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REPORTS

ULTRASTRUCTURE OF THE HUMAN DERMAL MICROCIRCULATION: THE HORIZONTAL PLEXUS OF THE PAPILLARY DERMIS

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Electron microscopy was used to define the ultrastructure of the various segments of the human cutaneous microcirculation in normal forearm skin. The organization of the vessels in the horizontal plexus of the papillary dermis was reconstructed from 1-μm plastic-embedded sections. Ultrathin sections were taken at 10- to 20-μm intervals over a distance of 450 μm. Arterioles were followed through the capillary bed to their venous connections. Terminal arterioles, arterial and venous capillaries, and postcapillary venules were identified on the basis of size, cellular composition of their walls, and their relationship to the other segments of the microvascular bed. The arterial segments were characterized by a homogeneous basement membrane and the venous segments by a multilaminated basement membrane. The elastic lamina in the arterioles was a discontinuous layer which gradually disappeared from the arteriolar wall to form an external sheath just before the arteriole connected with the arterial capillary segment. The vascular walls varied from 1 to 5 μm in all of the segments of the microvascular bed. Criteria are proposed for identifying the various segments of the microcirculation so that their roles in dermatoses and vascular malformations can be evaluated.

The blood supply of the human dermis is a microcirculatory bed [1,2]. The arterioles and venules form three important plexuses in the dermis: a horizontal network in the papillary dermis from which the capillary loops of the dermal papillae* arise, and individual plexuses around hair follicles and eccrine sweat glands. An arteriole entering the deep dermis may pass without interruption to the horizontal papillary plexus or it may send branches to a hair follicle or sweat gland as it ascends through the corium. Although there are many interconnections among the ascending arterioles, descending venules, and between arterioles and venules at all levels of the dermis, the three plexuses described above are the most important vascular meshes in the skin. In addition, the bulk of the microcirculation resides in the papillary plexus. Light microscopy has been able to divide the microcirculatory bed only into arterioles, "capillaries," and venules.

Electron microscopy has not been used in a systematic way to define the ultrastructure of the various segments of the human cutaneous microcirculation. Previous reports on the ultrastructure of human dermal blood vessels have been primarily descriptions of electron microscopic findings of individual vessels as they are randomly encountered in tissue sections rather than being a correlation between ultrastructure and the segmental location of a particular vessel in the microcirculatory bed [3–6].

Vascular alterations are an important feature of many dermatoses and the vessels most frequently involved are those in the papillary dermis. A knowledge of the ultrastructure of the various segments of the microcirculation would be helpful in understanding the pathogenesis of many dermatoses and in determining the basis for the various vascular malformations encountered in the skin.

Rhodin [7,8] studied the microcirculation in the fascia overlying the thigh muscles in the rabbit. In this system the blood vessels exist as a monolayer. He was able to determine the functional segments of the microcirculation on the basis of blood flow in vivo, and then, following in situ fixation with glutaraldehyde, he examined precisely by electron microscopy the different parts of this microcircula-

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*The horizontal network in the papillary dermis is synonymous with the "sub-papillary plexus" used by other authors. The "dermal papilla" refers to the dermal ridge which contains the capillary loops that supply nutrients to the epidermis and should not be confused with the identical term used to describe the dermal component of the hair bulb. Other synonyms for the capillary loop in the dermal papilla include "subepidermal plexus," "papillary plexus," and "papillary loops."

tory bed. On the basis of luminal diameters, the types of cells composing the vessel wall and the position of the vessel in relation to the other segments of the vascular bed, Rhodin was able to divide the vessels into arterioles, terminal arterioles, precapillary sphincters, arterial and venous capillaries, postcapillary venules, and larger venules. Rhodin's studies provide the best criteria for an ultrastructural evaluation of the human dermal microcirculation.

Unfortunately the vascular supply of the human dermis does not exist as a thin monolayer nor is it amenable to injection techniques during life or flow pattern studies by cinemicrophotography. Therefore, we reconstructed a portion of the papillary dermal plexus in forearm skin from serial sections and examined the vessels by electron microscopy as they went from the arterial to the venous sides. The dermal papillae are poorly developed in the skin of the forearm so that most of the vessels in the papillary dermis are horizontally disposed although with markedly undulating courses.

The ultrastructure of the capillary loops in well-developed dermal papillae will be reported in a separate paper.

MATERIALS AND METHODS

Three-millimeter discs of normal forearm skin were obtained from three individuals with a skin trephine. The three volunteers were all women, two of whom were 50 years old and one of whom was 45 years old. The flexor surface of the forearm which was biopsied did not show clinical evidence of actinic damage. An intradermal ring of anesthesia was produced with 1% lidocaine without epinephrine. The sample of skin was removed from the center of the ring and processed for light and electron microscopy by techniques previously described [9]. A serial reconstruction of the papillary dermal vessels, 450 μm long by 500 μm wide, was made from 1-μm sections of plastic-embedded tissues of one person. Ultrathin sections for electron microscopy were taken at intervals of 10 to 20 μm during this reconstruction. The thin sections were placed on slotted grids covered with Formvar (0.4% in ethylene dichloride) and the entire section was photographed. Montages were constructed and individual vessels were followed for the length of the reconstruction in order to define the various segments of the microcirculation. The vessels in the papillary dermis from the other two individuals were similarly studied over a distance measuring approximately 500 μm in width and 500 μm in length but graphic reconstructions were not made.

These studies concentrated on the vessels of the papillary dermis. Vessels in the deep dermis were not systematically investigated but measurements of their size were made in 1-μm sections with a calibrated graticule. The size of the papillary vessels was measured both in electron micrographs and in 1-μm sections.

Skin samples were also fixed in 1% osmium tetroxide in 0.2 M cacodylate buffer, pH 7.4, on ice for 2 hr before dehydration and embedding in Spurr's epoxy resin for comparison with material processed in Karnovsky's fixative.

Luminal diameters could not be used as a basis for vessel classification as Rhodin had done because they could not be measured accurately. There were two difficulties. Firstly, human blood vessels normally pursue a sinuous course so that most of the vessels were seen in cross section or tangential profiles and a long stretch of longitudinally sectioned vessel was not commonly found. Secondly, the thickness of an individual endothelial cell often varied from 0.3 to 1.5 μm along the length or circumference of its profile. Instead, we measured the outside diameters of the vessel and the endothelial tube, both of which showed much less variation over a given distance. These measurements permitted us to calculate a ratio between endothelial tube diameter and vascular wall thickness which is a close approximation of the ratio of luminal diameter to vascular wall thickness employed by Rhodin.

The degree of vascular collapse following biopsy was variable but never severe. Many vessels retained their circular shape while some became elliptical. The ellipses were converted mathematically to circles for the measurement of vascular diameters. These derived data agreed with the direct measurements of identically appearing noncollapsed vessels.

RESULTS

The flexor skin of the forearm had a relatively flat epidermis with poorly developed dermal papillae. These features are characteristic of the flexor forearm skin from individuals 20 to 55 years of age in our material. The majority of the dermal vessels were present in the papillary dermis and only a minority of vascular profiles were seen in the lower two-thirds of the dermis. The outside diameters of blood vessels in the papillary dermis varied from 10 to 35 μm but most were in the 17- to 22-μm range. The outside diameters of the deepest dermal vessels encountered were 40 to 50 μm.

