0022-202X/79/7301-0059$02.00/0
THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 73:59–66, 1979

Vol. 73, No. 1
Printed in U.S.A.

Structural Alterations in Exposed and Unexposed Aged Skin

ROBERT M. LAVKER, PH.D.

Department of Dermatology, Duhring Laboratories, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania, U.S.A.

The fine structural organization of the epidermis, dermal-epidermal junction, and papillary dermis from unexposed (upper inner arm) and exposed (dorsal forearm) sites of elderly people was compared to the organization of similar regions of young people. Despite an overall thinning of the viable epidermis there was no morphological evidence that the protective function of the epidermis was compromised by age. The differentiation products associated with the keratinization process were not altered in either appearance or amounts in epidermis from unexposed and exposed old skin. Both sites revealed the presence of a well-formed stratum corneum that was the same thickness as that of the young donors. Unexposed and exposed senile skin displayed a relatively flat dermal-epidermal junction devoid of the microprojections of basal cells into the dermis, an indication of a tissue less resistant to shearing forces.

Marked elastogenesis, as evidenced by large amounts of 8- to 11-nm (diameter) microfilaments and fibroblasts containing dilated cisternae of rough endoplasmic reticulum filled with flocculent material, was characteristic of the papillary dermis from unexposed and nonactinically damaged exposed old skin. Conversely, in the papillary dermis (Grenz zone) of actinically damaged senile skin the microfilaments were replaced by densely packed collagen fibrils in a co-linear arrangement, predominantly parallel to the skin surface. That this dermal architecture was similar to that seen in various scar tissues suggests the Grenz zone is a microscar.

Gerontological studies on skin are complicated by extrinsic stresses that intensify the intrinsic effects of time. Because aging changes are most evident in exposed areas, the dorsal part of the hands, forearms, and face have been the most intensively studied. Protected areas have received scant attention.

The histological profile of exposed aged skin is well known. The epidermis is usually thin, the rete ridges are flattened and the basal cell population displays a marked heterogeneity in size, shape, and staining properties [1]. The most striking alterations relate to the fibrous components of the middle and deep dermis; elastic hypertrophy and collagen degeneration are regarded as hallmark events [2–4].

Electron microscopic investigations of aged epidermis are limited. In a study on actinically damaged epidermis, Mitchell [5] did not observe much change in the fine structural appearance of the individual keratinocytes. He did report decreases in overall amounts of tonofilaments, keratohyalin granules, and rough endoplasmic reticulum. Fine structural information on the unexposed epidermis is limited to 1 study [6], which indicated that protected epidermis, unlike unprotected epidermis, has minimal cell irregularity and minimal wide intercellular spaces.

Most electron microscopic studies have focused on the elastic fibers of exposed skin. Braun-Falco [7] and others [8–10] reported that damaged elastic fibers (elastotic material) were characterized by the presence of irregularly shaped electron-dense osmiophilic inclusions within the fiber matrix. In addition, some fibers were extremely widened and contained many large holes and only thin strips of matrix. Other investigations [11–13] found that elastin from protected aged skin displayed structural changes similar to those in exposed regions but of lesser magnitude. These findings led Stadler and Orfanos [13] to postulate that physiological aging of elastin includes diminished synthesis of microfilaments and increasing amounts of osmiophilic groups (e.g., calcium). It should be noted that these electron microscopic investigations concentrated on the reticular dermis and paid little attention to the subepidermal region, where there have been important and perplexing findings, such as the Grenz zone, which seems to lack the marked elastotic distortions of the middermis.

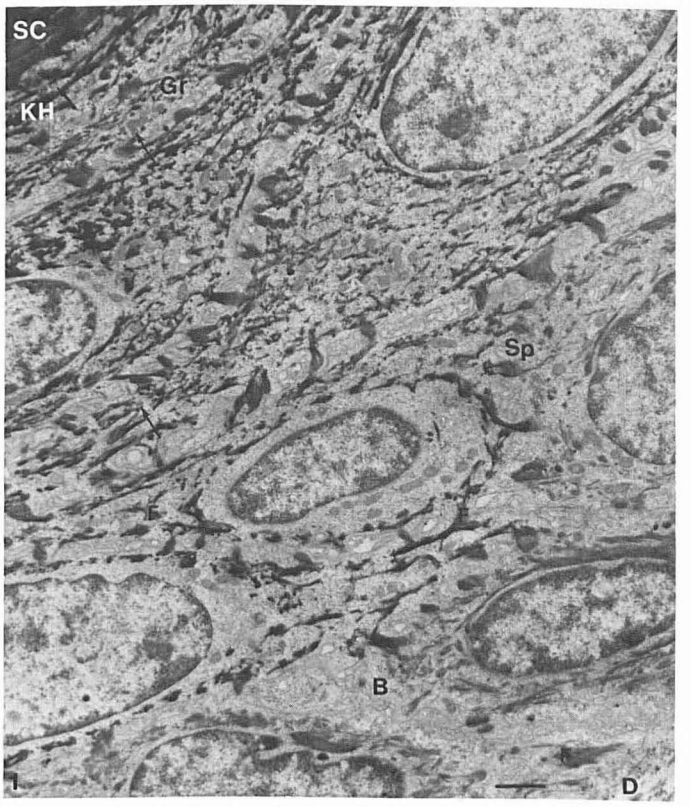

FIG 1. Full-thickness portion of the epidermis from the upper inner arm of an elderly person. *Scale* = 1μm. Despite an overall thinner viable epidermis, basal (*B*), spinous (*Sp*), and granular (*Gr*) cells displayed characteristic fine structural features associated with the keratinization process. *D* = dermis; *F* = filaments; *KH* = keratohyalin granules; (→) = membrane-coating granules; *SC* = stratum corneum (reduced from × 10,800).

The focus of this paper is the fine structural organization of the epidermis, the dermal-epidermal junction, and the papillary dermis from exposed and unexposed sites of young and elderly people.

MATERIALS AND METHODS

Subjects

Two age cohorts, 20 to 25 and 68 to 84, were compared. Ten biopsy samples were obtained from the dorsal forearm (exposed): 4 from the

Reprint requests to: R. M. Lavker, Ph.D., Duhring Laboratories, Suite 203, 3500 Market Street, Philadelphia, Pennsylvania 19104.

