes or adipocytes place the dermis under tension, limiting the mobility of skin.<sup>1</sup> As a consequence of these uncertainties, the calculation of ratios between *in vivo* tensile stress and tissue strain (Young's modulus, shear modulus, bulk modulus) can only be viewed as theoretical concepts with probably little relevance when applied *in vivo* to the complex composite of structures making skin and its subcutaneous tissue. This is particularly true in scleroderma.

Skin involvement in systemic scleroderma begins on the acral portion of the limbs, where it usually remains more prominent than on other body sites. It would be conceivable to choose other specific target sites for biomechanical assessments. However, the physical properties of normal skin vary greatly depending on the body site, and computation of many measurements should be performed before



recommending a specific body site other than the forearm for comparative assessments of acroscleroderma.<sup>37</sup>

The size of the test area influences the data, which may appear conflicting in some instances. The superficial dermis of scleroderma can be atrophic, and skin distension measured on a small area (2-mm measuring probe) increases. By contrast, hidebinding the skin to underlying tissues is responsible for low distensibility when measured on a larger surface area (8-mm measuring probe). The resistance to vertical stress is essentially due to the dermis rather than the hypodermis, although the relative contribution of each is not easily distinguished. The subcutaneous fat compartment is likely more involved by high suction pressure applied to large surface areas than by lower suction pressures to smaller surface areas. Because the main alterations in scleroderma are localized in the reticular dermis and hypodermis, a large measuring probe and a high suction force might appear to yield more relevant information. At all stages of scleroderma, skin distensibility decreases. This functional characteristic is linked to the stretching of the collagen fibers and reflects the skin induration and the deep tethering. The viscoelastic ratio is highly variable among patients and even in time in a given patient. This aspect may be ascribed in part to fluctuations in dermal edema and load in proteoglycans. The immediate retraction ability following the suction release is often decreased.<sup>36</sup> The biological elasticity is either unmodified or increased, particularly during the terminal sclerotic phase of the disease.<sup>2,37</sup>

It is acknowledged that the 2- and 8-mm probes of the suction device do not measure precisely the same aspect of the tensile properties of skin.<sup>41</sup> Their use in combination in the same patients allows one to somewhat disentangle the contribution of the different layers of the cutaneous connective tissue.<sup>38</sup> Using such a combined approach, the trends in biomechanical alterations of skin appear to be alike in all forms of the disease. Skin changes are then best identified by the decrease in the value of the 8-mm/2-mm skin distensibility ratio.<sup>37</sup>

Skin viscoelasticity can be assessed by the suction method by determining the ratio  $U_v/U_e$ . However, such a value is arbitrarily determined by choosing the time of measurement during the suction phase. Hence, this ratio is not standardized among the different investigators. Another way to assess skin viscoelasticity consists of measuring the speed of propagation of acoustic waves. The shear wave propagation shows physiological variability and directional differences on normal skin in relation to the mechanical anisotropy responsible for the Langer's lines and the resting tension lines.<sup>42-44</sup> According to the authors' experience, such evaluations are sensitive and can be used to monitor the edema severity of scleroderma.

## ASSESSMENT OF THERAPEUTIC EFFICACY

Objective evaluation of skin stiffening has obvious advantages over subjective clinical rating. It may be added to the range of biological and functional evaluations already in use for estimating internal organ involvement by scleroderma. The therapeutic efficacy may be markedly different on the various organs affected by scleroderma. For instance, improvement in pulmonary function is not usually correlated with recovery of skin mobility.<sup>37</sup>

A decrease in skin stiffness does not occur spontaneously or under various ancillary treatments. Only a few clinical studies have reported improvements of scleroderma. They are hardly confirmed when using the criteria of evidence-based medicine. Because of the natural course of acroscleroderma, any therapy resulting in stabilization of the skin involvement should be regarded as beneficial. A drug yielding a prominent regression of cutaneous sclerosis is not yet available.

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# 19 Mechanical Properties in Other Dermatological Diseases

*Hristo P. Dobrev*

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## INTRODUCTION

Human skin, as a complex multi-layered organ, has three major mechanical properties:<sup>1,2</sup>

- Stiffness, i.e., resistance to change of shape;
- Elasticity, i.e., ability to recover the initial shape after deformation;
- Viscoelasticity, i.e., time-dependent deformation with a “creep” phenomenon and nonlinear stress–strain properties with “hysteresis.”

These properties are altered in dermatological diseases, which are accompanied with pathological induration or softening of the skin. Noninvasive bioengineering measurements allow quantifying the alterations of skin mechanics *in vivo*. On the other hand, each mechanical parameter determined is related to the corresponding structure and composition of the skin and thus gives information regarding which components are affected.

This chapter describes the mechanical properties of the skin in dermatological diseases such as Ehlers–Danlos syndrome, scleredema of Buschke, psoriasis vulgaris, erysipelas, and lymphedema of the lower limbs and discusses the possibilities for diagnostics, differential diagnostics, and disease monitoring using bioengineering measurements.

## GENERAL DESCRIPTION OF THE INSTRUMENTS AND SKIN MECHANICAL PARAMETERS

Mechanical properties of the skin have been studied by Twistometer,\* Dermaflex A<sup>®</sup>,\*\* and Cutometer<sup>®†</sup> SEM 474. These instruments differ with regard

\* L'Oreal, France. The instrument based on L'Oreal invention that is now commercially available is the Dermal Torque Meter<sup>®</sup>, Dia-Stron, Hampshire, U.K.

\*\* Cortex Technology, Hadsund, Denmark.

† Courage and Khazaka, Cologne, Germany.

to measuring principle, direction of the mechanical stress, size of the test area, and mechanical parameters determined (Table 19.1).<sup>2-5</sup> Moreover, most studies have been performed using different measuring schemes (Table 19.2). Despite that, possibilities for comparison of general information obtained exist. Basic principles, which must be considered, are as follows:<sup>2-6</sup>

- The small-size measuring probes determine the mechanical properties of the epidermis and papillary dermis, whereas large measuring probes determine those of the whole skin.
- Mechanical parameters are related to the structure and composition of the skin and provide information about its three major mechanical properties. Skin distensibility parameters are linked to the stretching of collagen and elastic fibers and reflect the skin thickness and rigidity. Elastic parameters are related to the function of elastic fibers. Viscoelastic parameters are attributed to the water content of the skin and displacement of the interstitial fluid throughout the fibrous network in the dermis.
- Mechanical parameters determined are absolute and relative. Only the relative parameters are independent of the skin thickness and can be directly compared between subjects, anatomical regions, and time points.

Table 19.1 shows the comparable mechanical parameters of the skin determined by means of the three devices.

**TABLE 19.1**  
**Devices and Mechanical Parameters of the Skin**

Device	Twistometer	Dermaflex	Cutometer
Measuring principle	Torsion	Suction	Suction
Test-area size	1, 3, and 5 mm	10 mm	2, 4, 6, and 8 mm
Stress direction	Plane	Vertical	Vertical
<b>Mechanical Property</b>	<b>Mechanical Parameters of the Skin</b>		
Distensibility	$U_e$	TD	$U_e, U_f$
Elasticity	$U_r/U_e$	RER	$U_a/U_f, U_r/U_f, U_r/U_e, U_r$
Viscoelasticity	$U_v$	H, RD	$U_v, U_v/U_e, R8, H, R$

*Legend:*  $U_e$ , immediate distension (elastic deformation); TD, tensile distensibility =  $U_f$ , final distension; RER, relative elastic retraction =  $U_a/U_f$ , gross elasticity;  $U_r/U_e$ , net elasticity;  $U_r/U_f$ , biological elasticity;  $U_r$ , immediate retraction;  $U_v$ , delayed distension (viscous deformation);  $U_v/U_e$ , viscoelastic to elastic ratio,  $H$ , hysteresis; R8, viscopart; RD, resilient distension =  $R$ , residual skin elevation (residual deformation) after the release of the first suction. (For details see previous book chapters.)

**TABLE 19.2**  
**Measurement Schemes**

Disease	Device	Probe (test-size), mm	Mode <sup>a</sup>	Measuring Scheme	Ref.
Ehlers–Danlos syndrome	Twistometer	3	1	—	in 3
	Cutometer	4	1	500 mbar, 5s/5s, 3 cycles	7
Scleredema of Buschke	Cutometer	2; 8	1	400 mbar, 5s/5s, 1 cycle	9–11
Psoriasis	Dermaflex	10	2	300 mbar, 3s/3s, 9 cycles	12
	Cutometer	2; 8	1	450 mbar, 5s/3s, 5 cycles	13
Erysipelas	Cutometer	2; 8	1	450 mbar, 5s/5s, 3 cycles	14
		2; 8	2	450 mbar, 45 mbar/s, 10s/10s/5s, 3 cycles	11
Lymphedema	Cutometer	6	1	300 mbar, 3s/3s, 3 cycles	15

<sup>a</sup> Mode 1 = suction phase with constant negative pressure and relaxation phase at vacuum 0. Mode 2 = suction phase with linearly rising negative pressure followed by linearly decreasing negative pressure and relaxation phase at vacuum 0.

## MECHANICAL PROPERTIES OF THE SKIN IN DERMATOLOGICAL DISEASES

### EHLERS–DANLOS SYNDROME

Ehlers–Danlos syndrome (EDS) is a group of nine heritable connective tissue diseases of collagen metabolism characterized by clinical evidence for skin hyperextensibility.

#### Mechanical Properties of the Skin

Bramont et al. (cited in Reference 3) investigated the volar forearm skin of five patients with type 2 EDS by means of skin caliper and Twistometer. They found a significantly lower skinfold thickness and an increased skin extension ( $U_e$ ) in patients than in controls, whereas elastic modulus and the elasticity ratio  $U_r/U_e$  were found unaltered. The authors concluded that thinning of the skin is responsible for the clinically observed hyperextensibility.

Later, Henry et al.<sup>7</sup> determined mechanical properties on the volar forearm skin in 17 children with type 1 to 3 EDS using a Cutometer equipped with a 4-mm probe. They found a prominent increase both in skin extensibility ( $U_e$  and  $U_f$ ) and elasticity ( $U_a/U_f$ ,  $U_r/U_f$ , and  $U_r/U_e$ ). The viscoelastic-to-elastic ratio ( $U_v/U_e$ ) was decreased due to the raised  $U_e$  and lower  $U_v$ . Children with type 1 EDS were the most affected, whereas those with type 3 EDS had nearly normal skin.

#### Interpretation of the Changes of Skin Mechanical Parameters

Since distensibility of the skin inversely correlates to its thickness and rigidity, the increase of  $U_e$  and  $U_f$  in EDS suggests thinning of the skin as well as some alterations



in collagen tissue. On the other hand, the increased elasticity parameters suggest that pathological processes do not involve elastic tissue. This is in accord with histological examinations. Skin is atrophic in type 1 EDS; the collagen bundles are thin and rare in the dermis and hypodermic septae, whereas elastic tissue is relatively increased.<sup>8</sup> The alterations are much less evident in the mitis types of EDS. Data of bioengineering measurements correspond with these findings.

### **Correlation between Clinical Assessment and Mechanical Parameters of the Skin**

Clinical evaluation of patients with EDS shows that skin hyperextensibility is severe in disease type 1, moderate in type 2, and mild in type 3. This impression is confirmed by Cutometer measurements.

### **Diagnostics by Means of Measurements of Skin Mechanics**

Diagnosis of different types of EDS is based mostly on clinical criteria. Objective measurements of skin mechanical properties could be used for early detection and evaluation of the degree of skin involvement.

### **SCLERDEMA OF BUSCHKE**

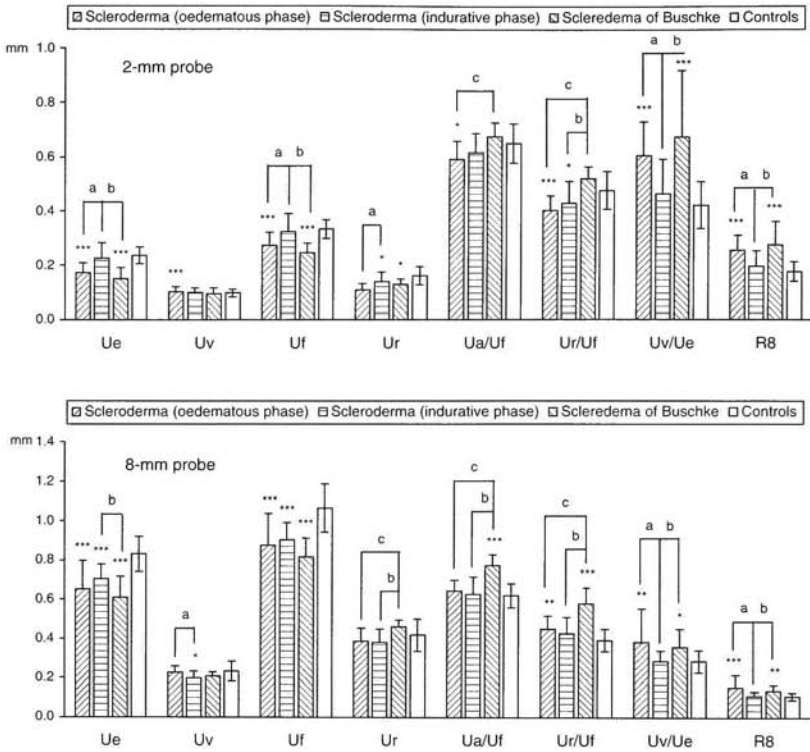
Scleredema of Buschke (SB) is a rare disease of unknown etiology, which is characterized clinically by nonpitting induration of the skin.

### **Mechanical Properties of the Skin**

The authors studied four patients with SB and one patient with SB associated with multiple myeloma.<sup>9-11</sup> Measurements were made by means of Cutometer equipped with 2- and 8-mm measuring probes over 9 anatomical regions. Affected skin showed lower skin distension ( $U_e$  and  $U_f$ ) and higher viscoelastic parameters ( $U_v/U_e$ , R8) in comparison with the skin of healthy controls. Elastic parameters ( $U_a/U_f$ ,  $U_r/U_f$ ,  $U_r/U_e$ ) were preserved as measured by the 2-mm probe and relatively increased as measured by the 8-mm probe (Figure 19.1). The changes were more expressive at infraclavicular regions, upper arms, and volar forearms (Figure 19.2).

