Permeability aspects of blood tissue exchange

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The exchange of substances between the blood and tissue compartments can be analyzed at both a structural and a functional level. Much remains to be learned concerning the participation of the several components of the capillary wall in the movement of substances to and from the bloodstream. Previous interpretations of the capillary wall as a biologic membrane with fixed structural features are probably not correct. It has been clearly shown that constituents such as the endothelial cells, basement membrane, and endocapillary lining change independently of one another. Especially striking is the tendency the endothelial surfaces have to separate from one another in response to physiologic mediators, despite the presence of supposedly "tight junctions." The contribution of the basement membrane to the permeability of small molecules and even plasma proteins remains to be demonstrated despite the provocative evidence provided by electron microscope studies of the passage of colloidal substances across capillaries and venules. On a functional level, a central role is taken by the opening and closure of precapillary sphincters as a mechanism for increasing or decreasing the surface area for exchange. The feedback tying this activity to parenchymal cell metabolism appears to be related to some substance in continuous flux responsive to reduced tissue clearance. Regional differences in permeability are present despite similar structural features, suggesting that local factors may affect the make-up of the barrier at a molecular level.

Discussions of blood tissue exchange invariably deal with the problem on a conceptual level in terms of net translocations of substances from one compartment into another. More recently, electron microscopy of the vascular barrier has sharpened our interest in the structural elements involved in the movement of materials between blood and tissue. The emphasis has shifted in turn from a vesicular transport process¹ to the basement membrane² and most recently to the significance of so-called tight junctions between cells.³ It is not clear whether substances of different molecular size and solubility permeate the barrier through similar pathways, and indeed whether different vessels may not possess different mechanisms for exchange. The data clearly demonstrate⁴ that substances move from the blood into the tissue compartment on the basis of purely physicochemical factors and not by active transport except in special secretory tissues. Transcapillary exchange hence is regulated by factors such as pressure (hydraulic, tissue, colloidal osmotic), distribution of blood, surface available for exchange, and shunting. Although changes in the properties of the barrier itself apparently come into play only in abnormal circumstances,⁵ considerable insight into the fundamental mechanisms of exchange can be obtained by an analysis of abnormal exchange, especially with regard to differences in the perme-
ability properties of the various components of the microcirculation. It is the purpose of the present report to document the interdependence of structural and functional aspects of the capillary bed and to attempt to fit into this frame of reference pertinent ultrastructural features of the hematoparenchymal barrier. An attempt will be made to distinguish between those features of the exchange process which are dependent on flow and those which are influenced by the properties of the barrier itself.

Structural aspects

The capillary vessels are frequently looked upon as irrigation channels whose extremely thin walls facilitate exchange between the blood and tissue compartments. It is quite clear however, that the terminal vascular bed is made up of several types of vessels whose unique organized activity serves to maintain the microcirculation in accord with the metabolic needs of the tissue cells.6

Blood coursing through the capillary bed tends to flow most rapidly in centrally located channels to reach the venous side. Close inspection and reconstruction indicate that these vessels are direct extensions of the terminal arterioles. Despite the fact that the direct continuations of the terminal arterioles within the capillary bed are also of capillary dimensions, the vessel can be readily recognized almost to the venous side. These thin-walled muscular vessels give off numerous offshoots which spill blood into the capillary network. The offshoots (the precapillary sphincters) arise at an abrupt angle from the parent trunk and can be shown to have smooth muscle only in the immediate junctional region. Beyond this the branches continue as endothelial tubes with occasional pericytes on their outer surface. Capillaries become confluent on the venous end to form wider channels which show no evidence of a muscular coat until vessels of from 50 to 60 µ in width have been formed. The major portion of the capillary network is, therefore, made up of non-muscular tubes which exhibit no active contractile movements and do not respond to physiologic constrictor and dilator stimuli.