The endothelial cells contained bundles of 75- to 100-Å filaments. Their walls varied in thickness from 0.3 to 1.5 μm except for the spots where the nuclei bulged into the lumen. Here the wall was often 2 to 4 μm thick. Pinocytotic vesicles measuring 500 to 700 Å were frequently present. Weibel-Palade bodies, rod-shaped structures 0.1 μm in thickness and up to 3 μm in length, which appear to consist of several tubules embedded in a dense matrix, were observed only infrequently in our material. Otherwise the endothelial cells were similar to those in the vessels of other organs and contained the usual complement of intracellular organelles.

Figure 1 shows the reconstruction of the vessels in the papillary dermis. The stippled vessels are arterioles which are easily identified in 1-μm and ultrathin sections because of the presence of elastin in the vessel wall. In areas where dermal papillae were poorly developed, blood vessels coursed parallel and close to the dermal–epidermal junction. Shallow dermal papillae with discrete capillary loops were present but they were not frequent.

The arterioles in the papillary dermis varied from 17 to 26 μm in outside diameter and would be called terminal arterioles in Rhodin's classification. The endothelial tubes ranged from 7.5 to 12 μm in their outside diameters. The thickness of the arteriolar walls varied from 1 to 3.5 μm. Occasion-

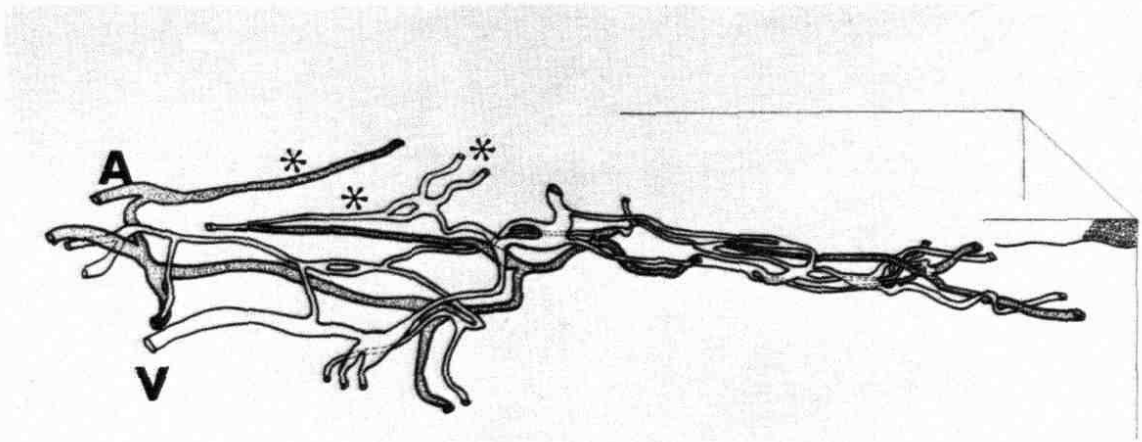

FIG. 1. Reconstruction of portion of horizontal plexus in papillary dermis. Stippled vessels represent arterioles (*A*) and clear vessels represent venules (*V*). Vessels (*) approach closely to dermal-epidermal junction without forming capillary loops.

FIG. 2. Terminal arteriole. Elastin (*EL*) present as interrupted layer between endothelium (*E*) and smooth muscle (*S*). Basement membrane material (*B*) is homogeneous. *Asterisks* indicate endothelial-smooth muscle contacts. *L* = lumen. *V* = veil cell. Bar = 10 μm.

ally, an arteriole with a wall 5 to 6 μm thick was seen. The ratio of endothelial tube diameter to vascular wall thickness ranged from 3:1 to 2:1.

Figures 2 through 9 illustrate the ultrastructural features of a terminal arteriole, 26 μm in diameter, as it was traced through the capillary bed to its venous connection. Figure 2 shows a typical terminal arteriole. The endothelial cells are surrounded by 1 or 1½ layers of smooth muscle cells. The vascular wall is composed of basement membrane material which has a relatively homogeneous appearance and completely surrounds and encompasses the elastin and smooth muscle cells. In some spots this band of relatively uniform basement membrane material is accompanied by a 350- to 500-Å basal lamina that is present immediately below the endothelial cells and around individual smooth muscle cells. Smooth muscle cells and endothelial cells send cytoplasmic processes toward each other to make frequent tight junctional contacts through breaks in the basement membrane (Fig. 3). The elastin appears to be present as

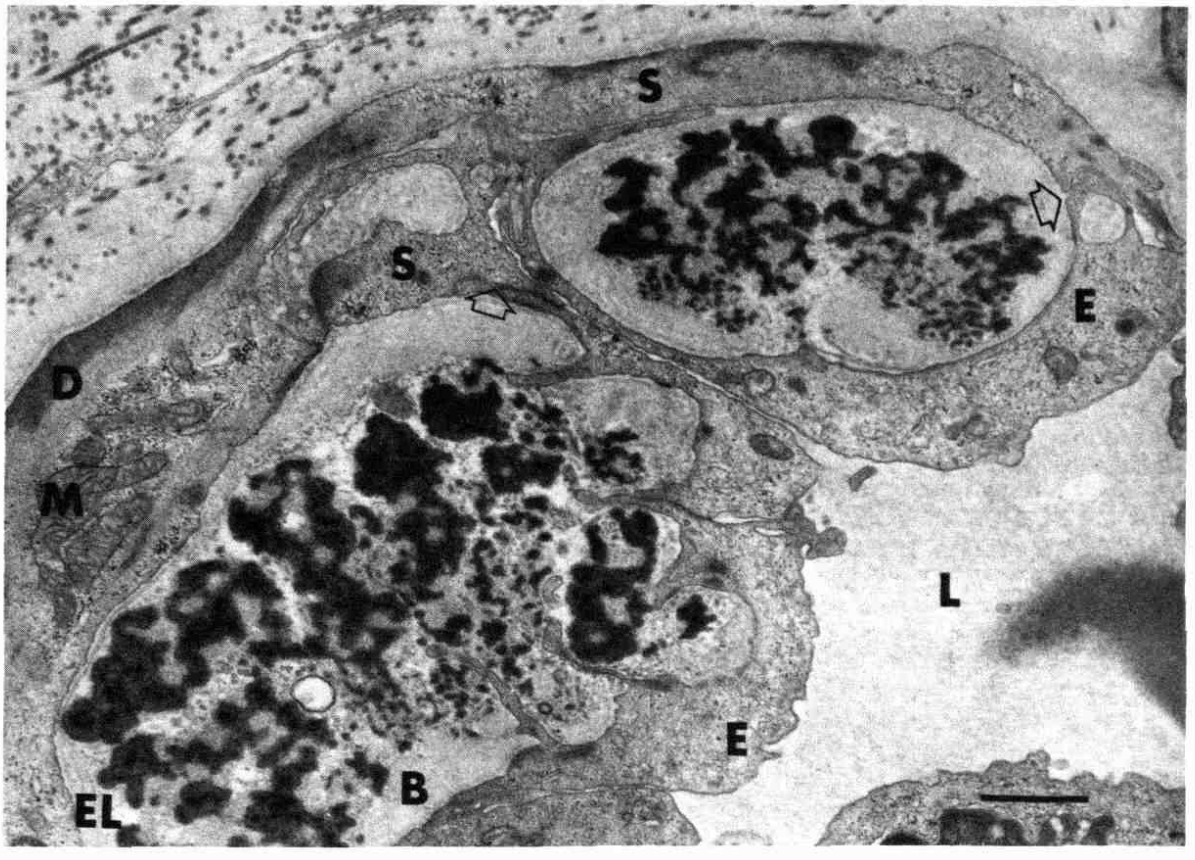

FIG. 3. Endothelial-smooth muscle contacts. *Arrows* indicate tight junctions between endothelial (*E*) and smooth muscle cells (*S*). Note projections of smooth muscle cells and endothelial cells toward each other. *EL* = elastin. *L* = lumen. *B* = basement membrane. *D* = dense bars. *M* = mitochondria. Bar = 1 μm.

an interrupted layer between the endothelial and smooth muscle cells.