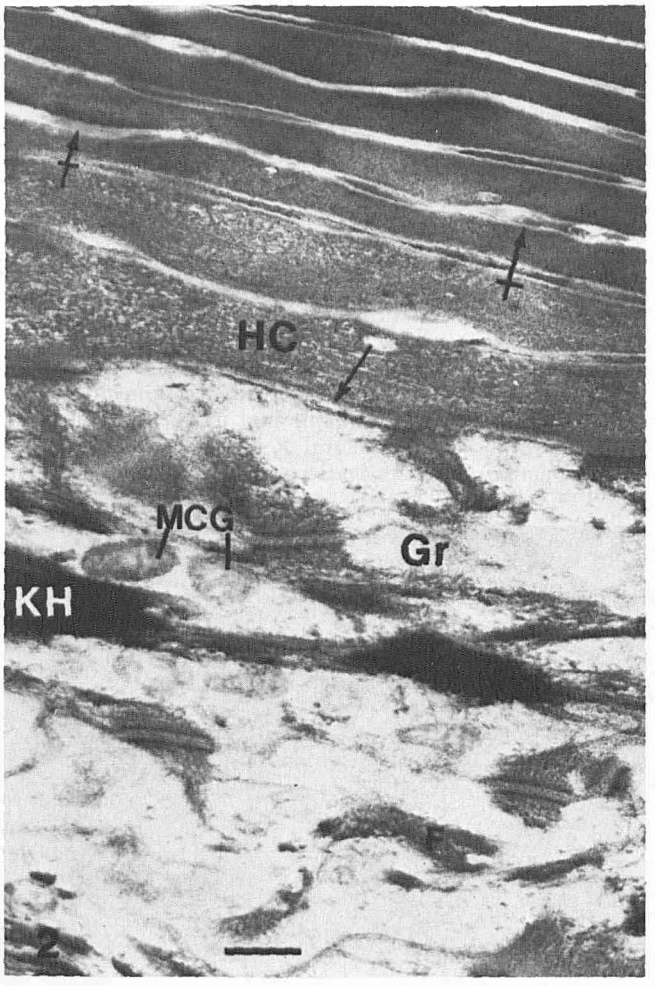

FIG 2. Portion of granular (*Gr*) and horny (*HC*) cells from the upper inner arm of an elderly donor. *Scale* = 2 μm. Filaments (*F*), membrane-coating granules (*MCG*), and keratohyalin granules (*KH*) showed no alteration in either structure or distribution. Horny cells were composed of a filament-matrix complex enveloped by a thickened membrane (→). Intercellular material was often arranged in membranelike figures (↔) (reduced from × 46,200).

20 to 25 group and 6 from the 68 to 84 yr group. Nine were taken from the upper inner arm (unexposed): 4 from individuals 20 to 25 yr of age and 5 from individuals 68 to 84 yr of age. The donors were caucasian males in good health. People with advanced actinic damage were excluded; the forearms did not show actinic necrosis, mottling, or great laxity.

Light Microscopy

Specimens were fixed in 10% buffered formalin; embedded in paraffin; sectioned at 7 μm; and stained with hematoxylin-eosin, periodic acid-Schiff, orcein, or for reticulin.

Electron Microscopy

Specimens were fixed by immersion in 2% paraformaldehyde with 2.5% glutaraldehyde in 0.1 M cacodylate-HCl, buffered at pH 7.4 [14] for 2 hr at 24°C, and postfixed in 1% osmium tetroxide for 1 hr. Some specimens were fixed in cold (4°C) 1% osmium tetroxide buffered at pH 7.4 with veronal acetate buffer [15] for 1 hr. Dehydration was accomplished by passage of the fixed tissues through a graded series of cold (4°C) ethanol baths. The samples were then infiltrated and embedded with Epon 812 [16]. Thin sections were cut with a diamond knife on a Porter Blum MT-2 microtome. Sections were stained with uranyl acetate and lead citrate [17] and examined in a Philips 300 electron microscope.

RESULTS

Epidermis

Unexposed skin. Aside from an overall thinner viable epidermis (basal, spinous, and granular region), the fine structural features of the individual basal, spinous, granular, and horny cells from elderly upper inner arms were similar to those from young people. Filaments, membrane-coating granules, and keratohyalin granules were all present in normal amounts and showed no alterations in the upper inner arms of elderly donors (Fig 1). The stratum corneum from this site consisted of horny cells composed of a filament-matrix complex enveloped by a thickened membrane (Fig 2). Horny cells were separated from each other by intercellular material often arranged in membranelike figures. No young/old differences were noted in the thickness of the stratum corneum.

Exposed skin. Basal cells from the dorsal forearm of elderly donors displayed a greater variability in size, shape, and electron density than similar regions from young donors. Cells containing a condensed, electron-dense cytoplasm composed almost solely of filamentous material surrounding a shrunken nucleus were observed in the basal cell population (Fig 3). Nuclear inclusions consisting of a fine filamentous ring surrounding an electron-dense chromatin core (Fig 3) were occasionally noted in basal cells of elderly dorsal forearms. Aside from these abnormalities in the basal cell population, the fine structure of the spinous, granular, and horny cell populations of elderly dorsal forearms was similar to that seen in young exposed skin.

Comment. The established morphological markers associated with the keratinization process were not altered either in appearance or in amounts in epidermis from unexposed and exposed old skin. In addition, both anatomical sites revealed

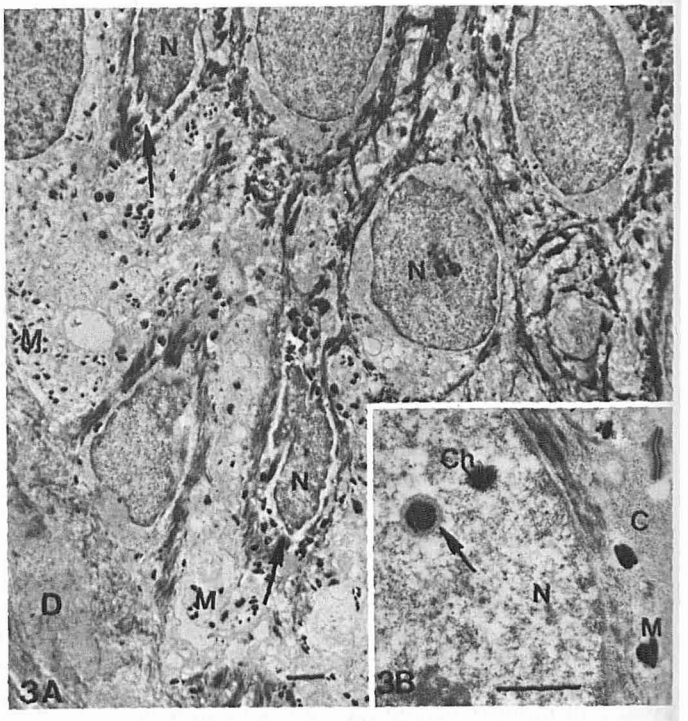

FIG 3. *A*, basal cell region from the dorsal forearm of an elderly person. *Scale* = 1 μm. Note the heterogeneity of the cell population. Cells containing a condensed, electron-dense cytoplasm surrounding a shrunken nucleus (→) were seen with a greater frequency in this tissue. *D* = dermis; *M* = melanosomes; *N* = nucleus (× 5,300). *B*, portion of a basal cell nucleus (*N*), from an elderly dorsal forearm, containing a nuclear body with an electron-dense fibrillar cortex surrounded by a fine filamentous ring (→). *Scale* = 1 μm. *Ch* = chromatin; *C* = cytoplasm; *M* = melanosomes (reduced from × 14,100).

