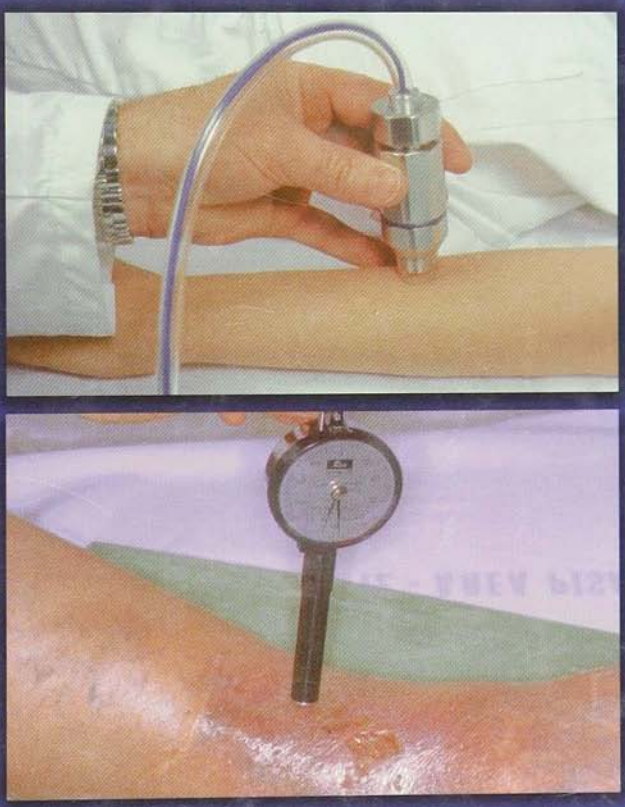
BIOENGINEERING OF THE SKIN

Skin Biomechanics



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

DERMATOLOGY: CLINICAL & BASIC SCIENCE SERIES

BIOENGINEERING OF THE SKIN

Skin Biomechanics

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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.

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.

The Editors

Peter Elsner, M.D., studied medicine at Julius Maximilians University, Würzburg, Germany, from 1974 to 1981 and was trained as a dermatologist and allergologist at the Department of Dermatology, Würzburg University, 1983 to 1987. He received his doctoral degree in 1981 and his lectureship in dermatology in 1987. From 1988 to 1989, he was visiting research dermatologist at the Department of Dermatology, University of California at San Francisco; and from 1991 to 1997, he was consultant and associate professor, Department of Dermatology, University of Zurich, Switzerland. Since 1997 he has served as professor and chairman, Department of Dermatology and Allergology, Friedrich Schiller University, Jena, Germany.

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).

Enzo Berardesca, M.D., is senior dermatologist and professor at the School of Dermatology of the University of Pavia in Pavia, Italy. Dr. Berardesca obtained his training at the University of Pavia and earned his M.D. in 1979. He served as resident and dermatologist at the Department of Dermatology, IRCCS Policlinico S. Matteo, Pavia, from 1982 to 1987, and as research assistant at the Department of Dermatology, University of California School of Medicine in San Francisco in 1987. He assumed his present position in 1988.

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.

He has authored five books and more than 200 papers and book chapters.

Klaus-P. Wilhelm, M.D., is president and medical director of proDERM Institute for Applied Dermatological Research, Schenefeld/Hamburg, Germany, and Lecturer of Dermatology at the Medical University of Lübeck, Germany.

Dr. Wilhelm earned his M.D. degree in 1986 from the Medical University of Lübeck and was awarded the degree of Lecturer by the same institution in 1995.

From 1988 to 1990, Dr. Wilhelm was a visiting scientist at the Department of Dermatology, University of California, San Francisco Medical School. He completed his residency at the Department of Dermatology, Medical University of Lübeck in 1993. In 1994 he founded the contract research institute proDERM in Schenefeld/Hamburg.