As the terminal arteriole is traced, its outside diameter reaches a dimension of 10 to 12 μm at the beginning of the capillary bed. As the diameter of the arteriole diminishes from 26 to 15 μm, the elastin assumes a more peripheral position in the basement membrane material of the vascular wall (Fig. 4). At the 15-μm level, the elastin disappears from the vascular wall and initially forms an incomplete sheath between the basement membrane and the surrounding flat fibroblast (veil cell) layer and, later, a similar sheath external to the veil cell (Fig. 5a,b). A longitudinal section through a similar-sized vessel is shown in Figure 6. The external elastin layer disappears at the 10- to 12-μm level. The basement membrane retains its homogeneous appearance during this transition.

Smooth muscle cells, which are identified by their numerous dense bodies and myofilaments, are not found below the 15-μm level. Their place is taken by pericytes which have less-well-developed dense bodies and many fewer filaments, and have the appearance of a poorly developed smooth muscle cell. This replacement probably occurs gradually but the lack of longitudinal sections did not permit us to evaluate this point. Other features that helped to distinguish smooth muscle cells from pericytes were the wider profiles of smooth muscle cells and their tendency to have clusters of mitochondria and ribosomes in the center of the cell (Fig. 3). Pericytes are thinner, have scattered individual mitochondria in the cytoplasm, and a more random distribution of free ribosomes.

After the external elastic sheath disappears, one encounters a vessel with an outside diameter of 10 to 12 μm and an endothelial tube diameter of 4 to 6 μm (Fig. 7). The basement membrane material retains its homogeneous appearance. Pericytes form tight junctions with endothelial cells through breaks in the basement membrane. Pinocytotic vesicles are very numerous at this level. These were the smallest vessels encountered and may properly be called capillaries. Because of their connection with the terminal arterioles and the homogeneous appearance of the basement membrane, we classify these vessels as arterial capillaries. The walls of these capillaries varied from 2 to 3 μm in thickness but in a few instances the endothelial tube was surrounded by a wall only 0.5 to 1 μm wide. Occasionally a capillary was seen with a wall 4 to 6 μm thick.

Veil cells closely surround these vessels with a thin cytoplasmic rim. Although veil cells can be found encircling the smallest arterioles and venules they are most prominent around the vessels of the capillary segment.

Pinocytotic vesicles first become conspicuous in endothelial cells and pericytes as the elastin begins to disappear from the arterioles and they continue

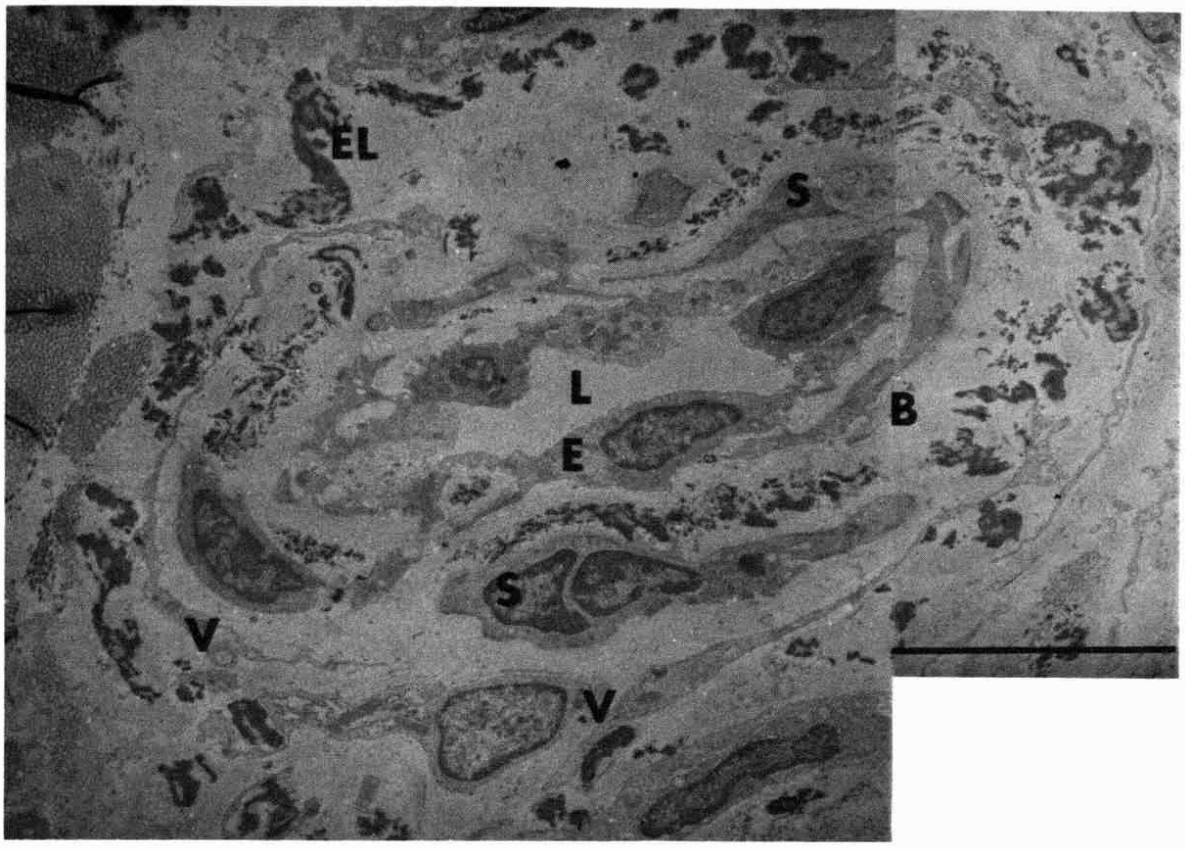

FIG. 4. Terminal arteriole. Elastin (*EL*) assumes a peripheral position in the vascular wall and perivascular locations. *S* = smooth muscle. *B* = basement membrane. *E* = endothelial cell. *L* = lumen. *V* = veil cell. Bar = 10 μm.