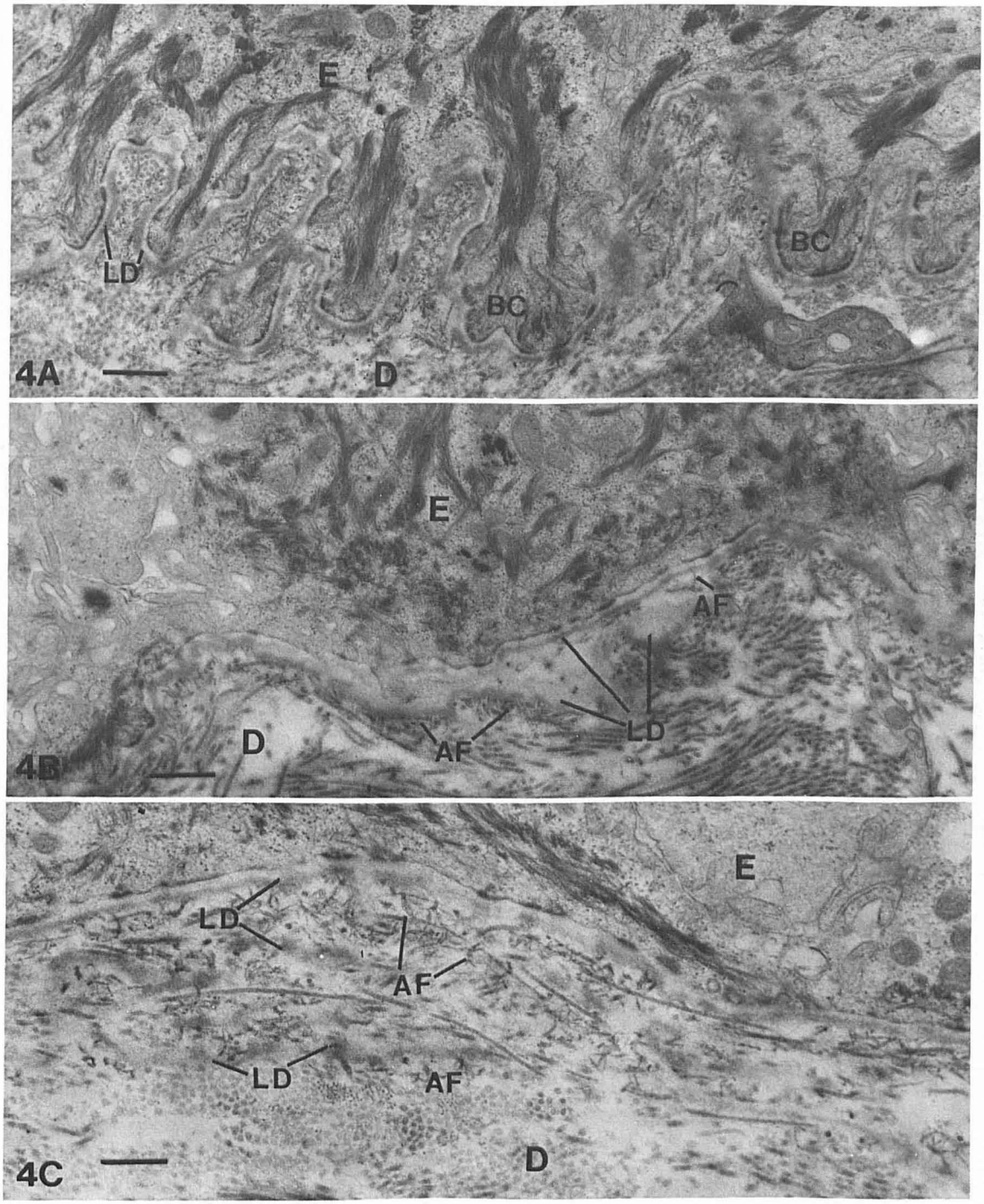

FIG 4. Dermal-epidermal junction from the upper inner arm of a young person (*A*), the upper inner arm of an elderly person (*B*), and the dorsal forearm of an elderly person (*C*). *Scale* = 0.5 μm. In the young sample, this junction was highly convoluted because of the numerous "footlike" projections of basal cells (*BC*) into the dermis (*D*). Note the single profiles of lamina densa (*LD*) along this junction. In contrast, this region in protected (*B*) and exposed (*C*) old skin was devoid of the "footlike" projections and there was a consequent flat epidermal-dermal interface. Lamina densa (*LD*) and anchoring fibril (*AF*) reduplication was routinely seen in protected (*B*) and to a greater extent in exposed (*C*) senile skin. *E* = epidermis; *D* = dermis (× 20,000).

the presence of a well-formed stratum corneum. Therefore, it can be concluded that aside from a generalized epidermal atrophy, there were very few age-associated cytologic changes in the epidermis.