### **Interpretation of the Changes of Skin Mechanical Parameters**

The decreased skin distensibility parameters indicate an increased thickness and hardness of the skin. This is due to the thickening of the collagen bundles and enlarged volume of the subcutaneous tissue as a result of a deposition of glucosaminoglycans in the dermis. The viscoelastic-to-elastic ratio ( $U_v/U_e$ ) is raised at the expense of highly decreased  $U_e$ . Values of the elasticity parameters suggest that the elastic tissue is not altered. On the other hand, the recovery of the skin is facilitated by the existing separation of collagen bundles from each other by spaces filled with mucin and reduced friction between fibers. This explains the relative increase of  $U_a/U_f$ ,  $U_r/U_e$ , and  $U_r/U_f$  as measured by the 8-mm probe.



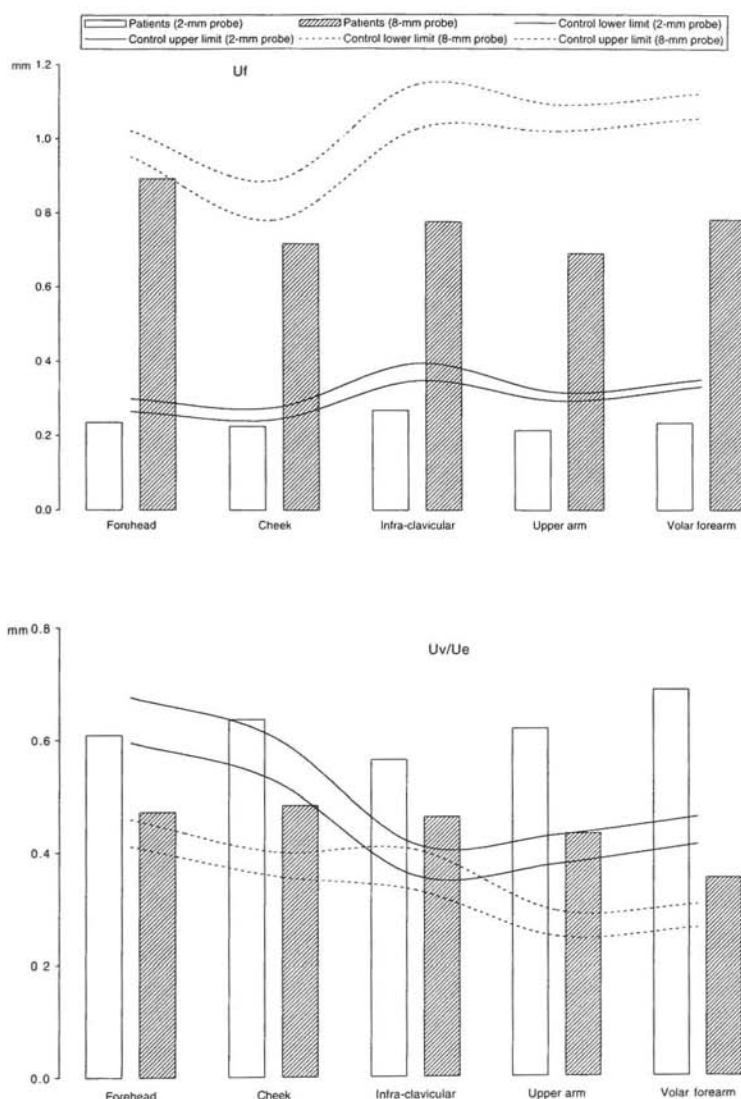
**FIGURE 19.1** Mechanical parameters of the volar forearm skin in patients with edematous phase of scleroderma ( $n = 14$ ), indurative phase of scleroderma ( $n = 16$ ), SB ( $n = 5$ ), and healthy controls ( $n = 30$ ) measured by Cutometer. The average values and standard deviations are shown. t-test between patients and controls  $*p < 0.05$ ,  $**p < 0.01$ ,  $***p < 0.001$ ; a, significant differences between edematous and indurative phase of scleroderma (t-test); b, significant differences between indurative phase of scleroderma and SB (t-test); c, significant differences between edematous phase of scleroderma and SB (t-test).

### Correlation between Clinical Assessment and Mechanical Parameters of the Skin

A significant inverse relationship was found between the severity score of skin induration and the parameters  $U_e$ ,  $U_v$ ,  $U_f$ , and  $U_r$ . Low values of extensibility correlated with severe skin induration (Figure 19.3).

### Diagnostics by Means of Measurements of Skin Mechanics

Bioengineering measurements of skin elasticity are very sensitive. They can detect minimal changes in skin mechanics and thus can be used for early diagnosis of SB. This is of special importance in patients with paraproteinemia. Because the pathological process involves the dermis and subcutaneous tissue, the larger measuring probes, which evaluate the viscoelastic properties of the whole skin, are more suitable

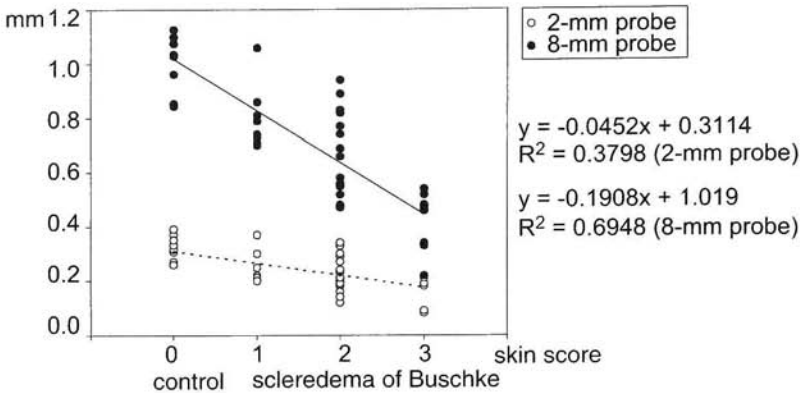


**FIGURE 19.2** Skin distensibility ( $U_f$ ) and viscoelastic-to-elastic ratio ( $U_v/U_e$ ) in patients with SB ( $n = 5$ ) measured by Cutometer at different anatomical regions compared with 95% confidence intervals of healthy controls ( $n = 20$ ).

than the smaller probes. Skin distensibility ( $U_f$ ) and viscoelastic-to-elastic ratio ( $U_v/U_e$ ) are the most indicative mechanical parameters to skin induration in SB. Between them an inverse correlation exists.

### Monitoring of Progress and Treatment Response of the Disease

The increase of skin distensibility ( $U_f$ ) and the decrease of viscoelastic-to-elastic ratio ( $U_v/U_e$ ) indicate a reduction of skin thickness, i.e., an improvement of the



**FIGURE 19.3** Correlation of final distension ( $U_f$ ) with clinical skin score in SB. (From Dobrev, H., *Acta Derm-Venereol.* (Stockh.), 78, 103–106, 1998. With permission.)

disease. Repeated measurements in patients with SB suggest that the traditional treatment approaches cannot essentially influence the disease course. Mechanical parameters initially worsen and then gradually and slowly normalize.<sup>9,11</sup> These data show that SB is a self-limited disease. In a patient with an association of SB and multiple myeloma, Grudeva and Dobrev<sup>10</sup> reported an improvement of skin involvement and mechanics after six-course myeloma polychemotherapy.

## PSORIASIS VULGARIS

Psoriasis is a genetically determined, inflammatory, and proliferative disease of the skin, which is characterized clinically by erythematous scaly plaques.

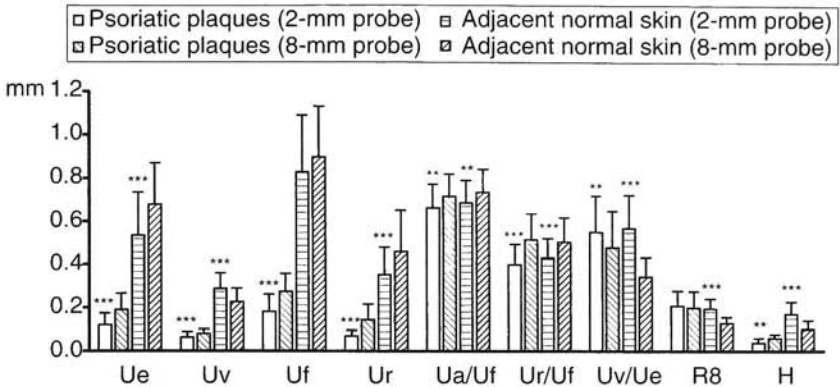
### Mechanical Properties of the Skin

Serup and Northeved<sup>12</sup> measured 23 plaques in ten patients suffering from psoriasis vulgaris by means of high-frequency ultrasound and Dermaflex A. They reported that skin thickness, hysteresis ( $H$ ), and resilient distension (RD) were increased, whereas tensile distension (TD) was decreased in psoriatic plaques as compared with regional control sites of unaffected skin.

The authors studied 82 psoriatic plaques in 19 in-patients with a Cutometer equipped with 2- and 8-mm diameter probes.<sup>13</sup> Using both probes, the plaques showed lower skin distensibility ( $U_e$  and  $U_f$ ) and elasticity ( $U_a/U_f$  and  $U_r/U_f$ ), and higher viscoelastic-to-elastic ratio ( $U_v/U_e$ ) compared with adjacent apparently normal skin. Delayed distension ( $U_v$ ) and hysteresis ( $H$ ) measured by the 2-mm-diameter probe were decreased, but were increased when measured by the 8-mm-diameter probe (Figure 19.4).

### Interpretation of the Changes of Skin Mechanical Parameters

In respect to biomechanics, stiffness and softness simultaneously characterize the psoriatic skin. The first is due to epidermal proliferation, whereas the second is due



**FIGURE 19.4** Mechanical parameters of psoriatic plaques ( $n = 82$ ) and adjacent normal skin measured by Cutometer. The mean values and standard deviation are shown. t-test between psoriasis and controls  $**p < 0.01$ ,  $***p < 0.001$ . (Adapted from Dobrev, H., *Acta Derm. Venereol.* (Stockholm), 80, 263–266, 2000. With permission.)

to vasodilatation and edema in the papillary dermis. The rigidity of the epidermis and the stretched dermal fiber network at rest reduce immediate distension ( $U_e$ ) and final distension ( $U_f$ ) of the skin. Additional degenerative changes in elastic fibers are most likely responsible for the decrease in skin elasticity parameters. The viscoelastic-to-elastic ratio ( $U_v/U_e$ ) is increased at the expense of the decreased  $U_e$ . Delayed distension ( $U_v$ ) and hysteresis ( $H$ ) are attributed to the displacement of the interstitial fluid throughout the fibrous network. These parameters as measured by the 2-mm-diameter probe are decreased, whereas they are increased as measured by the 8-mm-diameter probe. This discrepancy can be attributed to the different aspects of skin mechanics that the two probes measure. The increased epidermal thickness of the psoriatic plaques restricts the depth of measurement with the small-diameter probe. The values of  $U_v$  and  $H$  measured by the 8-mm-diameter probe reflect solely the availability of dermal edema in the psoriatic skin.

### Correlation between Clinical Assessment and Mechanical Parameters of the Skin

The relationships between Cutometer mechanical parameters and clinically assessed induration of the psoriatic plaques were influenced by the diameter of the measuring probe.<sup>7</sup> Using both probes, an inverse correlation between the induration and skin distensibility of the psoriatic plaques was established. Severe induration significantly correlated with higher  $U_v/U_e$  (8-mm probe).

### Diagnostics by Means of Measurements of Skin Mechanics

Measurements performed by means of Cutometer (2-mm probe) established statistically significant lower values of skin distensibility ( $U_e$  and  $U_f$ ) and higher values of viscoelasticity parameters ( $U_v/U_e$  and  $H$ ) of the uninvolved volar forearm skin in

psoriatic patients compared with the skin of age-matched healthy controls.<sup>13</sup> Besides the suggestion that the normal-appearing psoriatic skin is not entirely normal, this demonstrates the sensitivity of Cutometer measurements. More studies are needed to elucidate the value of noninvasive skin elasticity measurements for diagnosis and prediction of psoriasis.

### Monitoring and Comparison of Treatment Response of the Disease

After treatment with dithranol for 11 to 27 days, the mechanical parameters of psoriatic plaques altered toward those of adjacent control skin.<sup>13</sup> The changes in  $U_f$  and  $U_v/U_e$  were most indicative for the improvement of psoriasis. Between them, an inverse correlation exists. An increase of  $U_f$  and a decrease of  $U_v/U_e$  accompany the thinning of the plaques. These parameters can be used for comparison of different treatment methods.

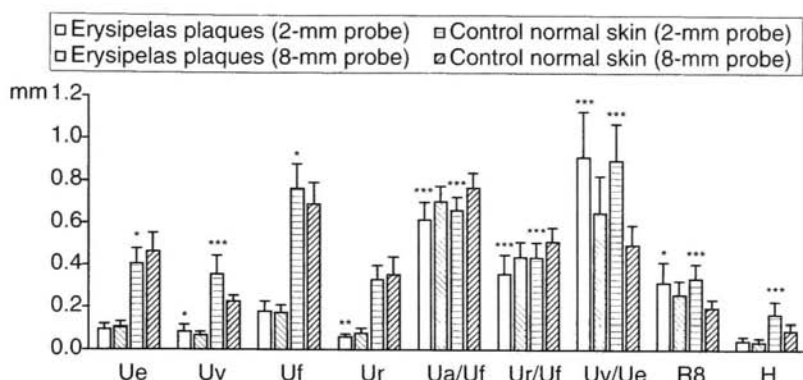
Using the Cutometer, Dobrev<sup>11</sup> compared two methods for occlusive therapy of plaque psoriasis. The first method included an application of 0.05% betamethasone dipropionate cream under hydrocolloid occlusive dressing for 7 days with three changes of the dressing. The second method included a 12-h daily application of ointment containing 1.5% coal tar, 0.02% flumethasone pivalate, and 1% salicylic acid under plastic occlusion for 21 days. The first method produced a significant increase in skin distensibility ( $U_f$ ) and a decrease in viscoelastic-to-elastic ratio ( $U_v/U_e$ ) of the plaques at the first week, whereas the second method provoked a gradual improvement with a maximum at day 21.

### ERYSIPELAS OF THE LOWER LEGS

Erysipelas is a streptococcal infection of the dermis and upper subcutaneous tissue with typical clinical features. Inflammatory dermal edema results in thickening of the skin and an alteration of its mechanical properties.