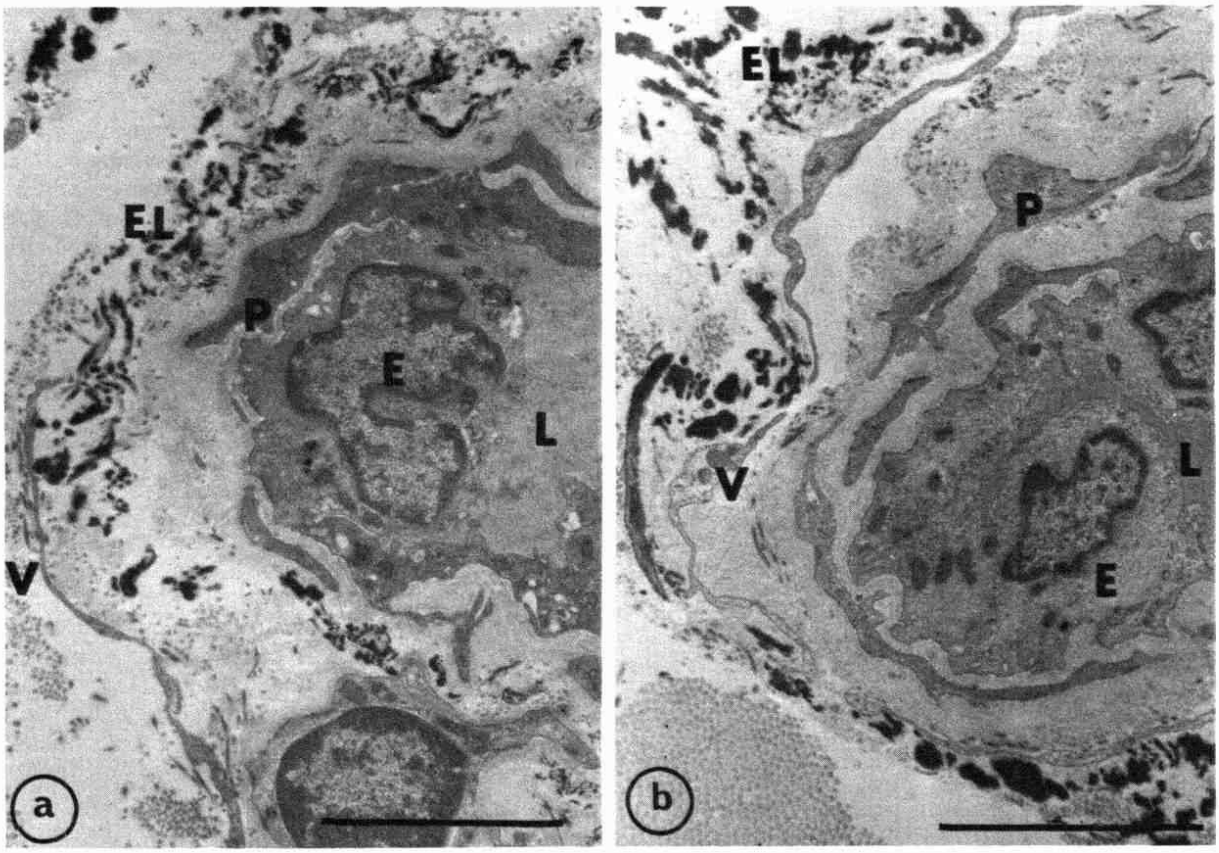

FIG. 5. *a:* Terminal arteriole. Layer of elastin present between basement membrane of wall and veil cell. *b:* Terminal arteriole. Sheath of elastin outside veil cell layer. *EL* = elastin. *V* = veil cell. *E* = endothelial cell. *P* = pericyte. *L* = lumen. Bar = 5 μm.

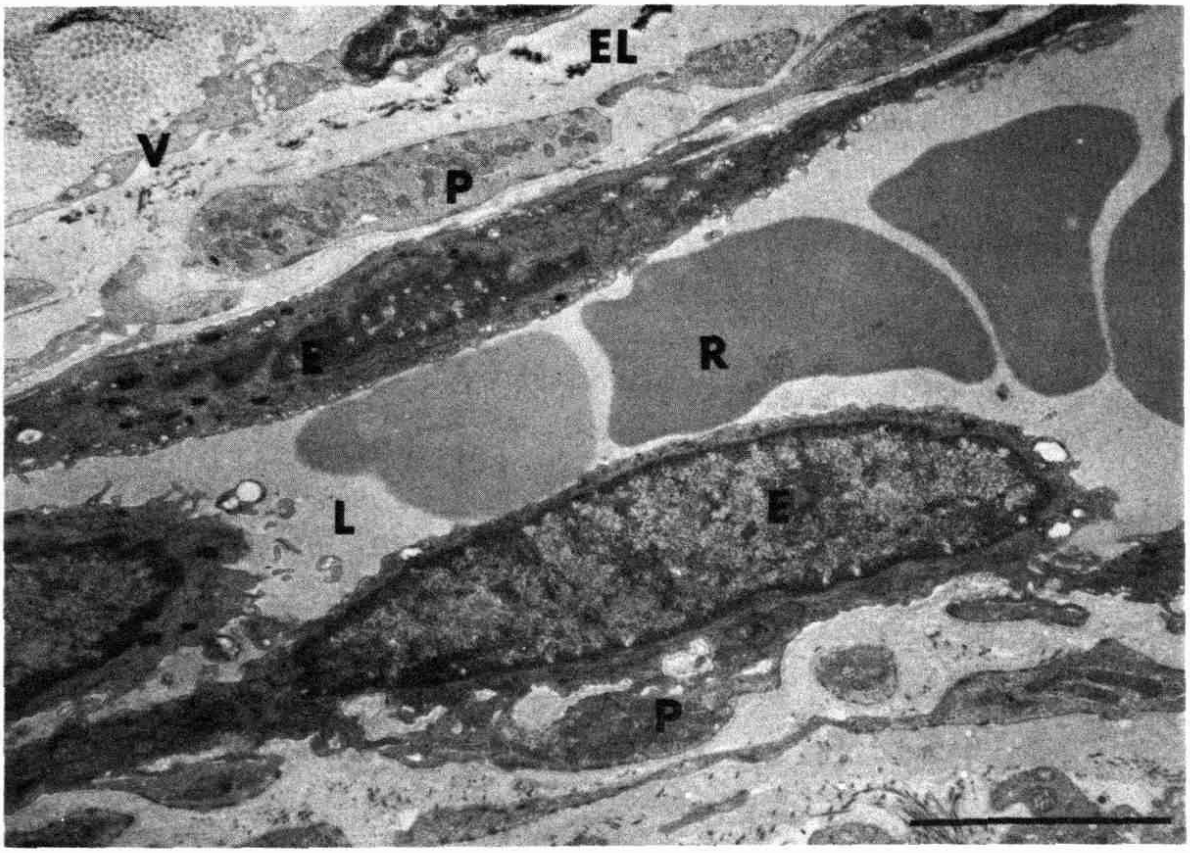

FIG. 6. Terminal arteriole. Longitudinal section. *L* = lumen. *R* = red cell. *E* = endothelial cell. *P* = pericyte. *V* = veil cell. *EL* = elastin. Bar = 5 μm.

to be present in large numbers throughout the arterial capillary segment.

As the arterial capillary is traced, the basement membrane material begins to develop lamellae within its previously homogeneous framework until a segment is reached in which the entire vascular wall is multilaminated. Dense layers of basement membrane material 250 to 1000 Å thick alternate with less-dense zones (Fig. 8). As many as 10 lamellae have been counted in some vessels. At this level the endothelial cells are less electron dense than in the arterial capillary segment and pinocytotic vesicles become less numerous. The nuclear cytoplasmic ratio of the endothelial cells in this segment tend to be smaller than in the arterial capillary segment.

The outside diameters of the vessels remain at 10 to 12 μm and their endothelial tubes at 4 to 6 μm. Pericytes and veil cells remain the important cellular elements in the vascular wall and in the immediately surrounding dermis, respectively. This multilaminated segment represents the venous capillary because of its location between the arterial capillary and a larger vessel having the characteristics of a venule.

We call the capillary segment in which the basement membrane shows both homogeneous and multilaminated features the transitional zone.

The ratio of endothelial tube diameter to vascular wall thickness for both arterial and venous capillaries ranged from 2:1 to 1:1. In this reconstruction it was possible to approximate the length of a single arterial and venous capillary segment. The arteriole capillary was at least 84 μm but no more than 98 μm long, and the length of the venous capillary was at least 52 μm but no more than 78 μm. The transitional zone was considered the dividing point between the two capillary segments.