Dr. Wilhelm is a member of the Executive Board of the International Society for Bioengineering and the Skin and a member of the European Society for Dermatological Research, the European Contact Dermatitis Society, the German Dermatological Society, and the American Academy of Dermatology. He has received three consecutive government grants and has published more than 40 scientific papers and book chapters. His research interests include physiology of healthy and diseased skin, irritant contact dermatitis, skin pharmacology, and evaluation of bioinstrumentation techniques for the skin.

Howard Maibach, M.D., is a Professor of Dermatology at the University of California, San Francisco, and has been a leading contributor to experimental research in dermatopharmacology, and to clinical research on contact dermatitis, contact uticaria, and other skin conditions. His work on pesticides includes clinical research on glyphosate, chlorothalonil, sodium hypochlorite, norflurazon, diethyl toluamide, and isothiazolin compounds. His experimental work include research on the local lymph node assay, and the evaluation of the percutaneous absorption of atrazine, boron-containing pesticides, phenoxy herbicides, acetochlor, glyphosate, and many other compounds.

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Section I

Introduction

1 Mechanical Properties of Human Skin: Biochemical Aspects

Aarne Oikarinen and Anina Knuutinen

CONTENTS

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.

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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%.[1] 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.[2] 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).[3,4] The BM of skin is a flexible sheetlike structure, which contains multiple different molecules.[5] 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 α chains, which can be similar or dissimilar polypeptide chains. Type III collagen, for example, consists of three identical $\alpha 1$(III) chains encoded by a single gene, whereas type I collagen is composed of two identical $\alpha 1$(I) chains, which are synthesized from the same gene, and an $\alpha 2$(I) chain, which is synthesized from another gene.[6] 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.[1,7,8]

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.[7] The reactions are catalyzed by specific enzymes, prolyl-4-hydroxylase, prolyl-3-hydroxylase, and lysyl hydroxylase, respectively, in the presence of Fe^{2+}, oxygen, 2-oxoglutarate, and

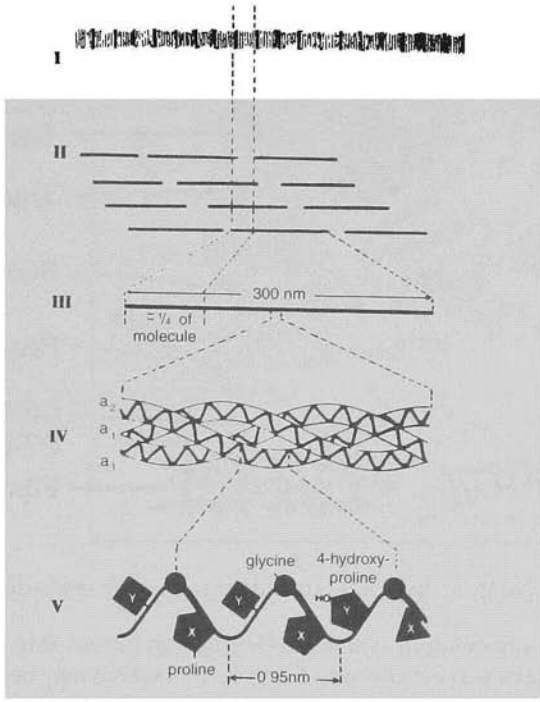

FIGURE 1.1 Schematic presentation of the structure of collagen. (I) The collagen fibers in tissues demonstrate repetitive periodicity when examined by electron microscopy. (II) The fibers consist of individual collagen molecules aligned in a quarter-stagger arrangement. (III) Each collagen molecule is approximately 300 nm long. (IV) The collagen molecules consist of three individual polypeptides, α-chains, which are twisted around each other in a right-handed, triple-helical conformation. (V) Each α-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 α-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.[9]

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 block* by specific endoproteinases.[10] This cleavage of propeptides enables the initiation of fibril formation.[11] The molecular weights of the aminoterminal propeptides of type I and III procollagens (PINP and PIIINP) are 35,000 and 45,000, respectively.[10] Since procollagens and mature collagens are synthesized in a ratio of 1:1, the amount of procollagen propeptides in serum and interstitial fluid reflects