Dermal-Epidermal Junction

Unexposed skin. In young people, the dermal-epidermal junction consisted of numerous villous like cytoplasmic projections of basal cells into the dermis (Fig 4*A*). These well-developed microfoot processes were responsible for the highly convoluted appearance of the dermal-epidermal interface. In contrast, old skin was devoid of epidermal "footlike" projections, a phenomenon that resulted in a flat dermal-epidermal interface (Fig 4*B*). In sections from the upper inner arm of young donors (Fig 5), the basal cell plasma membrane was separated from the electron-dense region known as the basal lamina or lamina

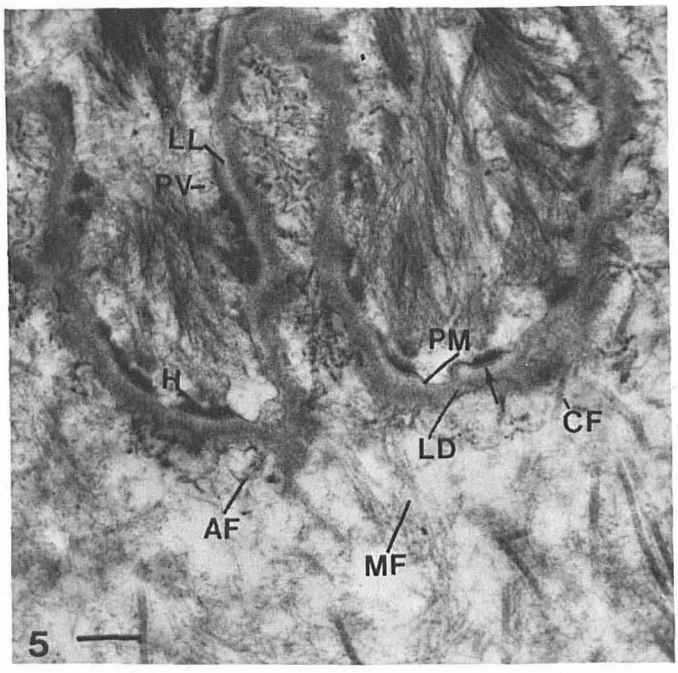

FIG 5. High-magnification micrograph showing the various components of the dermal-epidermal junction. *Scale* = 0.25 μm. Anchoring fibrils (*AF*) and microfibrils (*MF*) terminate in the lamina densa (*LD*); individual collagen fibrils (*CF*) are present in close proximity to this structure. *PV* = pinocytotic vesicles; *PM* = plasma membrane; *LL* = lamina lucida; *H* = hemidesmosomes; (→) = electron-dense line (reduced from × 39,000).

densa by an electron-lucent zone (lamina lucida). Pinocytotic vesicles were noted along the basal cell plasma membrane in addition to numerous hemidesmosomes. An electron-dense line was observed within the lamina lucida directly beneath the hemidesmosomes. Cross-banded anchoring fibrils and microfibrils terminated in the lamina densa. In cross section the microfibrils had a hollow tubular profile, 8 to 11 nm in diameter. In favorable longitudinal sections, microfibrils occasionally extended deep into the dermis, where they entered elastic fibers (Fig 6). In addition to microfibrils and anchoring fibrils, individual collagen fibers were often seen in close proximity to the lamina densa. All of the above components of the dermal-epidermal junction were present in unexposed skin of elderly donors (Fig 4*B*). The major change observed in the organization of this junction was a reduplication of the lamina densa and anchoring fibril complex. Redundancy of these structures was seen periodically beneath both keratinocytes and melanocytes.

Exposed skin. The dermal-epidermal junction in the dorsal forearm of aged people (Fig 4*C*) was flattened because of the absence of microfoot processes. Likewise, in elderly exposed skin, lamina densa and anchoring fibril reduplication was commonly seen. These alterations in the junction complex were more extensive in exposed than in unexposed skin.

Comment. Because an almost flat dermal-epidermal junction and excess amounts of lamina densa with attached anchoring fibrils were characteristic of both unexposed and exposed senile skin, these alterations were most likely the result of intrinsic aging.

Papillary Dermis

Unexposed skin. In young skin (Fig 7*A*), collagen existed as single fibrils in the area adjacent to the lamina densa. Collagen was organized into thin bundles about 1.0 to 1.5 μm beneath the lamina densa and persisted in this type of arrangement throughout the papillary dermis. These bundles were embedded in ground substance that appeared as electron-lucent spaces. Microfibrils, 8 to 11 nm in diameter, were present mostly as single fibers just beneath the lamina densa and in close association with collagen bundles. Fibroblasts in this region were relatively large and irregular in shape; contained a prominant nucleus; and had a cytoplasm filled with well-developed flattened cisternae of rough endoplasmic reticulum (Fig 7*B*). The major change in the upper inner arm of elderly donors was an increase in the amount of 8- to 11-nm (diameter) microfibrils (Fig 8*A*). Fibrillar material, present throughout the papillary dermis, existed as discrete masses or was interspersed between collagen fibrils. At a high magnification, these masses consisted entirely of microfibrils 8 to 11 nm in diameter (Fig 8*B*). Changes were also noted in the fibroblasts within this region (Fig 9). These cells contained extensive amounts of rough endoplasmic reticulum that enclosed widely dilated cisternae filled with flocculent material. Numerous vesicles were also present in the fibroblast cytoplasm.

Exposed skin. The organization of the papillary dermis of young dorsal forearms was similar to that of young upper inner arms. In the elderly cohort, some individuals showed little evidence of actinic damage at the light microscopic level; others had histological evidence of solar elastosis, with the presence of a Grenz zone. In those donors with a few histological signs of actinic damage, the fine structural changes in the papillary dermis were similar to those seen in elderly unexposed sites, except that the amount of microfibrils was more extensive. Profound changes were noted in the architecture of the papil-

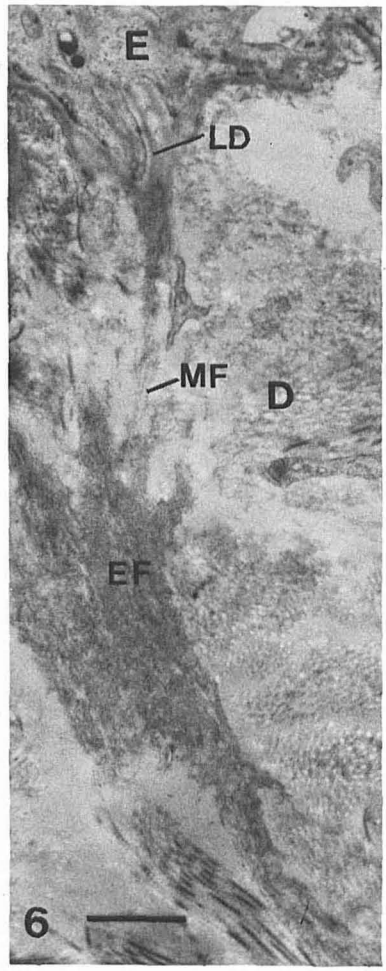

FIG 6. Electron micrograph showing continuity of microfibrils (*MF*) with the lamina densa (*LD*) and elastic fibers (*EF*) in the papillary dermis (*D*). *Scale* = 1 μm. *E* = epidermis (× 12,300).