The venous capillary connects with a vessel whose external diameter increases from 12 to 35 μm and whose endothelial tube diameter enlarges from 8 to 26 μm. This segment is the postcapillary venule (Fig. 9). In our material, most of the postcapillary venules seen in the papillary dermis measured 18 to 23 μm in external diameter and 10 to 15 μm in endothelial tube diameter. Pericytes are more numerous than in the venous capillary but they do not form a continuously overlapping layer. The basement membrane of the vascular wall is multilaminated. The wall is usually 3.5 to 5.0 μm wide. Collagen fibrils may be present between the lamellae or may form a thin sheath in the outer layer of the vascular wall. The ratio of endothelial tube diameter to vascular wall thickness in postcapillary venules ranges from 3:1 to 2:1.

In this study the papillary dermal vessels were composed entirely of terminal arterioles, arterial and venous capillaries, and postcapillary venules. The same spectrum of vessels was present as far as the mid-dermis. Some of the vessels in the lower

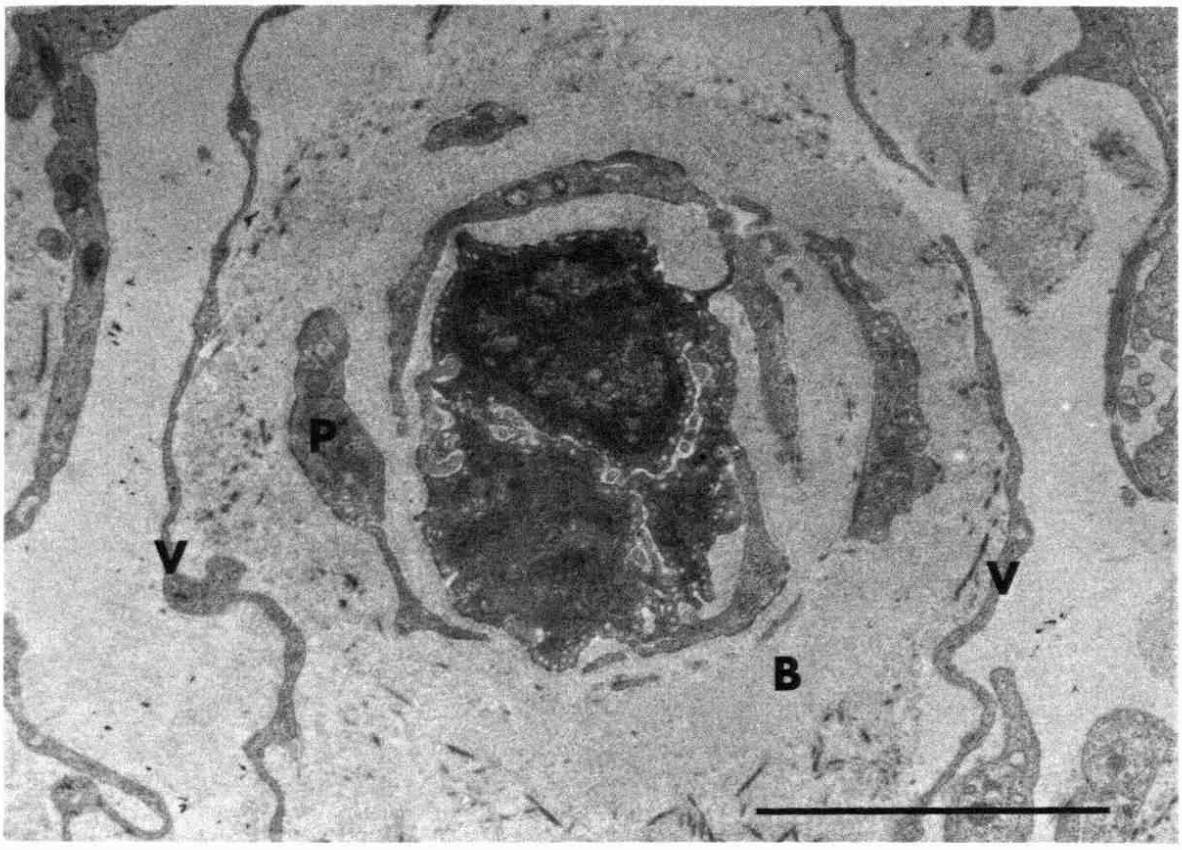

FIG. 7. Arterial capillary. Homogeneous basement membrane delimited by veil cells. Pericytes in wall. Note prominent pinocytotic vesicles. Lumen closed. *B* = basement membrane. *V* = veil cell. *P* = pericyte. Bar = 5 μm.

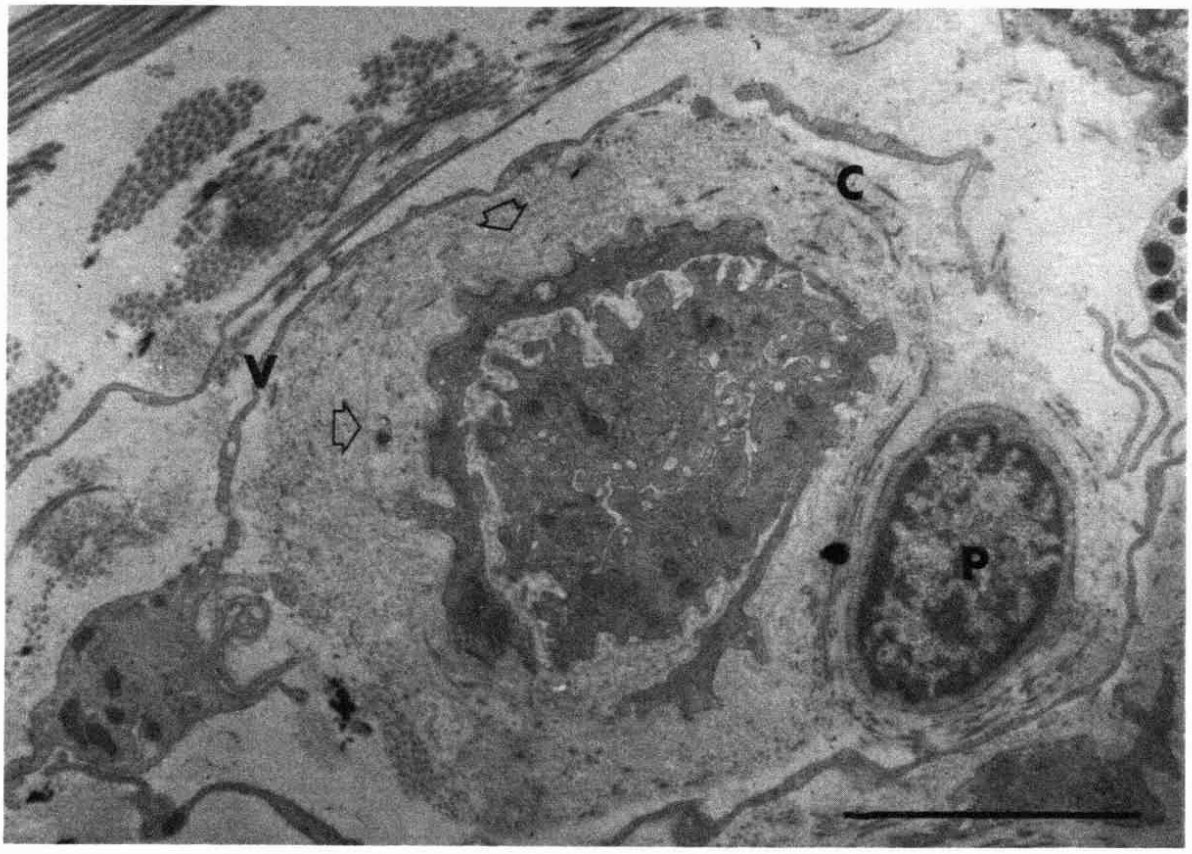

FIG. 8. Venous capillary. *Arrows* indicate lamellae in multilaminated basement membrane. Pericyte (*P*) invested by basement membrane of vascular wall. *V* = veil cell. *C* = collagen fibrils. Bar = 5 μm.