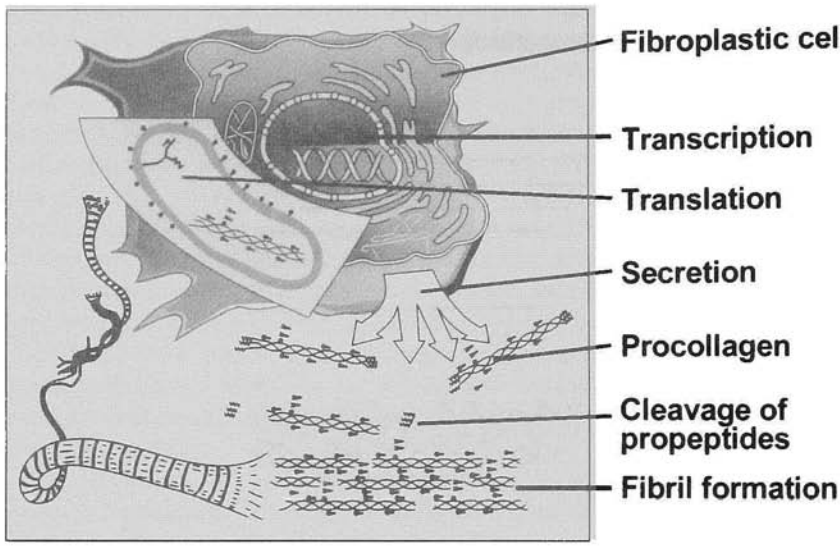

FIGURE 1.2 The intracellular and extracellular steps of the synthesis of fibrillar collagen.

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

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 ε-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 ε-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.[15]

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,[16,17] 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.[17,18] In diabetic thick skin, nonenzymatic glycosylation of collagen is the most likely cause of the changes observed in skin.[19] 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.[20]

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

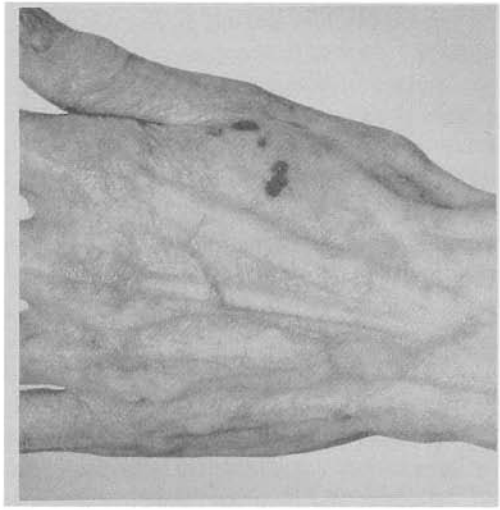

FIGURE 1.3 Skin atrophy after topical glucocorticoid treatment. Skin thickness was 0.65 mm in a steroid-treated dorsum of the hand, whereas skin thickness in age-matched controls was 1.3 mm.

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.[7,21,22] Several gene defects associated with collagen-related diseases have been elucidated. For example, defects in the genes encoding the proα1(I) or proα2(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,[22] and mutations in type III procollagen occurs in ED type IV.[6,23] 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.[24]

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.[25] Microfibrils contain several glycoproteins; of these, fibrillin has been studied in most detail.[26] 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.[25]

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.[27,28] 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.[26] 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.[29] 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 α-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.[26,27] 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[30] (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.[28] A defect in the fibrillin1 gene is

found in Marfan syndrome.[27,31] 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.[32] In elastoderma, conversely, local accumulation of abnormal elastic fibers leads to delayed recoil and elasticity of the skin (Figure 1.6).[33]

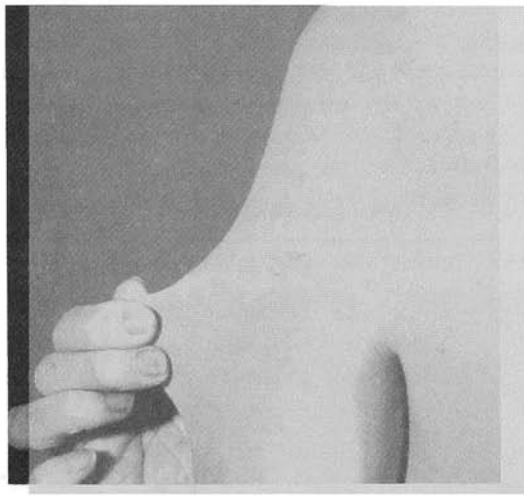

FIGURE 1.4 The skin of a patient with ED type I is hyperextensible.