### Mechanical Properties of the Skin

The authors investigated 25 patients with erysipelas of the lower legs by means of a Cutometer equipped with 2- and 8-mm-diameter probes.<sup>11,14</sup> Two measuring modes were applied. Mode 1 included a suction phase with an application of constant negative pressure and a relaxation phase at vacuum 0. Mode 2 included a suction phase with an application of linearly rising negative pressure followed by a linearly decreasing negative pressure and relaxation phase at vacuum 0. Using measuring mode 1, affected skin was characterized by increased parameters  $U_v$ ,  $U_f$ ,  $R$ ,  $U_v/U_e$ ,  $H$  and decreased  $U_e$ ,  $U_r$ ,  $U_a/U_f$ ,  $U_r/U_f$  (Figure 19.5). Using measuring mode 2, all parameters determined by Cutometer software were higher on the indurated skin except for  $R_8$ . The parameters of final skin distension and hysteresis were universal for the two measurement modes. They showed identical alterations. When the Cutometer is used, the application of measuring mode 2 does not provide any advantage and only burdens the vacuum pump of the device. The changes in skin mechanical parameters were more pronounced with the large than with the small measuring probe.



**FIGURE 19.5** Mechanical parameters of erysipelas plaques ( $n = 25$ ) and control normal skin measured by Cutometer. Measuring mode 1 is applied. The mean values and standard deviation are shown. t-test between erysipelas and controls \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . (Adapted from Dobrev, H., *Skin Res. Technol.*, 4, 155–159, 1998. With permission.)

### Interpretation of the Changes of Skin Mechanical Parameters

Erysipelas plaques are characterized by intense edema and vascular dilatation in the dermis. Therefore, the large-diameter measuring probe is more appropriate for evaluation of the disease. The collagen and elastic fibers are stretched at rest and the immediate distension ( $U_e$ ) is reduced. The great increase in delayed distension ( $U_v$ ), which indicates a decrease in the viscoelasticity of the interstitial fluid as a result of the increased water content, results in raised final distension ( $U_f$ ) of the skin. These changes of Cutometer parameters are indicative of the increased thickness but softness of the affected skin in erysipelas. The increase in parameters  $U_v$ ,  $U_v/U_e$ ,  $H$ , and  $R$  provide evidence of dermal edema. The decrease of relative elastic parameters can be attributed to the increased skin thickness and some alterations of the elastic fibers.

### Correlation between Clinical Assessment and Mechanical Parameters of the Skin

The visual score of edema and leg circumference significantly correlated with the increase in viscoelastic parameters  $U_v$ ,  $U_v/U_e$ ,  $H$  and the decrease in elastic parameters  $U_a/U_f$ ,  $U_r/U_f$ .

### Monitoring of Progress and Treatment Response of the Disease

After a 20-day treatment, a reduction of  $U_v$ ,  $U_f$ ,  $R$ ,  $U_v/U_e$ ,  $H$  and an increase of  $U_a/U_f$ ,  $U_r/U_f$  were observed. The changes in relative parameters  $U_v/U_e$  and  $U_a/U_f$  measured by the large, 8-mm-diameter probe are most suitable for evaluation of erysipelas. The decrease in  $U_v/U_e$  indicates a reduction of inflammatory edema, whereas the increase in  $U_a/U_f$  indicates an improvement of skin mechanics of the affected limb. Thus, the degree of restoration of skin mechanical properties could be used for prediction of the development of lymphovenous insufficiency.

## LYMPHEDEMA OF THE LOWER LIMBS

Lymphedema is due to disturbance of lymphatic drainage. It produces a firm, non-pitting edema with epidermal thickness that alters skin mechanics.

### Mechanical Properties of the Skin

Auriol et al.<sup>15</sup> studied 11 patients with lymphedema of the lower limbs using a Cutometer equipped with a 6-mm-diameter probe. They applied three consecutive measuring cycles, but, instead of the first cycle, they considered the last cycle for calculation of the skin mechanical parameters. In the authors' opinion, this reduces measurement sensibility. Moreover, the authors reported only values of absolute mechanical parameters. From data published, the authors were able additionally to calculate the values of the relative parameters. Decreased  $U_e$  and  $U_r$ , increased  $U_v$  and  $U_v/U_e$ , and lower biological elasticity ( $U_r/U_f$ ) characterized affected skin. The changes in residual deformation ( $R$ ) were not significant.

### Interpretation of the Changes of Skin Mechanical Parameters

Decreased extensibility of the skin is mainly due to the increased volume of the subcutaneous tissue. The fiber network is stretched at rest and immediate skin distension ( $U_e$ ) is reduced. Some degenerative changes of the collagen and elastic fibers are probably additional factors. The interpretation of the parameter residual deformation ( $R$ ) is difficult because it is a mixed parameter; i.e., it results from both the elastic and viscoelastic properties of the skin. On the one hand, the increased skin thickness and alterations in the elastic fibers raise the value of  $R$ . On the other hand, existing edema diminishes the friction between fibrils and tends to decrease  $R$ .

### Monitoring of Progress and Treatment Response of the Disease

The increase in immediate extensibility ( $U_e$ ) after treatment significantly correlates with the decrease in limb volume and diameter, and decrease in delayed distension ( $U_v$ ). According to Auriol et al.,<sup>15</sup>  $U_e$  is the parameter most indicative of the evolution of lymphedema and can be used as an objective indirect indicator for disease monitoring.

## DIFFERENTIAL DIAGNOSTICS BY MEANS OF SKIN ELASTICITY MEASUREMENTS

This section discusses the meaning of Cutometer measurements for differentiation of diseases that are characterized by induration of the skin. Table 19.3 presents the change tendency of skin mechanical parameters determined by a large 8-mm-diameter suction probe in four dermatoses.<sup>9-11,13,14,16</sup>

Generally, immediate distension ( $U_e$ ) and final distension ( $U_f$ ) of the indurated skin are simultaneously decreased, except in erysipelas. Thickening of the skin in the edematous phase of scleroderma and incipient SB produces identical alterations of skin mechanical parameters. Therefore, Cutometer measurements are not able to distinguish the two diseases.



**TABLE 19.3**  
**Mechanical Parameters of the Indurated Skin Determined by Cutometer**  
**Equipped with an 8-mm-diameter Suction Probe**

Disease/Parameter	$U_e$	$U_v$	$U_i$	$U_r$	$U_s/U_f$	$U_r/U_f$	$U_v/U_e$	R8	Ref.
Scleroderma (edematous phase)	↓	→	↓	↓	↑	↑	↑	↑	16
Scleroderma (indurative phase)	↓	↓	↓	↓	→	↑	→	→	16
Scleredema of Buschke	↓	→	↓	→	↑	↑	↑	↑	9–11
Psoriasis	↓	↑	↓	↓	↓	↓	↑	↑	13
Erysipelas	↓	↑	↑	↓	↓	↓	↑	↑	14

Note: The change direction toward control skin is presented. ↑, increase; ↓, decrease; and →, no alteration of the values.

The changes of the viscoelastic-to-elastic ratio ( $U_v/U_e$ ) are helpful to differentiate the edematous from the indurative phase of scleroderma as well as indurative phase of scleroderma from SB. The increase of  $U_v/U_e$  indicates the prevalence of the viscoelastic over elastic component of skin deformation. It is increased in all analyzed diseases except for the indurative phase of scleroderma. However, in the edematous phase of scleroderma and SB this is predominantly due to the decrease in  $U_e$ , whereas in psoriasis and erysipelas this is predominantly due to the increase in  $U_v$ . Thus, Cutometer measurements are able to distinguish the firm nonpitting edema in SB from the soft pitting edema in erysipelas.

The final distension ( $U_f$ ) is the skin mechanical parameter that can help to differentiate psoriatic plaques from erysipelas plaques. The decreased  $U_f$  in psoriasis is related to the increased epidermal thickness and stiffness, whereas  $U_f$  is increased in erysipelas at the expense of greatly increased delayed distension ( $U_v$ ).

## CONCLUSIONS

Skin diseases characterized by thickening, induration, or softness of the skin can be successfully studied and monitored by means of bioengineering measurement of skin mechanics. The use of measuring probes with different apertures allows one to obtain information on the mechanical properties of epidermis, dermis, and subcutaneous tissue. Regardless of the device used, all skin mechanical parameters determined must be simultaneously considered. Noninvasive measurements correlate well with clinical skin scoring systems and are more sensitive than human eyes and hands. They provide objective and quantitative information and can be used for evaluation of the therapy effect and for comparison of different treatment approaches.

## ACKNOWLEDGMENT

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## *Part 2*

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### *Product Testing*



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# 20 Skin Biomechanics: Antiaging Products

*Claudia Rona and Enzo Berardesca*

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## INTRODUCTION

Antiaging products are used to ameliorate various signs generally attributed to senescence; these signs develop from two different events,<sup>1-6</sup> characterized by specific peculiarities known as chronoaging, or intrinsic aging, and photoaging, or extrinsic aging.<sup>5</sup> Young people, who are often very concerned about aging, seek preventive approaches to reverse or slow down its manifestations, especially in view of the likelihood of a prolonged lifetime and an intensification of social relations. These preventive approaches are available mainly for the extrinsic aging process, which in fact seems to be responsible for 80% of facial aging.<sup>1,2</sup>

This chapter focuses on the relationship between antiaging treatment and skin biomechanical properties, since the major changes induced by aging (i.e., wrinkles) are localized at the dermal level and can be assessed and monitored via biomechanical parameters.

## SKIN AGING AND BIOMECHANICAL PROPERTIES<sup>5,7</sup>

Normal human dermis consists primarily of a ground substance, or extracellular matrix, and a fibrous component formed by collagen and elastic fibers. In particular,

the network of collagen fibers, which represents the most important element accounting for the 80% of the dry weight of the skin, provides resistance to deformation; elastic fibers, which account for 2 to 4% of the dry weight of the skin, provide elasticity, i.e., the ability to recover to the original position after a deformation; finally, glycosaminoglycans (GAGs—complex sugars, including hyaluronic acid) and proteoglycans (GAGs linked to a proteic core) function to retain large amounts of water and provide the viscous component of the deformation itself.

A general reduction of the synthesis of collagen fibers and of the ground substance is an event that contributes to the appearance of wrinkles and sagging skin. Elastic fibers are also primarily responsible for the biomechanical properties of the skin,<sup>8</sup> and their degeneration leads to a loss of elasticity. There is general agreement in the literature that a decrease in biological elasticity can be detected (independent of the method used) both in chronoaging and photoaging, due to the presence of elastotic material as well as to a rarefaction of the elastic network leading to a loss of functionality.<sup>9–14</sup>

### SKIN BIOMECHANICAL PROPERTY ASSESSMENT BY NONINVASIVE METHODS

Antiaging assessments aimed at measuring the recovery of skin mechanical function are performed by applying different mechanical stresses (suctional, torsional, tensional) that cause deformation to the skin; different mathematical models, depending on test, have been proposed. Deformation of the epidermis or dermis depends on the applied load and the probe size, and different structures are tested with different loads and probe sizes. When assessing skin aging, probes and stresses must be applied to all the skin components whose integrity is to be assessed. Low loads allow evaluation of the effects of cosmetic products, which are thought to exert superficial effects, whereas higher loads permit assessment of deeper structures, which should be the main target of an effective antiaging treatment.

### BIOMECHANICAL PROPERTIES AND SKIN INTRINSIC AGING

Uniassial and biassial tests exhibit a strong age-dependence because the magnitude of initial elastic deformation decreases with age in accord with the degenerative changes induced in the dermal elastic network. Compression tests provide similar results, with a progressive loss of elastic recovery of the skin and thus a progressive increase in the time required for viscoelastic recovery after a deformation as a result of changes in the ground substance.<sup>19</sup> Torsional techniques allow the quantification of several biomechanical parameters, such as distensibility, elasticity, viscoelastic deformation, and creep relaxation time. While elasticity decreases from early lifetime with the decades, distensibility remains constant until approximately 70 years of age<sup>15,19</sup> and then starts to change progressively, depending on the measuring technique. By using torsional techniques, distensibility appears to decrease if the area under study is well defined, due to an increase of Young's modulus;<sup>21</sup> with aging the structure becomes more rigid, allowing a lower deformation magnitude. *Copyright © Material* increased interaction between

collagen bundles and the size of the molecules. In contrast, when the measuring area is not well demarcated, for a given torque the deformation is larger for older people than for young; similar results have been reported with an indentometric technique.<sup>16,17,19</sup> This demonstrates that distensibility is not a good marker for the quantification of skin aging effects.

According to Daly and Odland,<sup>13</sup> the viscous part in total cutaneous deformation is due to displacement of the interstitial fluid,<sup>12,20</sup> which could explain the decrease in the creep relaxation time recorded among older subjects.

In conclusion,<sup>15</sup> biomechanical parameters vary with age in two different ways: some may change continuously from early age (elasticity, relaxation time following strong deformation), whereas others may remain somewhat constant until around 70 years of age and then rapidly change (distensibility). Among all parameters, skin elasticity shows a clear clinical biological relevance and represents the parameter of choice when quantifying the effect of the aging process on the dermis.

## BIOMECHANICAL PROPERTIES AND PHOTOAGING

Lévêque et al.<sup>18</sup> first described the effects of chronic sun exposure on the mechanical properties of the skin. The study reported striking differences in all the parameters investigated between chronically exposed and protected areas. These differences were not detectable in a control group of matched age. Long-term solar irradiation led to a decrease in skin extensibility and elastic recovery. The skin appears thicker, more rigid, and less susceptible to deformation. The authors suggest that changes in skin extensibility could be related to the increase in epidermal thickness.<sup>22</sup> In photoaging, distensibility decreases in parallel with the thickening of the skin as a result of actinic damage. Berardesca and Maibach<sup>19</sup> confirmed these results during ultraviolet A (UVA) treatment. In particular, impairment of skin elasticity after low UVA and UVB exposure can occur both in the short term, due to the acute effects of rays on skin (inflammation and edema), and in the long term, when elastosis develops after prolonged exposure.