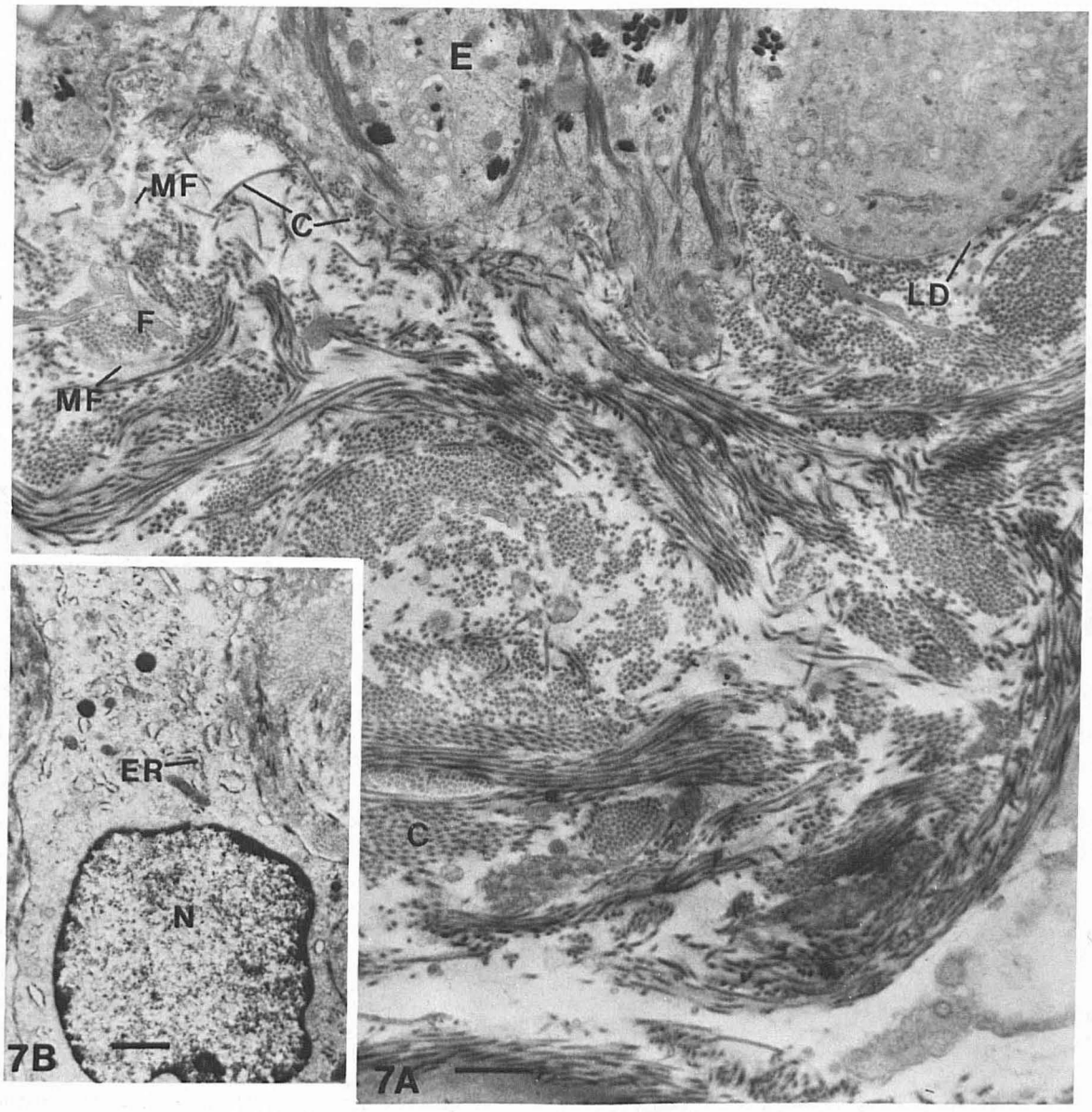

FIG 7. *A*, electron micrograph showing the organization of the papillary dermis from the upper inner arm of a young donor. *Scale* = 1 μm. Collagen (*C*) exists as single fibrils in the area adjacent to the lamina densa (*LD*) and in bundles deeper in the dermis. Microfibrils (*MF*) are seen beneath the lamina densa and in association with collagen bundles. Ground substance appears as electron-lucent spaces. *F* = fibroblast extensions; *E* = epidermis (× 10,800). *B*, typical fibroblast found in the papillary dermis from a young upper inner arm. *Scale* = 1 μm. Note the prominent nucleus (*N*) and the cytoplasm filled with well-developed flattened cisternae of rough endoplasmic reticulum (*ER*) (× 7,400).

lary dermis (Grenz zone) in those donors with histological signs of actinic damage (Fig 10), The area just beneath the lamina densa consisted of an approximately 1 μm-wide region of densely packed collagen fibrils in a co-linear arrangement, predominantly parallel to the skin surface (Fig 10). Also present within this mass of collagen were large amounts of lamina densa, anchoring fibrils, and microfilaments, all of which contributed to the overall compactness of the area. Beneath this region, collagen was organized into large discrete bundles separated from each other by a few electron-lucent spaces (Fig 10). In general, these bundles were parallel to the skin surface. Within this region mature elastin and scant amounts of 8- to 11-nm (diameter) microfibrils were noted.

Comment. The characteristic change seen in the papillary dermis from unexposed and nonactinically damaged exposed skin of elderly people was an increase in the amount of microfilaments. Fibroblast ultrastructure was also altered in this region. In actinically damaged old skin the bundles of microfilaments were replaced by massive amounts of tightly packed collagen fibrils.

DISCUSSION

The main function of the epidermis is protection, achieved by the formation of a stratum corneum. Even though the epidermis atrophies with age [1], the keratinocytes still elaborate the specific differentiation products [18,19] associated with the keratinization process. A well-formed stratum corneum was present in both unexposed and exposed old skin. From a morphological stand point, age does not seem to affect the ability of the epidermis to create a normal stratum corneum. This concept is supported by physiological studies on skin permeability [20] that indicate the capacity to restrict water loss is not compromised in senile skin.