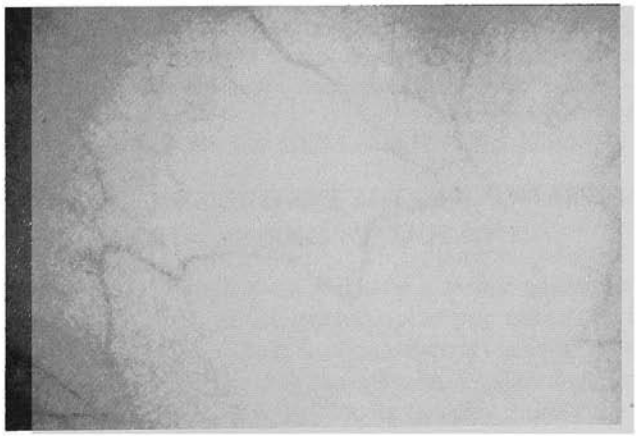

FIGURE 1.5 The skin of a 20-year-old male with ED type IV is translucent with readily visible blood vessels. The concentration of type III collagen propeptide (PIIINP) was 32.5 μg/L in the suction blisters of the patient, whereas the mean value in the controls was 106 μg/L, indicating markedly reduced 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

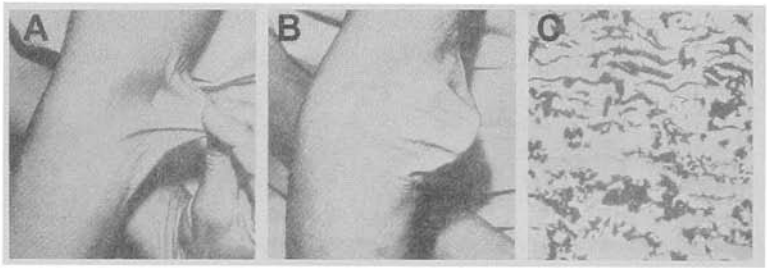

FIGURE 1.6 The right arm of a patient with elastoderma, demonstrating the laxity (A) and incomplete and delayed recoil (B) of skin. Histopathology revealed only a few normal-appearing fibers (the white arrow) and abnormal elastic structures (the black arrows) in the lower dermis (C) (Verhoeff–van Gieson 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.[34]

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.[35–37] In aging skin, collagen fibers become thicker and less soluble and the synthesis of collagen declines.[38] Skin thickness remains quite constant between 10 and 70 years of age, after which a marked decrease in skin thickness occurs.[39] 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.[40]

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.[41] 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.[25] As a result of the decreased number of elastic fibers in aged skin, the elastic recovery of skin decreases in elderly people.[4] Flattening of the dermo-epidermal junction is seen in both sun-exposed and sun-protected skin in elderly people.[42] Epidermal thickness declines with age in sun-protected areas, whereas sun-exposed regions develop an irregular epidermis with both thickened and atrophic regions.[43] A distinct feature of photoaged skin is a decrease in the ultrasound echogenicity of the upper dermis, which causes a subepidermal low-echogenic band.[44–46]

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.[47] 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.[13,48] 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.[49,50] It has also been demonstrated that elastin mRNA levels are elevated in photoaged skin, indicating transcriptional upregulation of the gene that codes elastin.[51] Reactive oxygen species activated by UV radiation are thought to play an important role in UV-induced DNA damage, cellular senescence, and aging.[47] Upon aging, the capacity to repair DNA decreases, thus increasing the risk of malignant transformations.[52]

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.[53] Matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) regulate the degradation of collagen, elastin, and other components of ECM.[54] 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.[54,55] 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.[56] The expression