## BIOMECHANICAL PROPERTIES AND ANTIAGING PRODUCTS

Many product categories for topical or oral use can be helpful in restoring and repairing the mechanical properties of the skin to treat or prevent skin aging. Among these, most of the data available in the literature refers to topical retinoids, AHAs in various combinations with vitamin C, and systemic antioxidants associated with fish polysaccharides.<sup>24-26</sup>

### AHAs

Together with retinoids, AHAs today play a major role in skin care and dermatological therapy; they include glycolic, citric, and lactic acids, the so-called fruit acids. AHAs act both on epidermis and dermis,<sup>6,15,28-35</sup> exerting opposite effects. They have a thinning effect on stratum corneum, inducing desquamation and

promoting cell renewal as well as stimulating collagen synthesis at the dermal level, increasing dermal thickness.

At the epidermal level, AHAs weaken intercorneocitary cohesion and stimulate stratum corneum desquamation by interfering with the formation of ionic bonds and desmosomes by inhibiting transferases and kinases. This leads to a reduction of the polarity of sulfate and phosphate groups on the corneocyte membrane; application of AHAs reduces pH even in the deeper layers of stratum corneum, contributing to dissolution of the desmosomes. Furthermore, AHAs stimulate epidermal turnover. These effects induce an increase in the flexibility of the stratum corneum.<sup>36</sup>

On the dermis, which is the primary contributor to skin biomechanical properties, AHAs increase glycosaminoglycan deposition in the ground substance and replace collagen and elastic degradation by promoting new collagen synthesis, without any sign of inflammation.<sup>15</sup> This effect is responsible for wrinkle improvement and recovery of such dermal mechanical properties as elasticity and “tone,” as shown by Smith and co-workers<sup>37</sup> using a ballistometer to assess and confirm changes in skin firmness.

## RETINOIDS

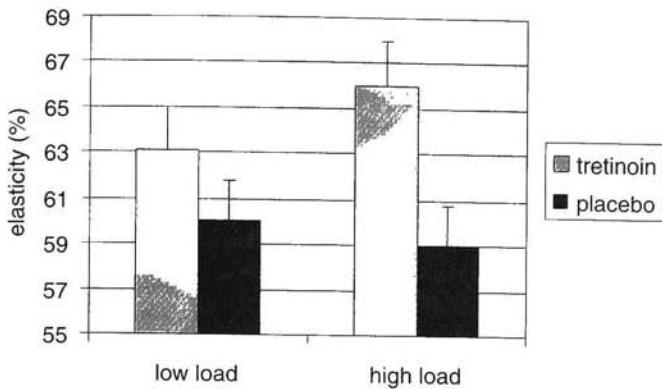
Originally used for acne treatment, today retinoids are a “standard” for the cosmetic treatment of aging signs. Initial studies of topical tretinoin were focused on photoaging: L. Kligman<sup>38</sup> showed in hairless mice irradiated with UVA and UVB that topical tretinoin was able to revert the histologic changes induced by UV irradiation and to restore the dermal structure by increasing fibroblast activity and collagen deposition. Later, A. Kligman et al.<sup>39</sup> published the first paper on human volunteers, which suggested that tretinoin can have the same effects on human photoaged skin. He described histological and physiological changes in skin treated with tretinoin 0.05% cream: in particular, the skin showed replacement of atrophic epidermis by hyperplastic tissue, elimination of dysplastic and atypical keratinocytes, disappearance of microscopic actinic keratoses, and uniform dispersion of melanin granules. Tretinoin-treated skin also showed new collagen formation in the papillary dermis, new vessels, and exfoliation of retained follicular horns.

Ellis et al.<sup>23</sup> performed a double-blind, randomized, vehicle-controlled trial to assess the efficacy of 0.1% tretinoin cream in the treatment of photoaged skin: Patients were clinically graded on face and forearm skin for fine and coarse wrinkles, telangiectasia, tactile roughness, pinkness, and dermal edema. In 30 patients who completed the treatment, a significant improvement was found for all parameters investigated in treated sites, whereas no changes were seen in vehicle-treated sites.

From a mechanical point of view, Berardesca et al.<sup>19</sup> found no changes in skin distensibility, but a significant increase in skin elasticity after a 4-month treatment with 0.05% topical tretinoin (Figure 20.1). The results were detected using high deformation loads, confirming that retinoids were useful in improving dermal mechanical properties. Indeed, low vacuum forces monitor epidermal and upper dermal physical properties.

Hysteresis (i.e., the viscoelastic component of the deformation) remained unchanged as did distensibility during the study. The authors hypothesize that





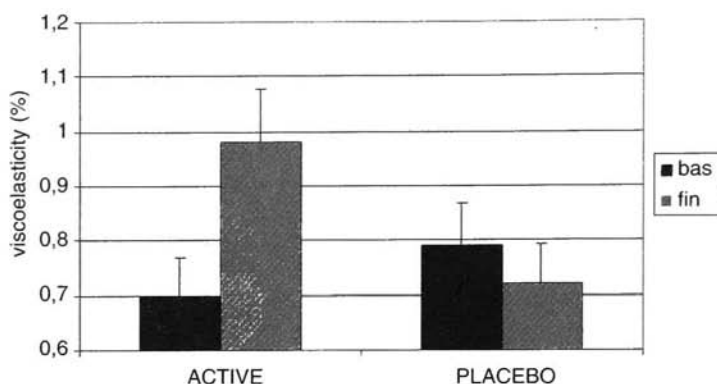
**FIGURE 20.1** Skin elasticity ( $U_e/U_c$ ) measured at low (100 mbars) and high (300 mbars) loads. Significant differences ( $p < 0.01$ ) are detected after 4 months of topical tretinoin treatment.

changes in resilient distension of the skin that determine the elastic variation consequent to an increase of newly formed collagen in the dermis are responsible for this effect. This confirms data reported on the dermal effects of retinoids after long-term application.

### FISH POLYSACCHARIDES

When taken orally, fish polysaccharides are reported to be effective in treating photoaging (with particular application to elastosis and wrinkles) and chronological aging (especially thinning of the skin). Their mechanism of action is still basically unknown. Previously reported data suggest a possible role in promoting collagen synthesis, in particular, procollagen and type III collagen, which stimulate repair processes within the dermis. The high content of mucopolysaccharides can improve dermal ground substance, thus improving skin mechanical behavior and skin thickness.<sup>25–27</sup> A study<sup>26</sup> reported clinical improvement of skin aging and some biophysical parameters such as thickness, microcirculation, transepidermal water loss (TEWL), and wrinkling. Other studies reported both improvement of skin mechanical properties and skin thickness.<sup>40</sup> In particular, when taken orally at a dose of at least 500 mg in combination with flavonoids and antioxidants, fish polysaccharides seem to exert a thickening effect at the dermal level, with significant reduction of deep lines. From a mechanical viewpoint, a significant increase in viscoelasticity is detectable (Figure 20.2) as compared with placebo treatment. This seems to be a peculiar marker of their effect on the dermis.<sup>41</sup> As a consequence, other mechanical parameters such as elasticity are also improved (Figure 20.3).

These results confirm that fish polysaccharides taken orally can be helpful in ameliorating some aspects of skin aging. Because of their peculiar properties, combination treatments in association with topical retinoids/AHAs would be interesting to investigate.

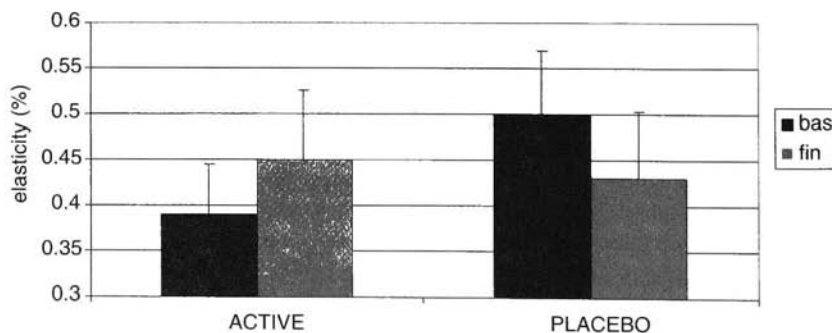


**FIGURE 20.2** Skin viscoelasticity, as measured by the Cutometer, after treatment with oral fish polysaccharides.

### METALLOPROTEINASE INHIBITORS

The matrix metalloproteinases (MMP)<sup>42</sup> are enzymes present in the skin that are responsible for the degradation of extracellular components. The extracellular matrix (EMC) establishes the three-dimensional integrity and functionality of the skin, so that it plays an essential omeostatic role. Damage to the EMC causes important alterations in the different biological functions of the skin. In healthy skin, the balance of the omeosthesis of collagen fibers depends on several factors: the synthesis of the collagen fibers themselves; the slow basal MMP action necessary to proceed to the natural and planned degradation of old or deranged fibers; the action of tissue inhibitors to control the MMP degradative activity.

The enzymatic balance of the metalloproteinases is in fact naturally controlled and ensured by tissue inhibitors (TIMPs). Aging and environmental insults, such as long-term exposure to UV rays, alter the physiological balance, increasing enzyme activity and decreasing TIMP expression and collagen fiber synthesis. These events



**FIGURE 20.3** Skin elasticity, as measured by the Cutometer, after treatment with oral fish polysaccharides.

give rise to the collapse of the meshwork in the ground substance and contribute to the visible effects of UV damage: wrinkling, loss of elasticity and tone, teleangiectasias. MMP inhibitors represent new and interesting tools that can be used by formulators in addressing different cosmetic issues and protection of the skin from external injury. In particular, the improvement in EMC properties could help in promoting skin tone, thereby reducing wrinkles and fine lines; cosmetics aimed at improving skin firmness and elasticity can, in turn, benefit from the addition of such active ingredients in their formulation. However, although preliminary findings have reported the usefulness of these molecules in improving some parameters such as skin microcirculation and skin smoothness, they have failed to show effects on mechanical properties.<sup>43</sup>

### ASCORBIC ACID

Among topical antiaging treatments, ascorbic acid has been introduced only recently because of its instability. It is an essential nutrient involved in many physiological processes and functions, by virtue of its excellent reducing capacity, which provides its antioxidant efficacy.<sup>44</sup> Thus, ascorbic acid can protect living tissues and cells from oxidative damage due to free radicals and oxygen-derived species. In particular, it works synergistically with vitamin E,<sup>45</sup> by serving as a donor antioxidant to restore the tocoferoxil radical; this reaction represents the major way to export oxidative free radicals from cell membranes. Thus, vitamin E protects membranes from free radical insult, while ascorbic acid in turn continuously restores the vitamin E.<sup>46</sup> This capability offers an important tool to prevent skin aging, with particular regard to tone and elasticity. In fact, ascorbic acid can preserve dermis components from sun damage by inhibiting free radical injuries charged to collagen and elastin. Regarding its mechanism of action in the treatment of skin aging, it seems to stimulate dermal deposition of new collagen.<sup>47</sup>

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# 21 Product Testing: Moisturizers

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## HYDRATION STATE OF THE SKIN

The presence of an adequate amount of water in the stratum corneum is important for maintaining the following properties of the skin: general appearance of a soft, smooth, flexible, and healthy-looking skin; and an intact barrier function allowing a slow rate of transepidermal water loss (TEWL) under dry external conditions, which are frequently encountered.<sup>1–4</sup> Clinically, dry skin is defined as a dry, less-flexible, scaly, and rough aspect of the upper layers of the epidermis.<sup>1–4</sup> Itching may accompany these symptoms. In more severe cases of dryness (a condition described by dermatologists as xerosis) and in pathological conditions, fissuring, scaling, and cracking occur.<sup>5–8</sup> There is no universally accepted definition of *dry skin*.<sup>9</sup> Some

authors consider that dry skin is related to disorders of corneocyte adhesion and desquamation (rough and scaly surface), to modifications in the composition of certain epidermal lipids (ceramides), or to disorders of the water-retaining properties of the horny layer (presence of natural moisturizing factors). The perception of a dry skin state by the patients themselves may differ from the diagnosis of the clinician.

There are currently very few data confirming that a situation of dry skin is linked solely to a diminution of the water content of the horny layer. However, the positive pharmacological effect of application of water and moisturizers to the skin surface to relieve the condition of dry skin has been repeatedly confirmed. Nevertheless, given the fact that the presence of an adequate amount of water is an essential prerequisite for the maintenance of the normal structure and function of the stratum corneum, research has been directed at evaluation of the water content of this tissue. The skin surface is covered with the stratum corneum, which acts as an efficient barrier protecting the whole skin from loss of water. The structure of the horny layer *in vivo* is very complex. The upper part of the horny layer, which is exposed to air, contains relatively much less water (about 10%), whereas the lower part of the stratum corneum is in direct contact with the water-saturated viable epidermis.

The water content of the stratum corneum is influenced by several factors:<sup>3,4,10</sup>

- *Water diffusing from the deeper viable layers of the epidermis.* This water is normally retained by the barrier function of the lipid bilayers in the stratum corneum.
- *Water present in the horny layer.* This water is fixed, among other elements, by the natural moisturizing factors (NMF), which constitute amino acids, lactic acid, pyrrolidone carboxylic acid, urea, and other salts. These substances present a high affinity for holding water (hygroscopy). The amount of water entrapped between the lipid bilayers may also play an important role. Stratum corneum lipids, especially ceramides, contribute to the water-retaining properties through the lamellar lipid structures.<sup>11</sup>
- *Equilibrium between water in the upper layers of the horny layer and the external ambient humidity of air.* Depending on the value of the external relative humidity, the upper layers of the stratum corneum may take on or release water. Dry skin is generally more prevalent in the winter (winter xerosis).
- *Treatment of the skin surface with moisturizers and/or emollients.* Moisturizers are hydrating products used to combat the symptoms of dry skin.<sup>3,4</sup> They may hydrate the skin in different ways either by reducing the loss of water due to the occlusive effects on the skin surface of oils and fats contained in the preparations or by adding water to the stratum corneum and fixing it with the help of humectants, or by a combination of both.<sup>3,4</sup> As a consequence, the *in vivo* determination of the degree of hydration of the horny layer is important for characterization of normal and dry skin, for assessment of pathological skin conditions with extreme dry skin, and, finally, for assessment of the efficacy of various moisturizing products. The use of such dermato-cosmetic hydrating products to restore softness, smoothness, and moisture to dry skin is widely practiced.