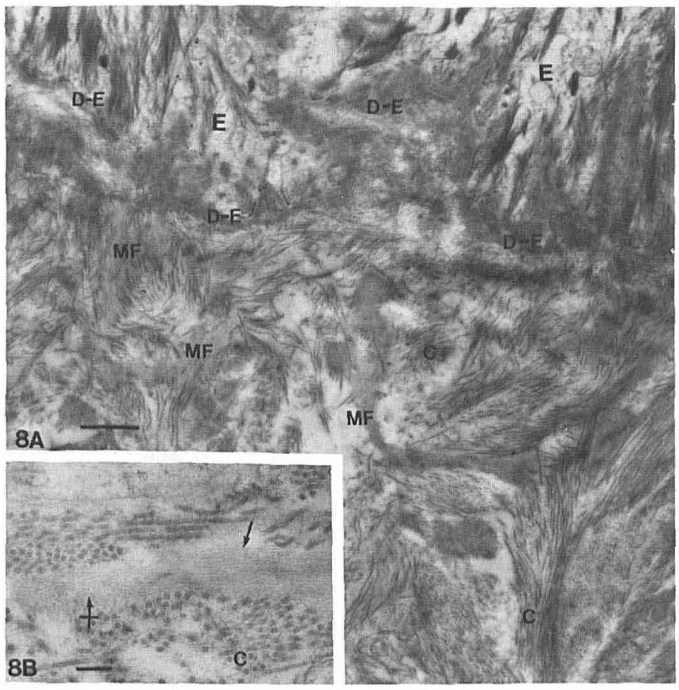

FIG 8. *A*, papillary dermis from the upper inner arm of an elderly donor. Note the large increase in amounts of microfibrils (*MF*). *C* = collagen; *D-E* = dermal-epidermal junction; *E* = epidermis (× 13,100). *B*, higher-magnification electron micrograph showing microfilaments (8 to 11 nm in diameter) in both cross section (↔) and longitudinal section (→). *Scale* = 2 μm. *C* = collagen (reduced from × 37,000).

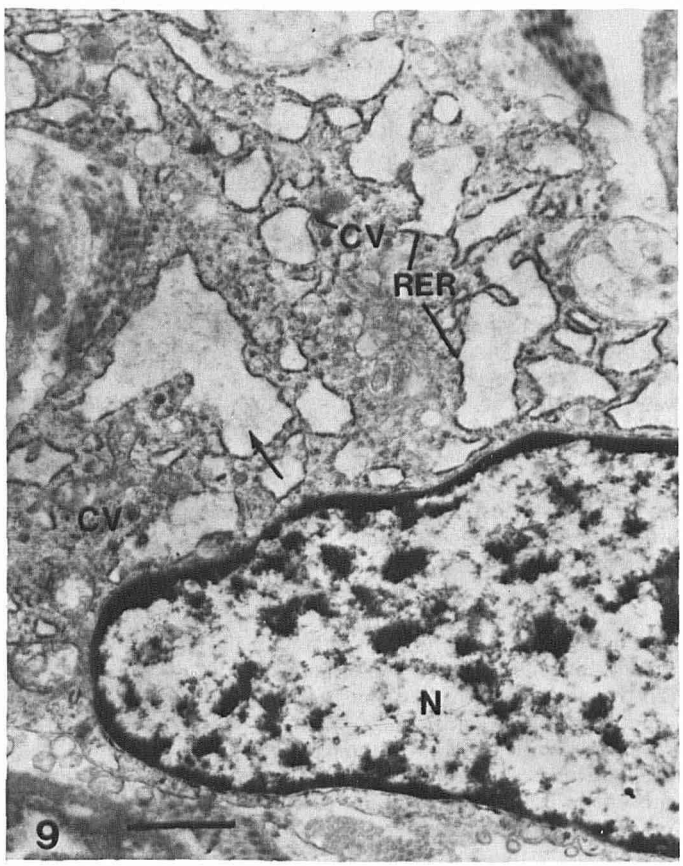

FIG 9. Portion of a fibroblast found in the papillary dermis from the upper inner arm of an elderly person *Scale* = 1 μ. These cells were typified by a cytoplasm filled with extensive amounts of rough endoplasmic reticulum (*RER*) that formed widely dilated cisternae. These cisternae were filled with flocculent matterial (→). *CV* = coated vesicles; *N* = nucleus (reduced from × 14,800).

Alterations in the elderly epidermis are slight, wereas the dermal-epidermal junction is markedly altered. In the young, the extensive interdigitation of basal cells with the dermis greatly increases the surface area of the dermal-epidermal junction and firmly anchors the epidermis to the dermis [21] to provide resistance to shearing forces. Conversely, a flattened dermal-epidermal junction would result in a more fragile tissue less resistant to tearing forces. For this reason, in old skin with its flat dermal-epidermal interface, the epidermis often can be peeled off by trauma. Similar flat dermal-epidermal junctions have been noted in scar tissue (reference 22 and W. Clark, personal communication). This finding also explains why suction blisters can be raised in much less time on elderly subjects [23].

Lamina densa reduplication has been noted in a variety of epidermal disorders [24–26] and is considered a nonspecific response to trauma. Routine observations of lamina densa and anchoring fibril redundancy in unexposed, and to a somewhat greater degree in exposed, aged skin suggests that this tissue is in a constant state of repair. Similar lamina densa changes have been reported in normal skin exposed to ultraviolet A (UVA) light [25] and in skin treated with psoralen UVA light [26]; these changes might be related to actinic damage. However, such damage does not explain lamina densa reduplication in unexposed aged skin. Recent studies on the recessive dystrophic variant of epidermolysis bullosa by Briggerman and Wheeler [27] and experiments on the human cutaneous basement membrane by Heaphy and Winkelmann [28] have demonstrated the importance of the lamina densa-anchoring fibril complex in the binding of the epidermis to the dermis. Perhaps reduplication of the lamina densa-anchoring fibril complex in aged skin represents an attempt by the epidermis to form a better bond with the dermis to compensate for dermal-epidermal flattening.

Elastin consists of 100- to 120-Å (diameter) microfibrils with a hollow appearance, dispersed within and surrounding an amorphous component [29–32]. Investigations of elastogenesis [29,33,34] and wound healing [35,36] indicate that the microfibrillar compenent is synthesized first. Thus, the presence of large amounts of hollow, 100- to 120Å-microfibrils in the papillary dermis of unexposed aged skin is suggestive of extensive elastogenesis. Further evidence of elastin synthesis is provided by the appearance in this region of fibroblasts containing dilated cisternae of rough endoplasmic reticulum filled with flocculent material, and numerous coated vesicles. These 2 markers are consistently found in fibroblasts actively engaged in elastogenesis [29,33,35,36]. The amount of microfibrils present in the papillary dermis was many times greater in exposed, nonactinically damaged skin than in protected skin. This fact parallels the histochemical [37] and biochemical [38] finding of an age-related increase, greater in the exposed areas, in elastin in both exposed and unexposed skin. An increased amount of microfibrils with age probably represents an attempt by the skin to replace the degraded elastin with new material. Alternatively, a large amount of microfibrils might be an indication of incomplete elastin synthesis due to some inability of old skin to manufacture the amorphous component necessary for maturely functioning elastin.