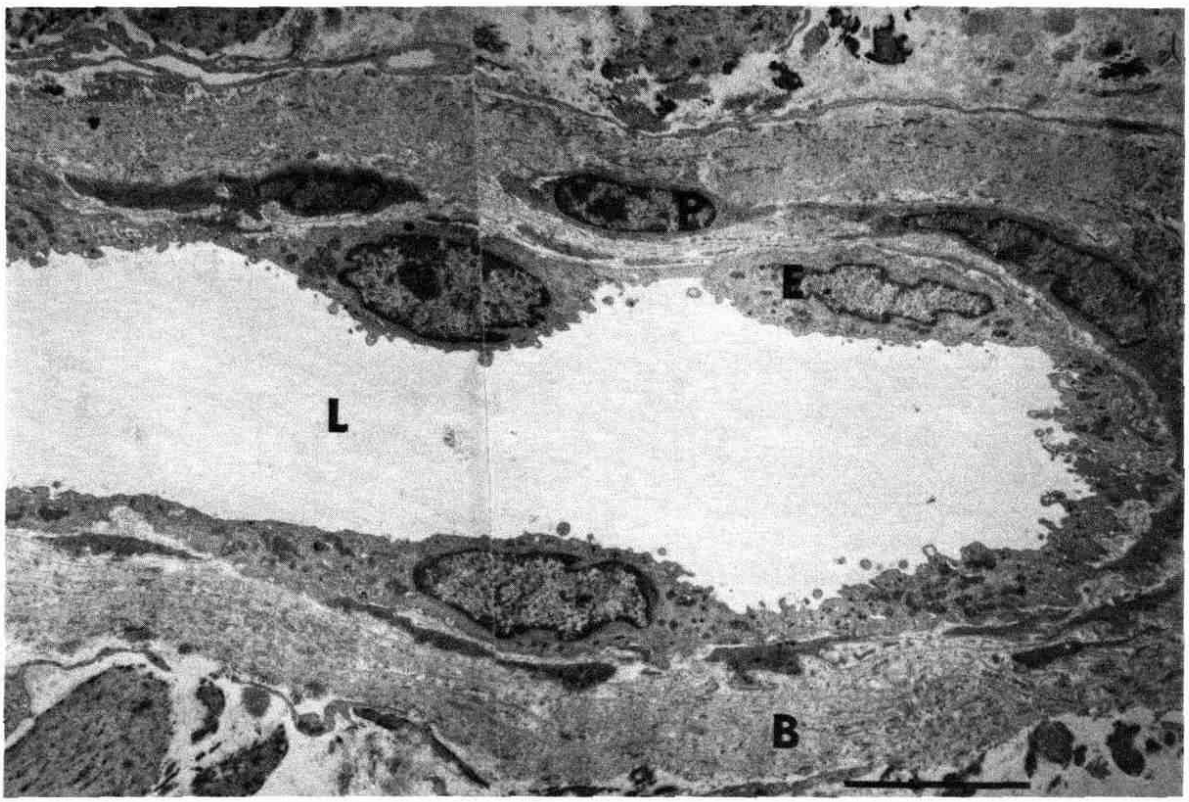

FIG. 9. Postcapillary venule. Longitudinal section. *B* = multilaminated basement membrane. *E* = endothelial cell. *P* = pericyte. *L* = lumen. Bar = 10 μm.

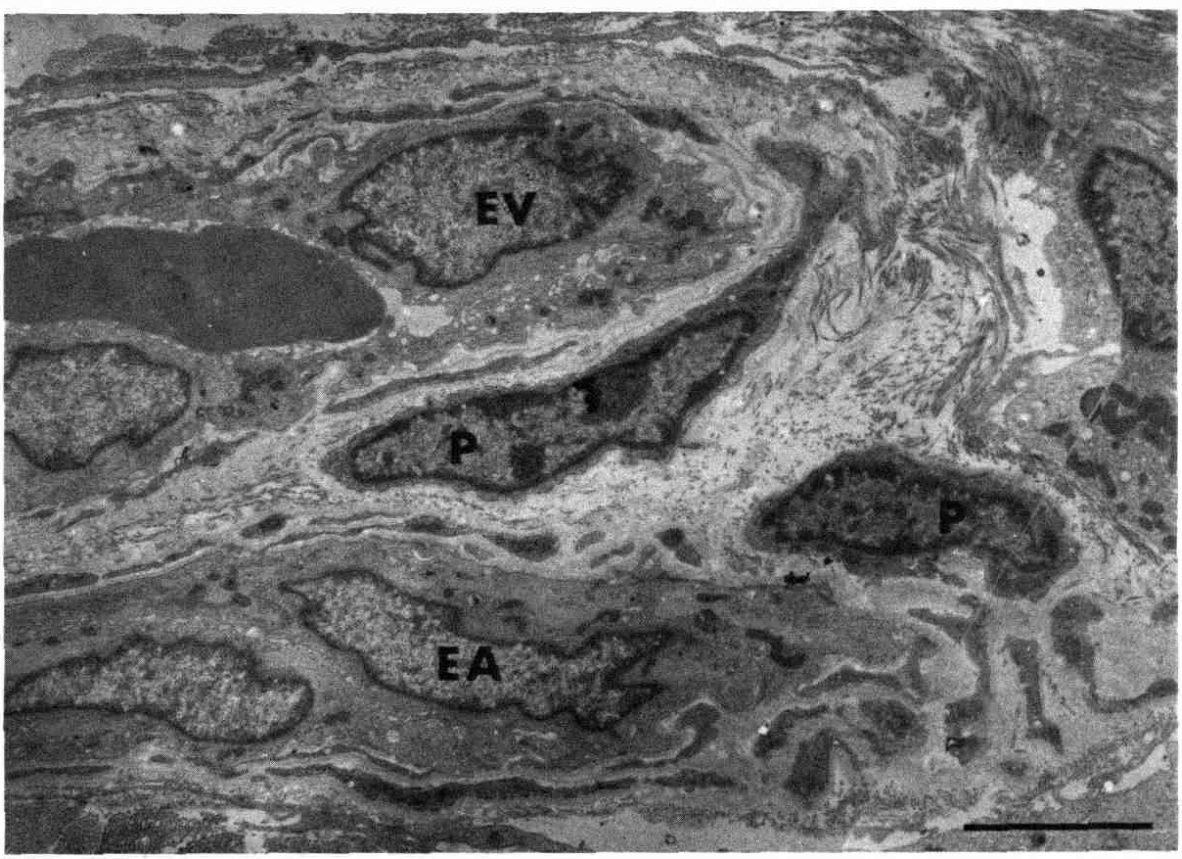

FIG. 10. Terminal arteriole and postcapillary venule in longitudinal section. Vascular walls in apposition show the contrast between homogeneous and multilaminated character of the basement membranes. *P* = pericyte. *EA* = endothelial cell of terminal arteriole. *EV* = endothelial cell of postcapillary venule. Bar = 5 μm.

third of the dermis were twice as large as the upper dermal vessels and may represent arterioles and collecting venules (40 to 50 μm) but we have not yet studied them in detail by electron microscopy. However, vessels identical in size to those found in the papillary dermis were also present in the deepest dermis.