This chapter is concerned with evaluation of the hydration state of the skin and assessment of the efficacy of moisturizers with the use of noninvasive bioengineering measurements of the elastic and viscoelastic properties of the skin. The chapter provides a critical overview of the different biomechanical methods (experimental devices and commercially available instruments) available to carry out mechanical measurements on normal skin, on well-hydrated skin, and on dry skin, respectively, and to assess quantitatively the efficacy of moisturizers. This chapter devotes a discussion to the significance in general of the quantitative variables obtained from *in vivo* biomechanical measurements. It is also important to evaluate the participation of the horny layer and epidermis in the global mechanical behavior of the skin *in vivo*. Some data suggest clearly an effective contribution of the horny layer to the overall mechanical properties of the skin. This is an important argument for the claim support related to biomechanical improvement of the epidermis horny layer after a topical cosmetic treatment, such as a moisturizing cream.

Several pertinent articles and reviews concerning the applicability of biomechanical measurements for cosmetic claim support have been published.<sup>12-15</sup>

### MECHANICAL PROPERTIES OF THE SKIN AND EXPERIMENTAL SYSTEMS DEVELOPED TO ASSESS BIOMECHANICAL PROPERTIES

Assessment of the mechanical properties of the skin is not simple, since the skin is a stratified composite material and the relationship between the various layers is complex. It is clear that the mechanical characteristics of human skin result from the global contribution of connective tissue, dermis, and hypodermis and, at least to some degree, of the epidermis and horny layer.<sup>13</sup> The properties of the fiber constituents, their orientation, network, and their relation with the interstitial medium constituted of proteoglycans are fundamental factors determining the overall properties of the entire organ.<sup>13</sup> Flexibility is characteristic of human skin, fundamental to allow movement without cracking or fissuring. Flexibility contributes to overall cutaneous cohesion and to the barrier function of the skin, depending on elastic, plastic, and viscous components, which are responsible for the extremely complex mechanical behavior (viscoelastic properties of the skin). The stratum corneum is a heterogeneous structure composed of protein-enriched corneocytes embedded in a lipid matrix. These lipids are arranged in lamellar structures and contribute considerably to the barrier function of the stratum corneum.

The different methods that have been developed for testing skin mechanics are based on forces and deformations working either in the skin surface or perpendicular to the skin surface. Methods based on forces working in the plane of the skin are stretching, torsion, and wave propagation. Methods based on forces perpendicular to the skin surface are suction, indentation, elevation, and ballistometry. Many very interesting experimental devices are not commercially available but are used only in research laboratories. Several instruments using the suction method are commercially available at the present time: the Dermaflex A from Cortex Technology (Denmark), the Cutometer SEM 475 (more recently replaced by the SEM 575

version) of Courage–Khazaka Electronic (Germany), the Dermalab from Cortex (Denmark), and the BTC-2000 from SRLI (United States). One commercial instrument using the torsion method is commercially available: the Dermal Torque Meter based on the Twistometer from the L'Oréal group.

Among these commercially available instruments, most biomechanical measurements have been carried out with the Torque Meter (Dias-Stron, Andover, U.K.) and two suction devices, the Dermaflex A (Cortex Technology, Hadsund, Denmark) and the Cutometer SEM 474 and more recently SEM575 (Courage–Khazaka Electronic, Cologne, Germany). Biomechanical measurements for evaluation of the hydration state of the skin surface using the two very recent commercial devices (Dermalab and BTC-2000) have not yet been published.

### **TORSIONAL DEFORMATION OF THE SKIN: TWISTOMETER AND THE DERMAL TORQUE METER**

Torsional testing of the mechanical properties of the skin has been used and developed by several research groups over the past 20 years, mainly by the L'Oréal group as described by Agache.<sup>12</sup> This work has led to the commercial version of the Dermal Torque Meter. The measurement technique consists of applying a disk to the skin surface (the disk is firmly adhered to the skin surface with double-sided adhesive tape). The Dermal Torque Meter applies a constant torque to the skin and measures the resulting angular distortion. This angular distortion induces an elongation of the skin, which can be limited by the introduction of a concentric guard ring (also firmly adhered to the skin surface), which delimits an annular area of skin and limits the sliding of the skin over the hypodermis. Thus, the angular deformation of the skin is confined to a narrow annulus (generally of 1 mm). According to the L'Oréal group, with low values of torque and with a ring gap of 1 mm, the obtained mechanical measurements result from the most superficial structures of the skin (horny layer and superficial part of the epidermis). Thus, the torsion method allows mechanical measurements pertaining to the efficacy of topical cosmetic applications. The instrument generates two types of experimental curves: strain–time and stress–strain.

### **SUCTION DEFORMATION OF THE SKIN: CUTOMETER SEM 474/575**

With the Cutometer, a variable vacuum ranging from 50 to 500 mbar is applied to the skin surface through the opening of a probe. Probes with apertures 2, 4, 6, and 8 mm in diameter are available. In the procedure, the skin surface is pulled vertically upward into the probe opening by the vacuum, and the vertical deformation of the skin is measured via an optical system (diminution of light intensity of an infrared light beam). The skin adjacent to the opening of the probe is maintained in position with an external guard ring. The measuring probe is manually applied vertically onto the surface of the skin, and a constant pressure is assured by a built-in spring. The instrument is linked to a personal computer using a standard software program provided by the company. The Cutometer generates two types of experimental curves: strain–time and stress–strain. According to some authors,<sup>14–17</sup> when the small, 2-mm probe is used, the Cutometer is capable of more selective study of the mechanical properties of the upper epidermal

### SUCTION DEFORMATION: DERMAFLEX A

With the Dermaflex A, a variable vacuum ranging from 0 to 500 mbar is applied on the skin surface through the opening of a probe. The only probe aperture available is 10 mm diameter. In the procedure, the skin surface is pulled vertically upward into the probe opening by the vacuum. Then, the vertical deformation of the skin is measured electronically by measuring the electric capacitance between skin surface and the electrode placed in the top of the suction chamber. The skin adjacent to the opening of the probe is maintained in position with an external guard ring, and the double-sided adhesive tape on the external steel ring prevents skin creeping during suction. The measuring probe is manually applied vertically onto the surface of the skin. The instrument delivers only one experimental curve: strain–time.

### EXPERIMENTAL DEVICES TO ASSESS *IN VIVO* THE BIOMECHANICAL PROPERTIES OF THE SKIN

Several experimental systems have been developed in research laboratories to assess the biomechanical properties of skin *in vivo*. The experimental devices are grouped in two major categories according to the orientation of the load toward the skin.

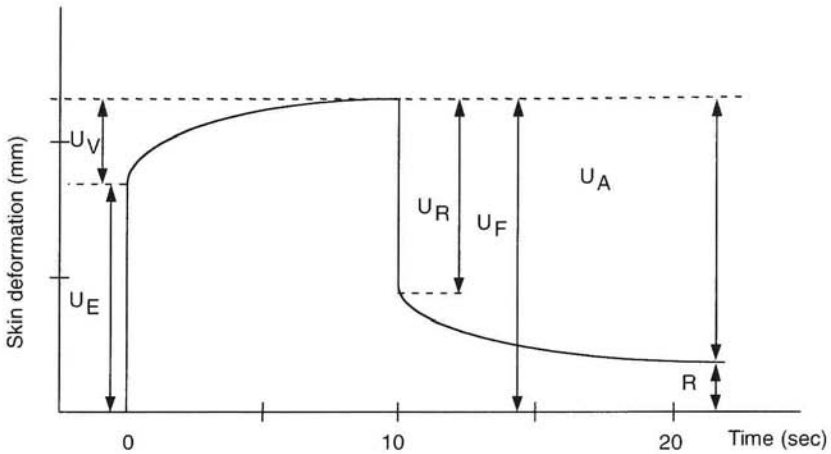
1. Methods using forces parallel to the skin surface:
  - Uniaxial stretching devices<sup>18</sup>
  - Gas Bearing Electrodynamometer<sup>19,20</sup>
2. Methods using forces perpendicular to the skin surface:
  - Levarometry<sup>21</sup>
  - Indentometry<sup>22</sup>
  - Ballistometry<sup>23</sup>
  - Resonance frequency<sup>24</sup>

A detailed description of each system can be found in other chapters of this book. Therefore, only those experiments dealing with the effect of moisturizers on biomechanical properties as measured with these experimental devices are discussed in this chapter.

### DESCRIPTION OF RECORDED VISCOELASTIC PARAMETERS

As already mentioned, the skin is a complex, five-layered organ,<sup>25</sup> which, similar to many other biological materials, presents the typical properties of elastic solids and various liquids in a combined way known as viscoelastic properties.<sup>26–28</sup>

Deformation of the skin as a function of time consists of an immediate, incomplete elastic deformation and a creeping viscoelastic deformation. These are followed by an immediate elastic recovery, a creeping recovery, and, always, a residual deformation (Figure 21.1).



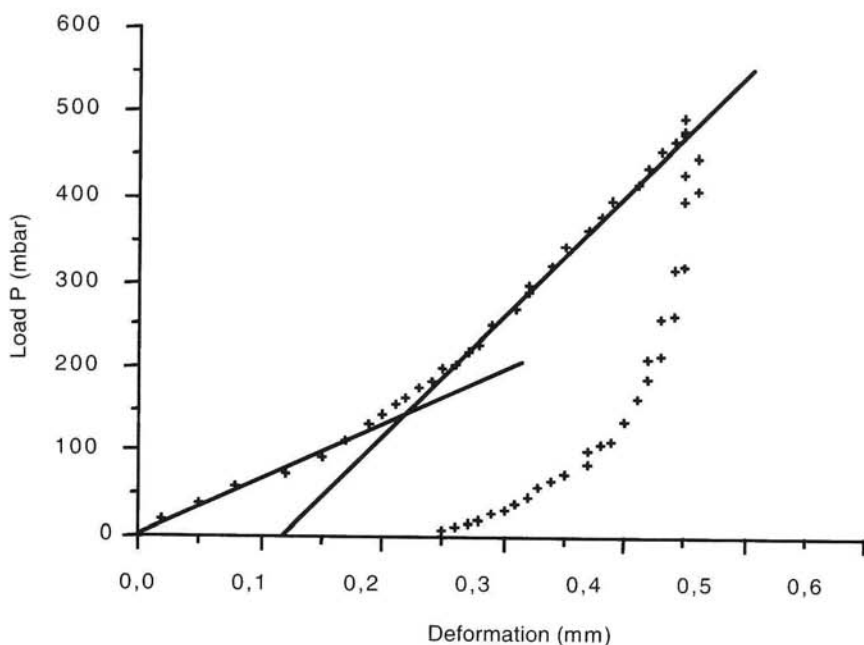
**FIGURE 21.1** Graphical representation of a strain–time curve obtained for forearm skin. Vacuum of 500 mbar, application and recovery time of 10 s, 2-mm probe.

Typical mechanical properties of viscoelastic material are nonlinear stress–strain properties with hysteresis (the stress–strain curve obtained during loading is superposed by the curve obtained during unloading (Figure 21.2).

### STRAIN–TIME MODE

The vertical deformation of the skin is measured as a function of time (see Figure 21.1). In this mode, for a given aperture of the probe, the pressure of the vacuum (from 50 to 500 mbar), the total duration of suction time (stress-on) and relaxation time (stress-off), and the number of measurement cycles can be selected. The parameters used in this measuring mode describe the elastic deformation and recovery of the skin, the viscoelastic creep after the initial deformation and the initial recovery, and the residual deformation.<sup>2</sup> Parameters of interest are as follows:

- $U_e$  is defined as the immediate elasticity, which corresponds with the steep linear section of the curve and which must be computed at a very short interval after application of the suction.
- $U_f$  is defined as the maximal deformation; it is equal to the sum of the elastic deformation  $U_e$  and the viscoelastic deformation  $U_v$ .
- $U_v$  is the delayed viscoelastic part of the skin deformation (creep).
- $U_r$  is defined as the immediate elastic recovery of the skin after removal of the suction.
- $U_r$  is measured in the steep linear part of the recovery.
- $U_a$  is equal to the total recovery deformation of the skin at the end of the recovery phase.



**FIGURE 21.2** Graphical representation of a stress-strain curve obtained for forearm skin. Linear increase and decrease of vacuum, 2-mm probe, total stress-on and stress-off time of 20 s. Maximum value of vacuum is 500 mbar.

$R$  is the residual deformation of the skin, which has not recovered after completion of the stress-off measuring time. When working with repetitive measuring cycles, the deformation-time curves obtained for the second, third, and subsequent deformation cycles are similar to the first, but progressively shift upward as a consequence of the residual deformation.

Hysteresis is defined as the difference between the maximal deformation  $U_f$  of the last curve and that of the first curve.

The deformation parameters are extrinsic parameters influenced by skin thickness.<sup>27</sup> To take into account potential differences in skin thickness when comparing men and women, young and old, different anatomical skin sites, and so forth, intrinsic skin deformation parameters must be computed (deformation  $\times$  skin thickness).

As pointed out by many authors,<sup>29-31</sup> the problem of standardized definitions of the different skin deformation parameters is important. For example, Gniadecka and Serup<sup>25</sup> propose the terms *skin stiffness* or *distensibility* for  $U_f$  and *resilient distensibility* for  $U_a$ , whereas Couturaud et al.<sup>32</sup> propose the terms *extensibility* for  $U_e$ , *plasticity* for  $U_v$ , and *tonicity* for  $U_r$ . From these extrinsic deformation parameters (see Figure 21.1), different elastic and viscoelastic ratios have been proposed to characterize the mechanical properties of the skin. Escoffier et al.<sup>27</sup> propose:

$U_a/U_f$  is defined as the overall elasticity. It is equal to the ratio of the total deformation recovery to the total deformation (biological elasticity).

$U_r/U_e$  is defined as the pure elasticity ratio. It is equal to the ratio of the immediate recovery to the immediate deformation without the contribution of the viscoelastic part (elastic function).

$U_r/U_f$  is defined as the elastic recovery. It is equal to the ratio of immediate recovery to the total deformation (relative elastic recovery).

$U_v/U_e$  is defined as the viscoelastic ratio. It is equal to the ratio of the viscoelastic deformation to elastic deformation.