Elastogenesis is accentuated in unexposed and nonactinically damaged exposed skin of elderly people, whereas collagen deposition is the hallmark of actinically damaged papillary dermis (Grenz zone). The dense masses of tightly packed co-linear collagen fibrils, primarily parallel to the surface of the skin, are very similar to the dermal architecture observed in scars [22, 39]. A decreased amount of elastic microfibrils, noted in the Grenz zone, is also consistent with scar formation. Soft x-ray absorption studies on actinically damaged skin [40] have revealed that this tissue strongly absorbs this type of radiation, a feature typical of fibrotic tissues. Thus, the Grenz zone may be regarded as a microscar.

Atrophy of the viable epidermis, epidermal-dermal junction flattening, basal lamina reduplication, and elastogenesis are characteristics of the protected skin of old people and might be

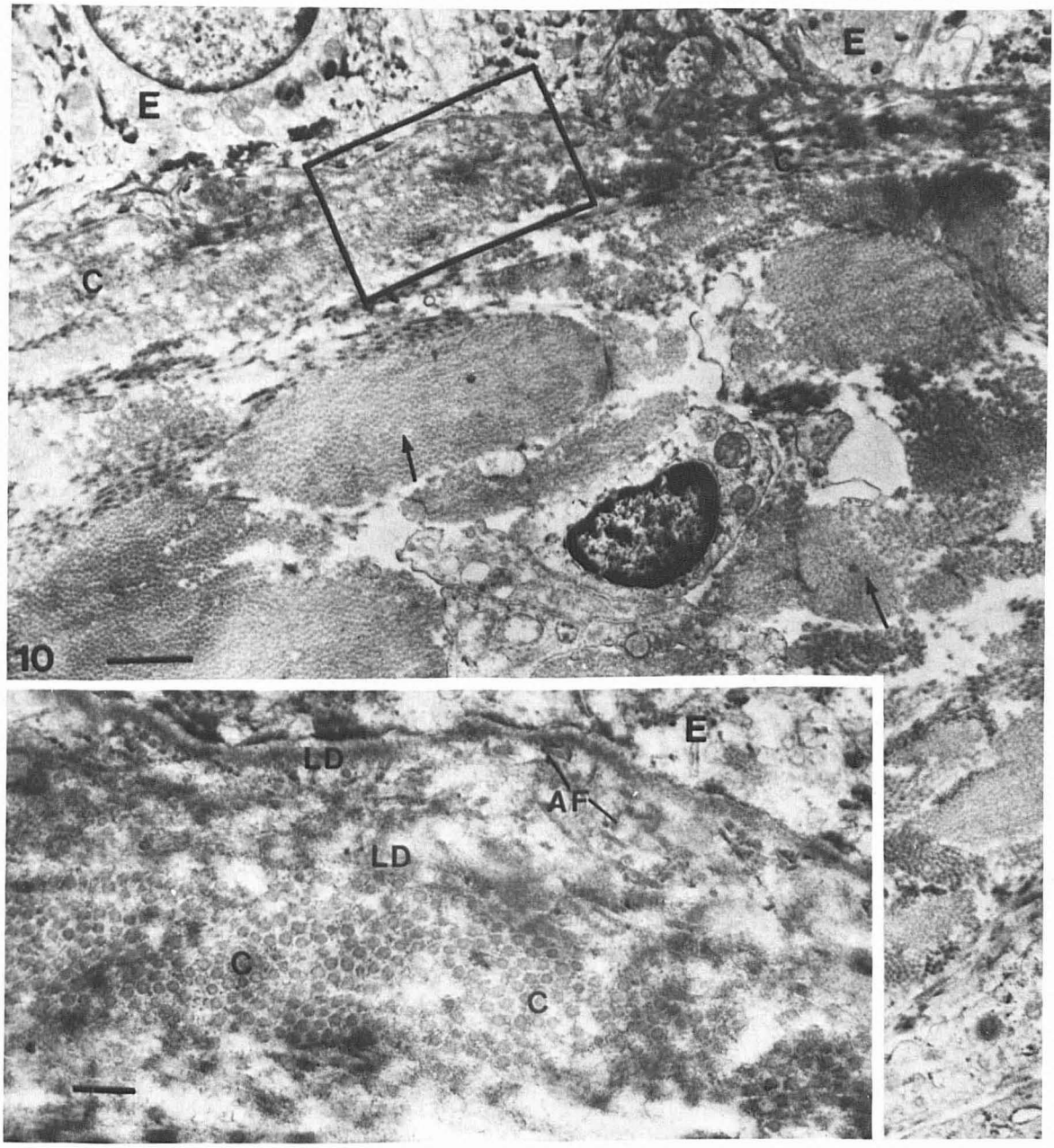

FIG 10. Electron micrograph of a portion of the papillary dermis from the dorsal forearm of an elderly person who displayed histological signs of actinic damage. *Scale* = 1 μm. The Grenz zone is characterized by extensive amounts of collagen (*C*) organized in a dense band directly beneath the epidermis (*E*). Beneath this dense band, collagen is organized into large bundles (→). Note that most collagen is parallel to the skin surface (× 11,400). *Inset*, high-power electron micrograph of an area with densely packed collagen fibrils (*C*) in a co-linear arrangement predominantly parallel to the skin surface. *Scale* = 0.25 μm. Within this dense band redundant amounts of lamina densa (*LD*) and anchoring fibrils (*AF*) were noted. *E* = epidermis; *D-E* = dermal-epidermal junction (reduced from × 36,000).

thought of as age-related structural changes. These alterations are more prominent in exposed old skin, a further indication that actinic radiation hastens the "aging" process in skin.

I would like to thank Dr. Max Listgarten, Chairman, Department of Periodontics, University of Pennsylvania, School of Dental Medicine, for the use of his electron microscope facilities. I would also like to thank Ms. Margaret Cullen for her valuable technical assistance.