Because of the lack of enough longitudinal sections, it was not possible to determine the presence or absence of precapillary sphincters in the papillary dermis, the orientation of the smooth muscle cells in the arteriolar wall, or the presence or absence of bridged fenestrations in the capillary segments.

The walls of terminal arterioles, composed of smooth muscle cells or pericytes enmeshed in homogeneous basement membrane material, were generally 1.0 to 3.5 μm thick but sometimes were as much as 5 μm wide. The capillary segment usually had walls 2 to 3 μm thick. The walls of the postcapillary venules were usually 3.5 to 5 μm wide. Individual collagen fibrils in circular and longitudinal arrays were sometimes present in the vascular wall but were usually always present as a thin sheath in its outermost zone. These arrangements of collagen fibrils were not correlated with the size or type of vessel.

The homogeneous and multilaminated appearance of the vascular basement membrane was much more distinct in tissues fixed in Karnovsky's fixative than those placed in buffered osmium tetroxide. Osmium fixation was also associated with small electron-lucent areas scattered through an otherwise homogeneous-appearing basement membrane thereby producing a pseudolaminated appearance.

The ultrastructural differences between the arterial and venous components of the microcirculation in the papillary dermis of flexor forearm skin have also been observed by us in the papillary dermis of human skin obtained from chest, back, flank, thigh, and leg.

DISCUSSION

The most important observations in this study can be summarized as follows.

The papillary plexus in forearm skin contains most of the dermal blood vessels, and is composed primarily of terminal arterioles, capillaries, and postcapillary venules. The postcapillary venules are the vessels most frequently encountered. The outside diameter of most of the venules in this layer of forearm skin was relatively uniform and ranged from 18 to 23 μm, identical to the findings of Wetzel and Zottermann [10] who had shown in earlier studies by capillary microscopic measurements that the average diameter of the venules† in the papillary plexus of forearm skin was 17 μm. These complementary data make us more confident that the diameters of the blood vessels measured in the histologic sections are very close to the in vivo dimensions.

The arteriolar and venous segments of the microcirculation can be distinguished from each other on the basis of the basement membrane: a homogeneous appearance in the former and a multilaminated character in the latter (Fig. 10). Terminal arterioles of 17 to 26 μm outside diameter have elastin and smooth muscle cells in their walls while postcapillary venules of comparable size have only pericytes in their walls.

We reviewed the previous reports dealing with the ultrastructure of human dermal blood vessels to discover why these observations had not been made previously. Several factors were involved: no attempt was made to correlate structure with the precise location of the vessel in the microcirculatory bed; osmium fixation was used exclusively so that the basement membrane was more difficult to evaluate; smooth muscle cells and pericytes were not clearly distinguished from one another; and, most importantly, the ultrastructural descriptions of blood vessels from other species were applied to human dermal vessels without any attempt to determine whether they were applicable.

Hibbs, Burch, and Phillips [3] were the first to study human dermal blood vessels and they focused on the deep vessels around the sweat glands. They pointed out that the main differences between the endothelial cells of dermal vessels and those in other organs were the greater thickness and the presence of bundles of filaments in the cytoplasm of the former. Odland [4] confirmed and extended these findings to the vessels in the papillary dermis. However Hibbs et al described two types of arterioles in human skin. In the subcutaneous layer they found that 20-μm arterioles had an internal elastic lamina and smooth muscle cells in their walls, but that identical-appearing vessels in the deep dermis lacked an elastica. Almost certainly, these dermal "arterioles" were muscular venules. Unfortunately, the concept of two different types of arterioles is still retained in a modern source book of dermatology [1]. White and Clawson [5] also reviewed the ultrastructure of human dermal blood vessels. Their descriptions were based upon findings in rabbit blood vessels from different organs and their pictures were those of vessels from human lymph nodes and synovium, but not skin. The human blood vessels illustrated in their report had multilaminated basement membranes. Those with the thicker lamellae were called arterioles, and the others, venules. Morretti [1] in the *Handbuch*, in summarizing the ultrastructure of the human microcirculation, also illustrates arterioles with vessels having multilaminated basement membranes. Cells designated as smooth muscle cells in the vascular walls in these figures are pericytes.

Breathnach, [6] in his monograph, illustrates

† The diameter of the venules is a measure of the column of blood. To this measurement one must add the thickness of the vascular wall. Wetzel and Zotterman also pointed out that the size of the venules varied with the region (63 μm on the cheek, 37 μm on the ear, and 32 μm on the finger knuckles).

vessels with multilaminated basement membranes which he calls arterioles or venules depending upon his interpretation of the nature of the periendothelial cell in the vascular wall. He does show a vessel in Figure 159 which has a homogeneous basement membrane but he does not ascribe any significance to it. Breathnach uses Rhodin's classification of the rabbit microcirculation to describe human dermal blood vessels. None of these reports describes the layer of elastin in the arterioles.

Stehbens and Ludatscher [11] studied the ultrastructure of the cherry angioma in man following fixation with glutaraldehyde. They observed that the vessels in the angioma had either a homogeneous or multilaminated basement membrane up to 5 μm in width—identical to our findings in normal blood vessels.

Friederici, Tucker, and Schwartz [12] studied the cutaneous blood vessels in the dorsum of the finger in diabetics and nondiabetics. They also observed the homogeneous and multilaminated character of the vascular walls in the papillary dermis. They interpreted their findings to indicate the very large variability of the cutaneous capillaries.

Rhodin's criteria for defining the various segments of the microcirculation can be applied to our studies in spite of structural differences between human and rabbit blood vessels. The concepts of location in the microcirculatory bed, size of vessels, and cellular composition of the vascular wall are general applicable principles. Although Rhodin's studies were concerned with the fascial (subdermal) vascular bed overlying the rabbit thigh muscles, two modern reviews on the ultrastructure of the microcirculation have erroneously stated that his observations were made on rabbit dermal blood vessels [13,14].

Rhodin divided the rabbit microcirculation into the following segments [7,8]. (a) Arteriole: vessels 100 to 50 μm in luminal diameter which contain 2 to 3 layers of smooth muscle cells and have a discontinuous internal elastic membrane. At 50 μm there is only one layer of smooth muscle. A basement membrane 0.1 μm thick is present beneath the endothelial cell layer and around each smooth muscle cell. (b) Terminal arteriole: microvessels <50 μm, which have a single layer of smooth muscle. The internal elastic lamina has virtually disappeared. The organization of basement membranes is identical to that in the arterioles. (c) Arterial capillary: capillaries <8 μm which are continuous with terminal arterioles, have a thin endothelium without bridged fenestrations, and are surrounded by occasional pericytes. (d) Venous capillary: capillaries <8 μm which are continuous with larger postcapillary venules, have a thin endothelium with bridged fenestrations, and have occasional surrounding pericytes. Ratio of luminal diameter to vascular wall thickness is 20:1. (e) Postcapillary venule: microvessels with a diameter of 8 to 30 μm which are continuous with venous capillaries. Pericytes and veil cells increase in number but neither form a complete layer around the endothelial tube. Ratio of luminal diameter to vascular wall thickness averages 10:1. (f) Collecting venule: vessels 30 to 50 μm, with one complete layer of pericytes and veil cells. Ratio of luminal diameter to vascular wall thickness is 30:1. (g) Muscular venule: microvessel 50 to 100 μm with 1 or 2 layers of smooth muscle cells. Ratio luminal diameter to vascular wall thickness is 50:1.