The computed values of  $U_r/U_e$  (elastic function) and  $U_r/U_f$  (relative elastic recovery) parallel each other closely for most studied skin sites. As a consequence, either one of the two parameters ( $U_r/U_e$  or  $U_r/U_f$ ) is computed for characterizing the intrinsic elastic properties of the skin, which are independent of skin thickness.<sup>27</sup> Some authors use the ratio  $U_a/U_f$  as a criterion for elasticity.<sup>33</sup> When evaluating more specifically the viscoelastic properties of the skin, the intrinsic parameter viscoelastic ratio,  $U_v/U_e$  is generally considered.<sup>27</sup> All these deformation parameters are directly computed from the Cutometer using the provided standard software. By using a standard software program, the following parameters can be computed in the Dermalflex:  $U_f$  distensibility;  $R = U_f - U_a$  resilient distension; the relative elastic retraction also described as the elasticity index RER;  $R = R/U_f$ ; and the hysteresis creeping phenomenon, which corresponds to the increase of  $U_f$  after four cycles ( $U_{f4} - U_{f1}$ ).<sup>14,15,25</sup>

All the deformation parameters described here can also be directly computed from the Dermal Torque Meter using the provided standard software.

## STRESS-STRAIN MODE

In this mode (see Figure 21.2), the total vertical skin deformation  $U_f$  is measured as a function of vacuum (mbar) during a 10-s linear increase (from 0 to 500 mbar) of vacuum followed by a similar linear decrease of suction during a relaxation period of 10 s. For almost all anatomical skin sites studied, nonlinear curves were obtained with hysteresis. The stress-strain curve on loading is not superposed by the relaxation curve. During the relaxation period, the values of strain do not return to zero since there is an intercept of the curve on the strain axis. Theoretically, considering the nonlinearity of the curve for human skin, Young's modulus  $E$  is not applicable.<sup>12,34</sup> As proposed by Piérard,<sup>28</sup> one can always define a pseudo-Young's modulus  $E$  as a type of coefficient of elasticity that corresponds to the derivative of the stress to the strain for a given stress value. However, most experimental ascending curves present a clear linear section between 150 and 500 mbar. From that linear section of the stress-strain curve, the slope can be calculated, corresponding to the pseudo-Young's modulus  $E$  or the coefficient of elasticity.<sup>28,30</sup>

For calculation of  $E$ , a theoretical simple model for the deformation of the skin in the circular aperture was proposed by Agache and co-workers.<sup>15,34</sup>

## RELATION BETWEEN SKIN MECHANICS AND HYDRATION AND THE APPLICABILITY POTENTIAL OF BIOMECHANICAL MEASUREMENTS TO COSMETICS CLAIMING SUPPORT OF HYDRATION OF THE SKIN

From a mechanical point of view the skin is a stratified composite material whose most superficial layer, the horny layer, is the stiffest but represents only  $1/100$  of the total thickness. As a consequence, its role in whole-skin mechanical properties is often overlooked.<sup>15</sup>

Many *in vivo* studies using noninvasive bioengineering techniques have been published to evaluate the relationship between the mechanical properties of the skin and the water content of the upper layers of the epidermis (for recent reviews, see Bernengo and de Rigal<sup>14</sup> and Agache and Varchon).<sup>15</sup> Determination of the hydration is based on electrical measurements of the conductance, capacitance, and impedance of the skin (for a recent review see Barel et al.<sup>10</sup>). The immediate hydration effects in the stratum corneum after a single application of water or moisturizers (short-term effect) and the hydration effect in the stratum corneum after repeated application of moisturizers (long-term effect) are considered here.

### RESULTS WITH THE TORSIONAL DEVICE

Torsional experiments with the Twistometer enabled Lévêque and de Rigal<sup>36</sup> to investigate the mechanical behavior of the horny layer *in vivo*. Using a low torque value and a small area of twisted skin (1-mm ring opening), they investigated the immediate effect of a simple application of water and the occlusion of the stratum corneum with a plastic sheet. Significant increases in the  $U_e$  parameter were observed. The variations in  $U_e$  were inversely related to the value of Young's modulus.

Application of simple vehicles such as O/W and W/O emulsions or petrolatum also induces a significant short-term increase in the  $U_e$  parameter. Addition of moisturizers such as 10% lactic acid, sodium pyrrolidone carboxylate, urea, and, particularly, glycerol provokes a significant increase in the  $U_e$  parameter.<sup>36</sup>

In a long-term study,<sup>37</sup> twice daily application for 3 weeks of an O/W vehicle containing 10% urea or glycerol as a moisturizer on the legs caused a significant rise in the  $U_e$  of the treated skin, whereas the skin treated with the vehicle alone did not differ from the control site. This study also found that total immersion of the forearm skin for 3 min in hot water (30°C) provokes a significant increase of the elasticity parameters  $U_e$ ,  $U_r$ , and  $U_r/U_e$ .<sup>37</sup> Significant modifications of skin extensibility and elasticity were also observed after removal of the stratum corneum by adhesive tape stripping (10-15-20 strippings on the forearm skin). During stripping,  $U_e$ ,  $U_r$ , and  $U_r/U_e$  increased steadily and significantly in comparison with the untouched baseline.<sup>37</sup>

Correlations between visual clinical assessments of symptoms of dry skin on the forehead and cheeks (using a 0 to 3 numerical scale) and torsional mechanical

properties were investigated by L ev eque et al.<sup>38</sup> Clearly, significant inverse relations were established between clinical dryness and the  $U_e$  mechanical parameter ( $r$  varies from  $-0.41$  to  $-0.66$ ).

## RESULTS WITH THE SUCTION DEVICES

Many *in vivo* studies conducted with the Cutometer and Dermaflex suction devices have demonstrated that the elastic and viscoelastic properties of the skin are modified after application of water or moisturizers to the skin.

It was shown by Jemec and Serup<sup>39</sup> that application of tap water for 20 min under occlusion changes the forearm skin mechanical properties substantially as measured with a Dermaflex suction instrument (10-mm probe aperture, repetitive cycles of 4 s stress-on and stress-off times and 300 mbar suction). The increase in hydration (capacitance method) is accompanied by the following changes in viscoelastic properties of the skin: an increase in distensibility and resilient distensibility and a decrease in elasticity. Subsequently, Olsen and Jemec<sup>40</sup> compared the short-term (10-min application) influence of tap water, paraffin oil, ethanol, and glycerine to the forearm skin on the mechanical properties of the skin. Significant increases in resilient distensibility, distensibility, and hysteresis were observed after application of a gauze pad soaked with tap water and paraffin oil. The results of Jemec and Serup<sup>39</sup> show a correlation between hydration measurements and some mechanical properties of the skin.

Murray and Wickett<sup>33</sup> conducted studies both on acute hydration, on the forearm skin, and on the long-term moisturizing effects on the outer calf region of the legs. Hydration was assessed using the DPM Nova instrument and the Cutometer for determination of the biomechanics of the skin (2-mm probe aperture, 2-s stress-on and stress-off times, and 100 and 500 mbar suction). The acute hydration treatment involved occlusive application of a warm, wet paper towel covered with Saran wrap for 10 min to the forearm skin. Pre- and post-treatment measurements were taken with both instruments. In the moisturizing study, a hydration lotion containing 10% glycerine was applied twice a day for 2 weeks on the calf region of the legs. Baseline, post-treatment, and post-regression measurements were made with the same instruments.

$U_v$  and  $U_v/U_e$  were the mechanical parameters most sensitive to hydration changes in the acute hydration test (10-min application of the wet paper towel).  $U_e$ ,  $U_v$ ,  $U_f$ ,  $U_a$ , and  $R$  were the most sensitive parameters in the moisturizing study. That the Cutometer data parameters did not consistently correlate with the DPM Nova hydration data was interpreted by the authors as the result of the Nova instrument measuring much shallower skin depth than the Cutometer.

Subsequently, Murray and Wickett<sup>41</sup> performed long-term hydration studies on dry leg skin to determine the sensitivity of the Cutometer and Dermal Torque Meter parameters to changes in hydration of the stratum corneum, as indicated by electrical capacitance measurements with the NOVA Dermal Phase Meter. The subjects used a moisturizing lotion twice daily for 2 weeks. The experimental conditions of the Cutometer were a 2-mm probe, 10-s stress-on and stress-off times, and 100 and 500 mbar suction. For the Dermal Torque Meter, they were 1-mm annulus between disk



and guard ring and 10-s stress-on and stress-off times. They found significant changes in most mechanical parameters:  $U_e$ ,  $U_v$ ,  $U_f$ ,  $U_r$ , and  $U_a$  for the Dermal Torque Meter and  $U_e$ ,  $U_v$ ,  $U_f$ , and  $U_a$  for the Cutometer. The  $U_e$  and  $U_a$  mechanical parameters as obtained with the Dermal Torque Meter showed the highest sensitivity to the effect of moisturizing lotions (compared with other mechanical parameters of the Dermal Torque Meter and with all the parameters of the Cutometer). Correlations between the torsional and suction instruments existed, but were weak ( $r = 0.41$  for  $U_r$ ,  $r = 0.54$  for  $U_e$ , and  $r = 0.62$  for  $U_f$ ). Again, no correlations were found between hydration and mechanical properties.

Determination of the biomechanical properties of the skin after topical application of glycerine and paraffin oil for 15 min on the volar forearm skin was carried out by Barel et al.<sup>31</sup> Cutometer measurements (2-mm probe aperture, 10-s stress-on and stress-off times, and 500 mbar suction) indicated no significant differences in the elasticity parameter  $U_r/U_f$  after application of glycerine and/or paraffin oil on the forearm skin were observed. On the contrary, the viscoelastic deformation ratio  $U_v/U_e$  was significantly increased after these topical treatments.

The same study also investigated stripping of the horny layer with adhesive tape. Intensive treatment of the skin with 40 strippings, which corresponds to the removal of the horny layer, provoked a small decrease in elasticity ( $U_r/U_f$ ), but a large increase in the viscoelastic parameter ( $U_v/U_e$ ). Because the study used a 6-mm probe aperture and a vacuum of 400 mbar, it is thought that, in fact, the mechanical properties of the whole dermis and perhaps of the subcutis were investigated. However, these preliminary data would indicate that changes in the viscoelastic properties of more superficial layers of the skin can also be detected with the suction method.

Other workers investigated the biomechanical properties of the skin after short-term topical application of O/W emulsions containing 5% glycerine or urea or both on the volar forearm skin with Corneometer hydration measurements.<sup>42</sup> Cutometer measurements were carried out with a 2-mm probe, 3- and 10-s stress-on and stress-off times, and 500 mbar suction. No significant changes in the elasticity parameters  $U_r/U_e$  and  $U_r/U_f$  after application of the three moisturizers were observed. On the contrary, the viscoelastic deformation ratio  $U_v/U_e$  was significantly increased after these topical treatments. There were no correlations between the capacitance hydration measurements and the three mechanical parameters  $U_r/U_e$ ,  $U_r/U_f$ , and  $U_v/U_e$ .

In a very recent study by Dobrev,<sup>43</sup> the topical effects of five different moisturizers and emollients (petrolatum, paraffin oil, glycerine, W/O and O/W emulsions) on the volar forearm skin were examined by hydration (Corneometer) and by mechanical properties (Cutometer, 2-mm probe, 5-s stress-on and stress-off times, and 400 mbar suction). Delayed distension  $U_v$  and viscoelastic ratio  $U_v/U_e$  were the most sensitive parameters to indicate changes in the hydration of the skin. No correlations between skin capacitance hydration measurements and mechanical parameters were found in this study.

The evaluation of the long-term moisturizer effect of a lotion containing 5% glycerin on the legs was recently carried out by Wickett<sup>17</sup> using the Cutometer and the Nova instrument. The Cutometer was used with the 2-mm probe at 200 and 500 mbar suction. This study indicated that using a lower vacuum level may improve

sensitivity to moisturizer-induced changes in mechanical parameters. The increase of  $U_e$  and  $U_r$  appeared to be more sensitive to the moisturizer effect than that of  $U_v$ .

## RESULTS WITH EXPERIMENTAL DEVICES

Experimental data obtained with noncommercially available laboratory devices have also clearly shown the effect of hydration of the skin on its biomechanical properties.

Very interesting results were obtained with the Gas Bearing Extensometer.<sup>15,20,44,45</sup> With this apparatus an ellipsoidal stress-strain curve is obtained for a viscoelastic material such as the skin. The slope of the major axis of the ellipse, which is called the dynamic spring rate, is an analogue of Young's modulus and reflects the softness of the skin. The openness of the elliptical loop reflects the viscoelastic behavior of the skin.<sup>20</sup>

Application of an emollient such as glycerol on the skin modifies the slope and the surface of the ellipse in a stress-strain diagram obtained by the Gas Bearing Extensometer.<sup>45</sup> Topical application of glycerol induces a reduction in the slope, indicating an increase in flexibility of the skin and a broadening of the ellipse, which is compatible with a diminution of the viscosity of the stratum corneum.<sup>15,45</sup>

Similarly, Maes et al.<sup>19</sup> demonstrated an improvement in skin softness as measured with the slope of the strain-stress curves obtained with the Gas Bearing Extensometer after application of water and O/W and W/O emulsions. Water had a clear short-term effect on the elliptical loops, whereas the O/W and W/O emulsions displayed a distinctly longer lasting effect.

The tactile sensor,<sup>24</sup> which determines the changes in resonance frequency that occur when a vibrating probe comes in contact with the skin surface, can be used to assess the stiffness/softness of the skin. Using this experimental device, Sakai et al.<sup>24</sup> have recently shown a correlation between the shift in the resonance frequency of the sensor and the hydration of the horny layer (as measured by conductance) after topical application of water and a moisturizer. The softness of the skin as determined with the tactile sensor was compared with the skin elasticity parameter  $U_r/U_f$  obtained with the Cutometer. At a low pressure of application of the sensor, highly significant negative correlations were observed ( $r = -0.73$ ) between the shift in resonance frequency and the conductance hydration data. Moderately significant positive correlations ( $r = +0.49$ ) between shift in resonance frequency and the Cutometer elasticity parameter  $U_r/U_f$  were seen.

## CONCLUSIONS

Results of mechanical measurements clearly show that upon hydration of the horny layer by topical addition either of simple water or of moisturizers (glycerine, urea, etc.) or emollients (petrolatum), some elastic mechanical parameters and viscoelastic parameters are significantly modified. These changes in the hydration state of the stratum corneum, which were assessed by electrical hydration measurements and by mechanical properties, occurred during both short-term and long-term hydration treatments.