REFERENCES

1. Montagna W: Morphology of the aging skin: The cutaneous appendages, Advances in Biology of Skin, vol VI. Aging. Edited by W. Montagna. Oxford, Pergamon Press, 1965, pp 1–16
2. Lund HZ, Somerville RL: Basophilic degeneration of the cutis. Data substantiating its relationship to prolonged solar exposure. Am J Clin Pathol 27:183–190, 1957
3. Smith JG, Davidson EA, Sams WM, Clark RD: Alterations in human dermal connective tissue with age and chronic sun damage. J Invest Dermatol 39:347–350, 1962
4. Kligman AM: Solar elastosis in relation to pigmentation, Sunlight and Man. Edited by TB Fitzpatrick, MA Pathak, LC Harbert, M Seiji, A Kurita. Tokyo, University of Toyko Press, 1974, pp 157–163
5. Mitchell RE: Chronic solar dermatosis: An electron microscopic study of the epidermis. Aust J Dermatol 10:75–91, 1969
6. Nagy G, Janner M: Altersueranderungen in der den Witterungseinflussen nicht ausgesetzten menschlichen Epidermis. Arch Klin Exp Dermatol 239:167–175, 1970
7. Braun-Falco O: Die morphogenese der senil-aktinischen Elastose. Eine elecktronenmikroskopische Untersuchung. Arch Klin Exp Dermatol 235:138–160, 1969
8. Banfield WG, Brindley DC: Preliminary observations in senile elastosis using the electronmicroscope. J Invest Dermatol 41:9–17, 1963
9. Constantine VS, Hartley MN: Collagen and elastic fibers in normal dermis and severe actinic (senile) elastosis. A light and electron microscopic study. Ala J Med Sci 3:329–342, 1966

10. Mitchell RE: Chronic solar dermatosis: A light and electron microscopic study of the dermis. J Invest Dermatol 43:203–220, 1967
11. Danielson L. Kobayasi T: Degeneration of dermal elastic fibers in relation to age and light-exposure. Acta Derm Venereol (Stockh) 52:1–10, 1972
12. Nurnberger F, Schober E, Marsch WCh, Dogliott M: Actinic elastosis in black skin. Arch Dermatol Res 262:7–15, 1978
13. Stadler R, Orfanos CE: Reifung and alterung der elastischen fasern. Arch Dermatol Res 260:97–112, 1978
14. Karnovsky MJ: A formaldehyde gluteraldehyde fixative of high osmolality for use in electron microscopy. J Cell Biol 27:137A, 1965
15. Palade GE: A study of fixation for electron microscopy. J Exp Med 95:285–298, 1952
16. Luft JH: Improvements in epoxy resin embedding methods. J Biophys Biochem Cytol 9:409–414, 1961
17. Venable JH, Coggeshall R: A simplified lead citrate stain for use in electron microscopy. J Cell Biol 25:407–408, 1965
18. Lavker RM, Matoltsy AG: Formation of horny cells. The fate of cell organelles and differentiation products in ruminal epithelium. J Cell Biol 44:502–512, 1970
19. Matoltsy AG, Parakkal PF: Keratinization, Ultrastructure of Normal and Abnormal Skin. Edited by A Zelickson. Philadelphia, Lee and Febiger, 1967, pp 76–104
20. Christophers E, Kligman AM: Percutaneous absorption in aged skin, Advances in Biology of Skin, vol VI. Aging. Edited by W Montagna. Oxford, Pergamon Press, 1965, pp 163–175
21. Briggerman RA, Wheeler CE: The epidermal-dermal junction. J Invest Dermatol 65:71–84, 1975
22. Bason CR, Longacre JJ, Unterthiner RA, Townsend SF: Electron microscopic study of fibrillogenesis and hyperthrophic scar formation, The Ultrastructure of Collagen. Edited by JJ Longacre. Springfield, Charles C Thomas, 1976, pp 294–315
23. Kilstala U: Dermal-epidermal separation. I. The influence of age, sex and body region on suction blister formation in human skin. Ann Clin Res 4:10–22, 1972
24. Wilgram GF: Pempliigus and bullous pemphigoid, Ultrastructure of Normal and Abnormal Skin. Edited by A Zelickson. Philadelphia, Lee and Feiger, 1967, pp 335–346
25. Kumakiri M, Hashimato K, Willis I: Biologic changes due to long-wave ultraviolet irradiation on human skin: Ultrastructural study. J Invest Dermatol 69:392–400, 1977
26. Hashimato K, Kohda H, Kumakiri M, Bender SL, Willis I: Psoralen-UVA treated psoriatic lesions. Arch Dermatol 114:711–722, 1978
27. Briggerman RA, Wheeler CE Jr: Epidermolysis bullosa dystrophica-recessive: A possible role of anchoring fibrils in the pathogenesis. J Invest Dermatol 65:203–211, 1975
28. Heaphy MR, Winkelmann RK: The human cutaneous basement membrane-anchoring fibril complex: Preparation and ultrastructure. J Invest Dermatol 68:177–186, 1977
29. Fahrenbach WH, Sandberg LB, Cleary EG: Ultrastructural studies on early elastogenesis. Anat Rec 155:563–567, 1966
30. Greenlee TK Jr, Ross R, Hartman JL: The fine structure of elastic fibers. J Cell Biol 30:59–71, 1966
31. Hashimato K, DiBella RJ: Electron microscopic of normal and abnormal elastic fibers of the skin. J Invest Dermatol 48:405–423, 1967
32. Ross R: The elastic fiber: A review. J Histochem Cytochem 21:199–208, 1973
33. Kewley MA, Williams G, Steven FS: Studies of elastic tissue formation in the developing bovine ligamentum nuchae. J Pathol 124:95–101, 1978
34. Albert EN: Developing elastic tissue. An electron microscopic study. Am J Pathol 69:89–102, 1972
35. Williams G: The pleural reaction to injury: A histological and electronoptical study with special reference to elastic tissue formation. J Pathol 100:1–7, 1970
36. Williams G: The late phase of wound healing: Histological and ultrastructural studies of collagen and elastic tissue formation. J Pathol 102:61–68, 1970
37. Montagna W, Parakkal PF: The Structure and Function of Skin, New York, Academic Press, Inc, 1974, p 129
38. Sams WM, Smith JG: Alterations in human dermal fibrous connective tissue with age and chronic sun damage, Advances in Biology of Skin, vol VI. Aging. Edited by W. Montagna. Oxford, Pergamon Press, 1965, pp 199–210
39. Linares HA: Granulation tissue and hypertrophic scars, The Ultrastructure of Collagen. Edited by JJ Longacre. Springfield, Charles C Thomas, 1976, pp 93–107
40. Serri F, Tosti A, Cerimele D, Fazzini ML, Villardita S, Compagna G: Studies on the pathomechanics of chronic actinic dermatosis, Research in Photobiology, Edited by A Castellani. New York, Plenum Press, 1977, pp 547–553,