There are important differences between the rabbit vessels in Rhodin's study and human dermal vessels. In Rhodin's system, elastic components have disappeared almost entirely in arterioles smaller than 50 μm in diameter and only occasionally is there an indication of a spotty localization of an elastic component between endothelium and smooth muscle cells. In human vessels an interrupted elastica is still present in 20-μm arterioles, and the elastin gradually disappears from the wall to form an external sheath just before the beginning of the capillary segment. In rabbit arterioles, the internal elastica simply vanishes without forming the peripheral patterns seen in human vessels. The basement membranes of rabbit arterioles and venules are thin and lack the thick homogeneous or multilaminated appearance found in human vessels. The ratio of luminal diameter to wall thickness in rabbit arterioles and venules varies from 20:1 to 10:1. In human vessels the comparable ratio varies from 3:1 to 2:1. These findings reinforce the concept that the vascular system in different organs may have unique features and that one cannot generalize the findings from one organ or species to another.

Rhodin's classification of the rabbit microcirculatory bed is adaptable to the study of human vessels. After the ultrastructure of the 40 to 50-μm vessels in the deep dermis is determined, one may only need to adjust the sizes of human dermal vessels and take into consideration the few differences in structure in order to apply Rhodin's classification to the human cutaneous microcirculation. Thus far, our studies indicate that the outside diameters of the endothelial tubes of terminal arterioles vary from 7.5 to 12 μm, those of capillaries 4 to 6 μm, and those of postcapillary venules 8 to 26 μm.

We distinguish arterial and venous vessels by the character of the basement membrane noted above. In addition, the arterial endothelial cells in the smallest arterioles and in the capillary segment tend to be more electron dense and contain more pinocytotic vesicles than the venous endothelium. The endothelial cells of the arterioles tended to have a greater nuclear cytoplasmic ratio than the endothelial cells in the venules.

Rhodin noted that fenestrations of the bridged type were present in rabbit venous capillaries, but not in arterial capillaries or postcapillary venules. We were unable to evaluate this observation in our material because of the lack of sufficiently long longitudinal sections. Takada and Hattori [15] found a few fenestrations in the papillary vessels of the skin of the human finger and chest wall.

Stehbens and Ludatscher [11] found many bridged fenestrations in the vessels of the cherry angioma. We have previously reported the presence of bridged fenestrations in the venous capillaries, which constitute most of the capillary loop, in psoriatic papillae [9,16]. In the papillae of normal skin, in which arterial capillaries predominate, bridged fenestrations are very uncommon (in preparation).

Rhodin's concept that bridged fenestrations are a marker of venous capillaries is further reinforced by the studies of Casley-Smith [17] who found that bridged fenestrations were 12 times more common on the venous limb than on the arterial limb of the capillary in the intestinal villus of the mouse. Mohamed [18] found fenestrations on the venous limb but not the arterial limb of the capillary loops in rabbit gingivae. The fenestrations allow the exchange of water and other molecules between the vessels and the interstitium, and their almost exclusive presence in the venous limb of capillaries may be a useful marker to correlate structure with function in different dermatoses.

A striking feature of dermal blood vessels is the thick vascular wall composed of basement membrane material in which are embedded elastin, smooth muscle cells or pericytes, and variable amounts of individual collagen fibrils. The walls can be as wide as 5 to 6 μm. Some of the individual collagen fibrils form a thin external limiting sheath in the basement membrane as Odland has pointed out [4]. The veil cells characteristically surround the smallest vessels and set them off from the rest of the dermis. The pericyte, veil cell, external elastic layer and thick basement membrane probably provide a mechanical support for the vessels against the shearing forces to which the skin is constantly subjected.

The postcapillary venules are the most common vessels in the papillary dermis. This segment has important physiologic functions not present in other parts of the microcirculation. A gradient of permeability, which begins in the arterioles, reaches a peak in the postcapillary venule and then decreases gradually along the veins [19]; diapedesis of white cells occurs here in response to a variety of stimuli [20]; histamine, serotonin, and bradykinin act on this segment to produce endothelial cell contraction and gap formations resulting in increased vascular permeability [21,22]; and circulating, soluble immune complexes act upon this portion to produce vasculitis [23]. These properties play an important role in the various dermatoses which one encounters and it explains why the papillary dermal vessels are so frequently and prominently involved in most skin disorders.

The rabbit fascial vessels and human dermal vessels have a feature in common. In the terminal arterioles there were frequent tight junctional contacts between smooth muscle cells and endothelial cells as well as between adjacent smooth muscle cells. In the capillaries and postcapillary venules there were frequent tight junctional contacts between pericytes and endothelial cells. Rhodin proposed that these contacts may serve to mediate an impulse to the smooth muscle, possibly initiating muscular contraction in the arterioles and precapillary sphincters [7,8]. They may also allow the endothelium of the capillary and postcapillary venules to more easily sense and react to chemical substances such as histamine and serotonin released during inflammatory and allergic conditions.

Rhodin located and analyzed the precapillary sphincter area in the microcirculatory bed of the rabbit. We were unable to investigate this point because the papillary plexus is not a monolayer. However the search for precapillary sphincters as well as arteriovenous anastamoses and thoroughfare channels ought to continue because Saunders [24] demonstrated in fetal forearm skin by x-ray projection microscopy that direct vascular connections bypassing the capillary net were visible between the arteriolar and venous plexuses in the papillary dermis.

The multilaminated basement membrane with its unusual degree of thickening is a normal finding in human dermal vessels and should not be confused with the basement membrane thickening found around the skeletal muscle capillaries of patients with diabetes mellitus. The ultrastructural characteristics of this increase in basal lamina thickness of diabetic microangiopathy were delineated by Vracko and Benditt [25,26]. They had proposed that the thickening developed as a result of repeated episodes of endothelial cell death followed by endothelial cell replacement. The new endothelial cell used the previous basal lamina as a scaffold, and as it regenerated it formed a new basal lamina internal to the old one. Thus, layers of basal lamina are built up resembling the rings in a tree, as a result of repeated endothelial cell death and cell replacement.

The multilaminated character of the basement membrane in human venous dermal vessels neither resembles the vascular changes of diabetic microangiopathy ultrastructurally nor does it display any of the criteria which Vracko and Benditt proposed as an explanation for the vascular wall thickening in diabetes mellitus. Their criteria included fusion of individual basal lamina; presence of cellular debris thought to be remnants of former endothelial and pericytic cells between lamellae; occasional crescentic spaces between lamellae, proposed as sites of former pericytes; and a single basal lamina between the viable endothelial cell and its pericyte in the newly regenerated capillary.

None of these features was seen in the multilaminated basement membranes of the dermal venous microvessels. In addition, the basement membrane lamellae in dermal vessels measure 250 to 1000 Å in contrast to the basal laminae of diabetic microangiopathy which range from 800 to 2000 Å.

In Figures 9 and 10 there are multiple lamellae

between the endothelial cell and its pericyte. Friederici et al [12] had compared diabetic dermal vessels with those of normal individuals and noted identical multilaminated vascular wall thickening in both groups. They had concluded that although they did not understand the nature of the vascular wall thickening it could not be related to the diabetic state itself.

We have proposed criteria for the differentiation between arterioles and venules and between arterial and venous capillaries. Applying these criteria to three vascular disorders, it appears that in leukocytoclastic angiitis, only the postcapillary venules are affected [23]; the telangiectatic spots in Fabry's disease are composed of arterial capillaries (unpublished observations); and cherry angiomas are composed primarily of venous capillaries with a small admixture of arterial capillaries [11].

The capillary loops in the normal dermal papillae which do represent a monolayer system will be described in another paper.

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