The mechanical devices that were capable of detecting in a significant way changes in elastic and viscoelastic properties of the skin were the Twistometer–Dermal Torque Meter, the Cutometer, the Dermaflex, and some experimental systems, such as the Gas Bearing Extensometer and the tactile sensor.

When considering only the commercially available devices, it is surprising to note that, although there are great differences in the methods (torsion vs. suction), in the surface of the skin that is mechanically modified (1 mm annulus between disk and guard ring in the torsion device, from 2- to 10-mm probe aperture in the suction device), and in the amount of stress (low torque and from 100 to 500 mbar suction), the three instruments are sensitive enough to measure significant changes in the biomechanical properties of the skin when the hydration state of the horny layer is modified.

Which instrument is the most sensitive device for measuring most specifically the mechanical properties of the horny layer? Considering the fact that in the torsion method a small skin surface between rotating disk and guard ring is submitted to small values of stress (torque), the Dermal Torque Meter has a significant sensitivity to measure more specifically the mechanical properties of the horny layer.

Because of the size of the Cutometer probe (2 to 8 mm) and Dermaflex probe (10 mm), and the deformation magnitudes involved, it is obvious that their mechanical measurements involve not only the entire stratum corneum but also other layers, such as the viable epidermis, dermis, and possibly the subcutis.<sup>41</sup> However, by using the Cutometer with the small, 2-mm probe and lower values of suction (200 mbar), a better sensitivity to moisturization effect is observed and the instrument measures mainly the contribution of the mechanical properties of the horny layer.<sup>17</sup> It is clear that measurements with the Dermaflex involve the mechanical properties of the whole skin with probably a contribution of the subcutis. However, Jemec and Serup<sup>39</sup> found correlations between some mechanical properties and capacitance measurements with the Corneometer.

Which mechanical parameters are the most sensitive to changes in hydration of the horny layer? Very contradictory results are found in the literature. Surprisingly, pure elastic parameters as well as viscoelastic parameters are sensitive to hydration of the horny layer and to the effect of moisturizers. Some elastic and/or viscoelastic parameters are more sensitive than others to moisturization effects and some moderate correlations are observed between the mechanical parameters as measured with the Dermal Torque Meter and with the Cutometer.

Concerning the correlations between electrical hydration measurements (capacitance and conductance) and mechanical properties, very contradictory results are observed. Some studies have clearly shown a correlation between the electrical hydration measurements and elastic and viscoelastic parameters (although the correlations were generally moderate), and in other studies no correlations at all were found.

In conclusion, hydration of the horny layer as produced by various moisturizers influences the elastic and viscoelastic properties of the skin. Noninvasive skin elasticity measurements carried out with the Dermal Torque Meter and with the Cutometer (2-mm probe at low vacuum) are appropriate for quantitative evaluation

of the complex effects of various cosmetic hydrating products on the mechanical properties of the skin.

Ideally, the effects of moisturizers on the skin should be first assessed by electrical hydration measurements (Corneometer, Nova, DermaLab, or Skicon) and these assessments complemented by study of the effect of the moisturizers on epidermal elastic and viscoelastic properties.

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# 22 Antikeloidal Products

Wolf-Ingo Worret

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## HISTORICAL OVERVIEW

Since ancient times, scars have caused cosmetic and psychic impairment. As early as 3000 to 2500 B.C., keloids were described in the “Smith papyrus.”<sup>1</sup> The English term *scar* is derived from the Greek word *eschara*, i.e., fireplace. The Saxons at this time had a term for this phenomenon, as well: *scaur*. In France, scars were called *eschare*. The present scientific Latin term *cicatrix* was used in the Middle Ages for white spots of the skin as a sign of imperfection.

In dermatology, keloids and hypertrophic scars are separate entities. Keloids are scars in which the wound healing tissue grows out over the actual wound edges. In contrast, hypertrophic scars respect the wound edges. Such symptoms as itching, burning, and pain are more often observed in keloids than in hypertrophic scars.

Jean Louis Alibert (1768–1837), the French dermatologist, first described the clinical characteristics of the condition. He used the Greek term *chele* (which means claw of a crayfish) and changed it into *cancroide* (i.e., similar to cancer) in 1806. Later he changed the term into *cheloid* to avoid confusion with malignant tumors, in particular with cancer.<sup>2</sup> In 1854, Addison suggested the terms *true* and *false keloids*. As true keloids he described ones that appeared spontaneously, whereas false keloids are ones that appear post-traumatically.<sup>3</sup>

## PATHOPHYSIOLOGY

Scar formation and the pathophysiology of the origin of scars is not fully understood. However, there are some extraordinary phenomena in the genesis of keloids and hypertrophic scars. In early wound healing, in the early inflammation phase,<sup>4</sup> virtually no differences between normal tissue restoration and keloid formation can be observed. This phase is followed by fibroplasia, consisting of increased vessel formation and moderate perivascular cellular infiltration with mast cells, plasma cells, and lymphocytes. These also begin the formation of collagen clusters, fibers, and proteoglycans (components of the matrix). Contrary to normal wound healing, the massive fibroplasia of keloids originates in the third week.

Typically, keloids form nodular, vascular proliferations with an avascular, knotty accumulation of collagen and coating proteoglycans.<sup>5</sup> This mass mainly comprises fibroblasts. Fibroblasts are arranged in a storiform pattern and continue to proliferate in a hyalinated collagen cluster, which is typical for disturbed wound healing. One unique cell type in keloids — the myofibroblast — is a mixture of muscle cells and fibroblasts.<sup>4</sup> Its exact function is not understood, and it diminishes in fully developed scars. In hypertrophic scars and keloids, there is an increased cellular activity from the elevation of the DNA concentration with increased production of type I procollagen mRNA.<sup>6</sup> The fibroblasts in keloids are larger than those in hypertrophic scars. Also, the activity of these cells is significantly greater than that of hypertrophic scars.<sup>7</sup>

The raised metabolic activity results from an increase in various enzymes, for example, glycolytic enzymes, glycoproteins, and the fibronectin deposits. Not only the quantity of fibroblasts, but also their density increases.<sup>7</sup> The expectation that collagen degradation is enhanced is not correct; the opposite is true: degradation is decreased.<sup>8</sup> The local extent of keloids is mainly caused by an increase of ground substance.<sup>4</sup>

A further difference between keloids and hypertrophic scars is water content: the higher proportion of water in keloids can be explained by the increased production of hyaluronic acid, which has a strong water-binding capacity. This fact is important for the mode of action of glucosteroid treatment.<sup>9</sup>

## ANTIKELOIDAL PRODUCTS WITH PROVEN EFFECTS

Keloid treatments include surgical excision, pressure bandaging, connective tissue massages (now with a new hydraulic device: LPG, Sophia Antipolis, France), cryotherapy, low-dose radiotherapy, topical silicone gel sheet, a topical onion extract gel (Contractubex®, Merz&Co, Frankfurt, Germany), interferon, and intralesional injection of corticosteroids, mostly triamcinolone acetonide. Today, in most clinics a polypragmatic procedure is accepted: excision, then cryotherapy, then triamcinolone injections, rarely X-ray radiation, and after that pressure bandages. However, there remain keloids unresponsive to this management.

Earlier, primarily subjective gradings (for example “good/poor results”) or subjective clinical scores were used for assessing efficacy. For quantitative assessment, however, noninvasive bioengineering methods, i.e., skin thickness measurements by means of high-frequency ultrasound and measurements of mechanical properties or



of skin color, are used. Because keloids diminish with time and are virtually not seen in elderly people, it is mandatory to test antikeloidal products by objective methods over a short period of time, i.e., some months.

This chapter discusses antikeloidal substances that have been proved to be efficient by objective bioengineering methods: corticoid injections, silicone gel sheet, and Contractubex. Nevertheless, not all measurements were reliable, and this is discussed below.

### INTRALESIONAL CORTICOSTEROIDS

The mechanical properties of 17 keloids in nine patients before and during treatment with intralesional triamcinolone acetonide were studied using a noninvasive suction device (Cutometer®, Courage and Khazaka, Cologne, Germany) for measuring skin elasticity and viscosity *in vivo*.<sup>10</sup> This method provides quantitative assessment of the mechanical properties of scars. It is well suited for comparative studies on the efficacy of various scar therapies. Each keloid was treated with intralesional injections of triamcinolone acetonide 10 mg/ml without local anesthetic at intervals of 3 weeks. Four measurements per keloid were performed before treatment and 3 weeks after the first, second, and third treatments (Figure 22.1).

The parameters used were immediate distension ( $U_e$ ), delayed distension ( $U_v$ ), immediate retraction ( $U_r$ ), and final distension ( $U_f$ ). Relative parameters independent of skin thickness were calculated:  $U_v/U_e$ , the ratio between the viscous and the elastic deformation of the skin, and  $U_r/U_f$ , representing the ability of the skin to return to its initial position after deformation (biologic elasticity).

After three injections of triamcinolone acetonide a marked decrease of  $U_v/U_e$  and a less-pronounced increase of  $U_r/U_f$  compared to baseline values was observed

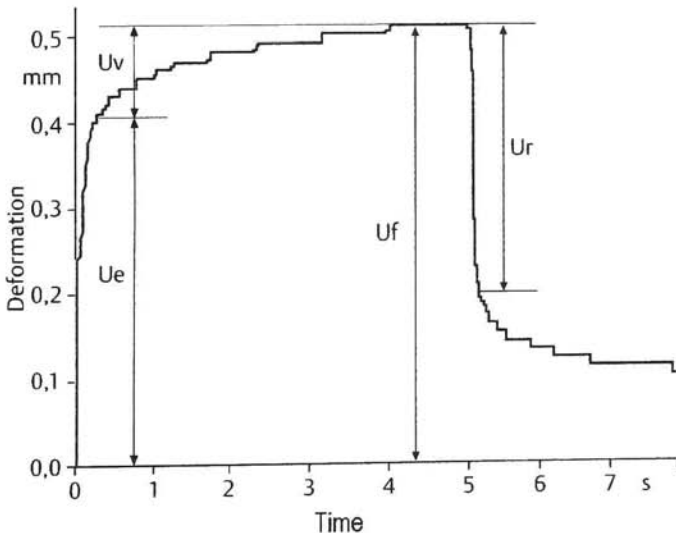


FIGURE 22.1 Graph from physiological skin as released from the Cutometer.

(Figure 22.2). These findings indicate that the primary effect of intralesional corticoids on the connective tissue of keloids is decreased viscosity as a result of a loss of ground substance. A comparison of the results of Cua et al.<sup>11</sup> for normal skin and the baseline values of keloids in the present study shows that  $U_i/U_e$  is higher and  $U_r/U_e$  is considerably lower in keloids, indicating that the viscous component in keloid tissue is increased whereas elasticity is decreased. The results of the investigation described above suggest that the decrease of viscosity, represented by the ratio  $U_i/U_e$ , is the main parameter that marks the beginning of the triamcinolone action on the connective tissue of keloids. Although  $U_r/U_f$ , the biological elasticity, was enhanced significantly after therapy, it seems untrue that this is the hallmark of the improvement of scars.

What alterations in the structure of keloid tissue might correspond to these changes in mechanical properties? The viscous component of the mechanical properties is thought to be dependent on the ground substance in the dermis.<sup>11</sup> The ground substance contains water and glycosaminoglycans, which are linked to peptide chains to form macromolecules called proteoglycans. Vogel<sup>12</sup> showed that the viscosity of rat skin correlated to the content of glycosaminoglycans and soluble collagen in the ground substance.

Glucocorticoids inhibit the synthesis of glycosaminoglycans at low concentrations in human skin fibroblast culture,<sup>13</sup> and this inhibition may be important for mediating the rapid thinning of the dermis after glucocorticoid treatment. This may be due to the ability of the glycosaminoglycans to retain water, and thus a reduced amount of glycosaminoglycans in the dermis may lead to a decrease in water content and to smaller interfibrillar spaces between the collagen and elastic fibers.<sup>14</sup> After 6 weeks of occlusive application of clobetasol propionate to normal skin, a loss of ground substance was observed by electron microscopy,<sup>15</sup> resulting in a rearrangement of the dermal fibrous network, while the fibers themselves were not altered.

Although the effects of glucocorticoids on the metabolism of the glycosaminoglycans can be observed within a few weeks, the degradation of collagen and elastin occurs much later. The apparent resistance of dermal fibers to short-term corticoids may reflect the longer half-life of these components.<sup>14</sup> Thus in this study, which was completed 9 weeks after the first application of intralesional steroids, no considerable effect on the collagen and elastic fibers can be expected.

## SILICONE GEL SHEETS

The results in the reduction and improvement with the treatment of keloids and hypertrophic scars with silicone gel sheets are undisputed.<sup>16-18</sup> The several similar silicone sheets available differ only minimally in size, shape, and price. The composition of the foils is nearly identical. The exact mode of action of the silicone sheets on hypertrophic scars and keloids has not yet been clarified. However, it is certain that the silicone does not penetrate directly into the skin, and that there is no foreign body reaction.<sup>18,19</sup> Chemical effects have not been totally excluded, but are unlikely.<sup>20</sup>

Although placement of the sheet on the skin requires that a certain pressure be applied, this pressure is not sufficiently powerful to provoke an improvement of the

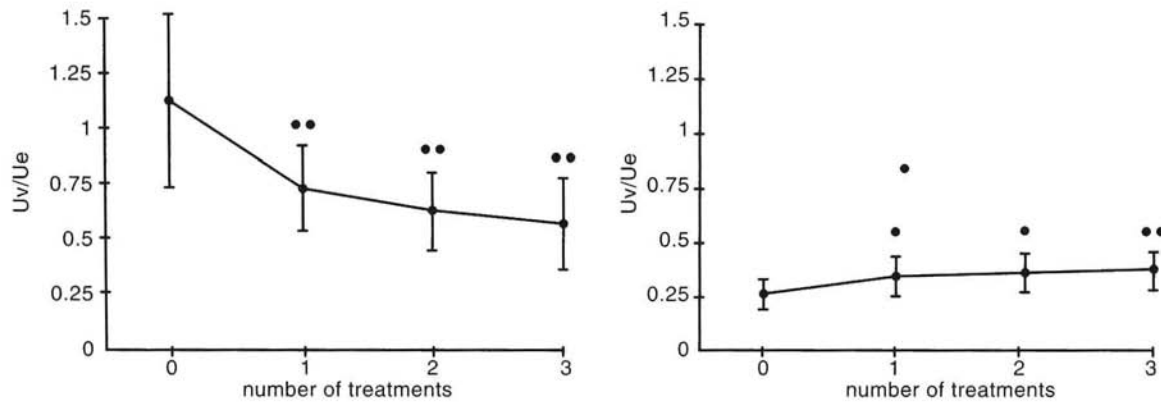


FIGURE 22.2 Results of intralesional triamcinolone injections (\* = significance).

scar. To be successful with bandage therapy it is necessary to reach pressures between 15 and 40 mm Hg<sup>21</sup> over at least 4 to 6 months. Under the silicone sheet only pressure values between 1 and 12.8 mm Hg<sup>20</sup> were recorded, which is not enough to affect the scar. Water vapor transmission seems to play an important role in treatment with silicone gel foil. Normal skin releases about 8.5 g/m<sup>2</sup> water per hour, hypertrophic scars only about 4.5 g/m<sup>2</sup> per hour.<sup>22</sup> The development of an electrical field, for example, by rubbing of the clothing on the surface of the foil, probably has a positive impact on the scars. These electrical fields can reduce the number of the mast cells in healing wounds.<sup>16</sup>

### COMPARISON OF CORTICOID INJECTIONS AND SILICONE GEL SHEETS

To compare the treatment of keloids with corticoid injections vs. silicone gel sheets, a study was carried out in the author's clinic.<sup>23</sup> The study examined 25 keloids in 11 patients: 11 keloids were injected with triamcinolone acetate (Volon A 10®); 8 were treated with silicone gel foil (EPI-DERM™ Silicon Gel Folie; Fa. INAMED GmbH, Düsseldorf, Germany); and 6 scars served as the control group and were not treated. The mean age of the patients was 28 years (between 21 and 54 years). The sex distribution male to female was 7:4. The scars were mostly located above the sternum,<sup>5</sup> on the back,<sup>4</sup> and in the scapular region.<sup>4</sup> Other keloids were situated on buttocks, nape, and the upper arm. The duration of the scars varied between 3 months and 12 years.

Measurements were taken before and 4 weeks after the individual first and second treatment, respectively. The keloids were photographed, first, to trace the specific spot of measurement, especially in multiple scars, and, second, to demonstrate the clinical results of the treatment.

For determination of elasticity and viscosity, the Cutometer was used as above. For our calculations we used:

$$R_0 = U_f$$

$$R_6 = U_v/U_e \text{ (viscosity)}$$

$$R_7 = U_r/U_f \text{ (biological elasticity)}$$

Skin thickness was measured by 20 MHz ultrasonography (DUB 20, Taberna pro Medicum, Lüneburg, Germany).

### Results with the Cutometer

Both the maximal expansion of the skin ( $R_0$ ) and the viscosity ( $R_6$ ) did not show any changes as compared with the pretreatment values. In the elasticity modulus ( $R_7$ ) (Figure 22.5 and Table 22.3), there was an increase in time, but it was not related to therapy. By using the Friedmann test, however, no significance was seen. This observation is in contrast to the findings regarding corticoid injections alone as mentioned above.

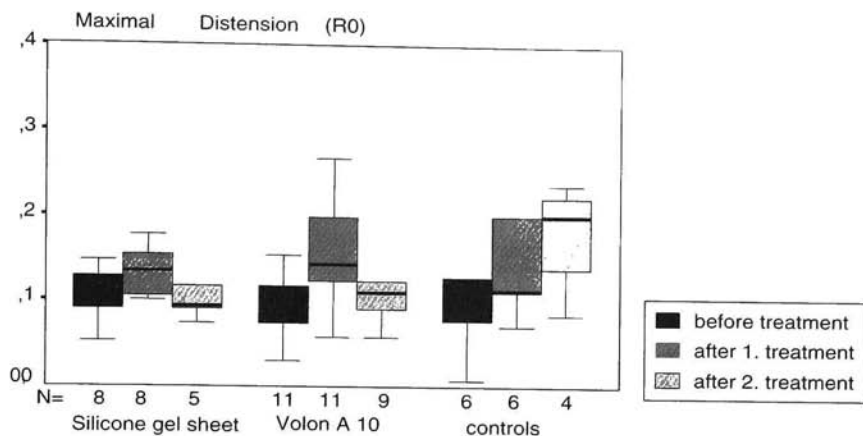


FIGURE 22.3 Results of maximal distension.

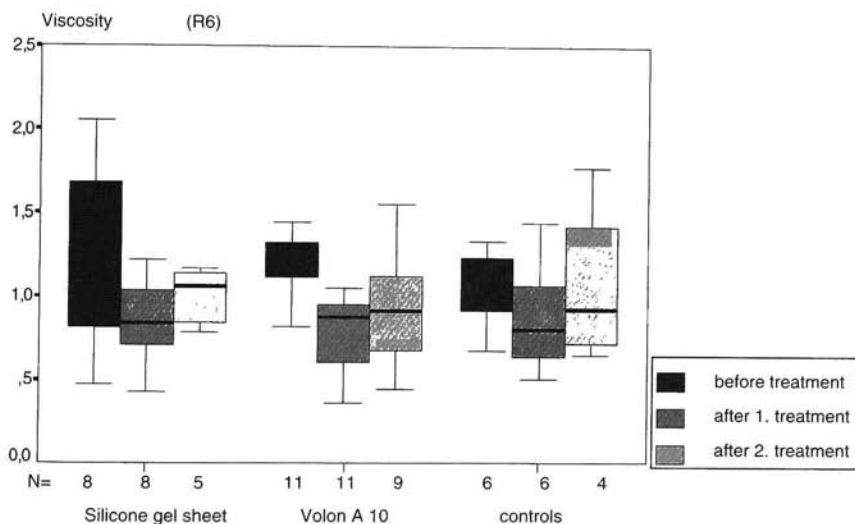


FIGURE 22.4 Results of viscosity.

In discussing the divergent results obtained using an objective skin bioengineering device, one has to reflect upon the possibilities and the limits of the Cutometer. The measurement principle of this device is a probe with an aperture 2 mm in diameter. Through this opening about 3 mm<sup>2</sup> of skin is drawn by a defined negative pressure of 500 mbar. Relaxation to zero occurs 5 s later, and this relaxation of the skin is calculated during this time via photoelements.

To obtain precisely reproducible results with such a small aperture, it is mandatory to perform the measurements on the same point of the keloid. Also, the forces of the negative pressure into the deeper tissues are not known and may vary.<sup>24</sup> In

**TABLE 22.1**  
**Maximal Distension**

	Median	Minimum	Maximum	Mean	Std. Dev.
<b>Silicone Gel Sheet</b>					
Before treatment	0.125	0.053	0.147	0.111	0.032
After first treatment	0.134	0.100	0.177	0.133	0.029
After second treatment	0.093	0.073	0.267	0.128	0.079
<b>Volon A 10</b>					
Before treatment	0.107	0.030	0.153	0.099	0.037
After first treatment	0.143	0.057	0.267	0.158	0.068
After second treatment	0.110	0.057	0.390	0.130	0.101
<b>Controls</b>					
Before treatment	0.117	0.007	0.207	0.109	0.066
After first treatment	0.113	0.070	0.373	0.163	0.111
After second treatment	0.200	0.083	0.237	0.180	0.067

**TABLE 22.2**  
**Viscosity**

	Median	Minimum	Maximum	Mean	Std. Dev.
<b>Silicone Gel Sheet</b>					
Before treatment	1.088	0.467	2.056	1.212	0.568
After first treatment	0.835	0.429	1.214	0.850	0.254
After second treatment	1.056	0.783	1.167	0.997	0.175
<b>Volon A 10</b>					
Before treatment	1.194	0.782	2.0	1.228	0.326
After first treatment	0.876	0.363	1.833	0.863	0.389
After second treatment	0.916	0.445	1.556	0.923	0.370
<b>Controls</b>					
Before treatment	1.089	0.678	1.333	1.057	0.234
After first treatment	0.802	0.508	1.444	0.878	0.339
After second treatment	0.924	0.652	1.776	1.069	0.502

addition, one must take the pretension of the tissue into account. This must be absolutely similar in each measurement.<sup>25</sup> The areas near joints must be measured always in the same angle of the joint to calculate with the same pretension. From all these points, it becomes evident that the Cutometer is not the correct device to obtain exact reproducible data of the improvement of keloids and hypertrophic scars *in vivo*.

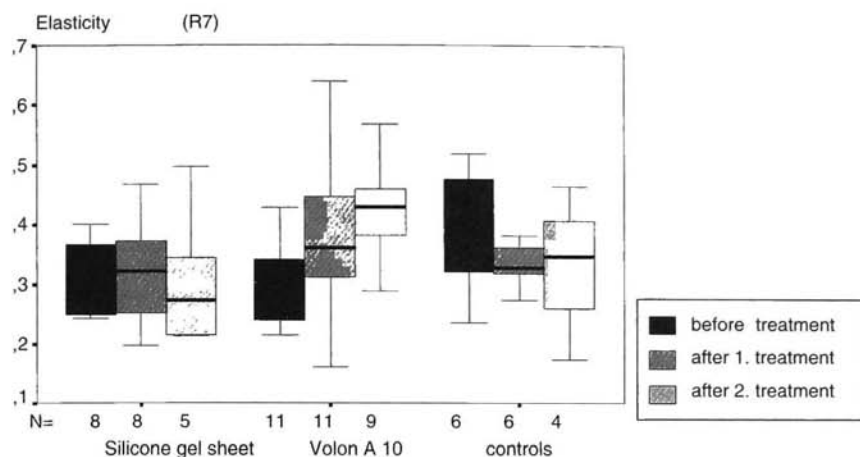


FIGURE 22.5 Results of elasticity.

TABLE 22.3  
Elasticity

	Median	Minimum	Maximum	Mean	Std. Dev.
<b>Silicone Gel Sheet</b>					
Before treatment	0.294	0.244	0.400	0.308	0.063
After first treatment	0.322	0.198	0.467	0.320	0.089
After second treatment	0.274	0.213	0.498	0.309	0.119
<b>Volon A 10</b>					
Before treatment	0.274	0.215	0.429	0.298	0.073
After first treatment	0.362	0.161	0.640	0.381	0.130
After second treatment	0.430	0.289	0.568	0.417	0.084
<b>Controls</b>					
Before treatment	0.367	0.236	0.520	0.381	0.106
After first treatment	0.327	0.274	0.382	0.331	0.038
After second treatment	0.347	0.173	0.465	0.333	0.120

### Results with Ultrasonography

In the group treated with corticosteroids, the thickness of the scars was reduced as much as 60%. Also the skin thickness regressed quickly for 29% after the first treatment. In the silicone sheet-treated group this regression was only about 5%. In the course of the treatment, echogenicity of the dermis and the input echo increased. A disadvantage of the ultrasonograph is that the maximal input depth of the device is only about 7 mm. The thickness of keloids, of course, could be larger. In these

cases the objectivity of this method is reduced. With both, the ultrasonography and the clinical inspections combined with interviews, treatment with corticosteroids was superior to the silicone gel sheet.

The decrease of skin thickness in the control group (-7%) is noteworthy. Despite no treatment, the keloid tissue shrank. This is explained by the tendency of self-healing in the course of time.

### EXTACTUM CEPAE GEL

Contractubex is the only topical antikeloidal substance with proven effects on the international markets. Although the main active agent is a phytoextract from onions, it has not yet been determined precisely which ingredient is responsible for the improvement of scars. Several effects on keloids and hypertrophic scars could be demonstrated that act together in softening and diminishing such lesions.

*Antiproliferative effect:* In cultures of human fibroblasts of different sources (scars, keloids, embryonal tissue) the inhibition of skin fibroblasts was maximal between 43 and 46%; in fibroblasts of keloids it was more pronounced between 38 and 53%.<sup>26</sup> An inhibition of proliferation of keloid fibroblasts and fibroblasts of other tissues was established for all three components of Contractubex: heparin, allantoin, and the onion extract.<sup>27</sup>

*Inhibition of proteoglycan and collagen formation:* The effect of the formulation on the formation of such extracellular matrix components as proteoglycans and collagen was studied in cultures of human skin.<sup>28</sup> The results showed a clear and dose-related reduction of proteoglycans and collagen. In an animal experiment it was established that pathologically enhanced synthesis of collagen was inhibited, which was true in scar tissue but not in normal skin.<sup>29</sup> Based on these results, it is assumed that Contractubex in scars with pathologically increased concentration of collagen and proteoglycans — as is the case in keloids and hypertrophic scars — can lead to improvement of scar structures.

*Breaking up the arrangement of scar tissue:* In specimens of human scars it has been histologically proved that the combination in Contractubex inhibits the polymerization of collagen and stimulates the decartelization of collagen.<sup>30</sup> In this manner, a certain breakup of the scar tissue is achieved. In fresh scars, excessive collagen polymerization is prevented.

*Improvement of scar elasticity:* The effect of Contractubex on the elasticity of scars was studied in animal experiments on the basis of viscoelastic characteristics.<sup>31</sup> At the end of the treatment the "stiffness index" was measured and calculated against the untreated scars of the control group. The index was markedly diminished in treated areas. It also became evident that normal skin treated with the onion extract was not affected by the therapy. The improvement of scar elasticity is of clinical importance in scars that cause functional impairment.

### CONCLUSION

Noninvasive bioengineering methods seem to be well suited for studies on the efficacy of various therapies in keloids and hypertrophic scars. As the mechanical



properties are only one aspect of keloid tissue, elasticity measurements should be combined with other bioengineering methods such as skin thickness assessments by means of high-frequency ultrasound or quantitative measurement of skin color with a colorimeter. In the author's experience, the Cutometer is probably not the optimal device for the evaluation of keloid tissue. Other methods should be defined to obtain more precise measurements. A more versatile instrument may be the uniaxial extensometer described by Edwards (Cardiff) at the 13th Congress of the International Society of Bioengineering and Skin in March 2000. At the same meeting, Marshall (Glasgow) presented a new method of picture analysis applied to scar tissue. The disadvantage is that it is an invasive histological technique. The method is based on calculating the alignment of the nuclei of fibrocytes. In hypertrophic scars, the bridges of collagen and the fibrocytic nuclei are oriented in a parallel manner to the skin surface, whereas in a keloid, most nuclei are located within a 30° angle. Further, by measuring these angles it is possible to obtain an accurate notion of the severity of a scar.

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