A similar pattern of organization (Fig. 1) can be demonstrated in most vascular beds which serve primarily a nutritive function, the essential feature of this model being that the pattern of branching together with the arrangement of smooth muscle enables the blood to be distributed through selected capillaries in a systematic manner. Differences in the various tissues of the body reflect the basal level of metabolic activity of the parenchymal cells, fluctuations in tissue work which occur during periods of inactivity and activity of the organ, structural peculiarities of the tissue, etc.

It should be pointed out that the phenomenon referred to as "capillary permeability" encompasses exchange across the wall of vessels ranging from the terminal arteriolar class down through all of the various capillary subdivisions and including the large collecting venules. Let us consider systematically the various structural units involved.7

The terminal arterioles of most mammals are from 20 to 25 µ wide, have a wall thickness of 2 to 3 µ, and in tissues such as mesentery may be from 4 to 6 mm. long. Although the walls contain smooth muscle, the cells are flattened and disposed in the form of a loose spiral with gaps between them. Visually small molecular dyes injected into the bloodstream can be seen to leave the arterioles almost immediately. There is thus no doubt that water and small molecular species can exchange across this barrier. Vessels of this type transmit a considerable volume of blood, the velocity of flow being about 100 times higher than in the capillaries or venules.

The morphologic characteristics of the arterioles change gradually as they extend distally and subdivide, the vessels becoming narrower (15 to 20 µ), the walls thinner (1 to 2 µ), the spiral smooth muscle...
arranged much more loosely, and the muscle elements extremely flattened. The name "metarteriole" has been given to this section of the vascular tree. Numerous side branches are distributed from this section of the bed. As indicated previously, the metarterioles can be traced through the capillary network into the venous tributaries in many tissues. The volume flow here is still high, the blood having a velocity about 40 to 50 times that of the capillaries.

The true capillaries, which are by far the most numerous subunits of the microcirculatory tree, are from 4 to 12 \( \mu \) in diameter, have a wall thickness of approximately 1 \( \mu \) and a flow velocity of from 20 to 100 \( \mu \) per second. The narrowest capillaries have a reduced hematocrit (from 10 to 15 per cent by volume as estimated from photographs). In the mesentery, for example, a capillary channel from sphincter to venule is, on the average, 1,000 to 2,000 \( \mu \) long. Thus, with an average velocity of 500 \( \mu \) per second, the blood in these vessels has a transit time of from 2 to 4 seconds.

The collecting venules range from 25 to 40 \( \mu \) in width, have a wall thickness of 2 to 3 \( \mu \), and a flow velocity of 2 to 3 mm. per second. In terms of surface area available for exchange in the mesentery, the arterioles make up 5 per cent, the metarterioles 10 per cent, the capillaries 52 per cent, and the venules 33 per cent. The coefficient of permeability of these several constituents probably differs; unfortunately, precise figures are not available.

Although the capillaries are distributed in a characteristic pattern, there is a surprising lack of uniformity in the length or caliber of the many vessels which are essentially endothelial tubes. It is almost axiomatic that the capillaries of different species have an average diameter compatible with the size of the red blood cells (RBC) in that particular animal. Red blood cells throughout the animal kingdom vary in diameter from 6 to 8 \( \mu \) up to 75 to 80 \( \mu \).
In general, the smallest capillaries have a somewhat smaller cross section than their RBC.

The capillary branches in the subcutaneous, mesenteric, or serosal regions are usually somewhat larger than the red blood cells. For example, in the rat in which the RBC are from 8 to 10 μ in diameter the majority of the capillaries are from 10 to 14 μ wide. Only about 25 per cent of the capillaries in the mesentery are narrower than RBC. The capillary vessels in skeletal muscle, on the other hand, are unusually long (3,000 μ) and have an average cross-sectional diameter of 4 to 6 μ, so that the RBC are deformed during the forward movement along the vessels. The transit time from precapillary sphincter to collecting venule in the intestinal mesentery or omentum of laboratory animals varies from 0.5 to 2.0 seconds, depending on the pathway used. In skeletal muscle (spinotrapezius of the rat), the transit time may be as long as 5 to 7 seconds.

Local blood flow

Three separate constituents of the terminal vascular bed, the precapillaries, arterioles, and venules, serve to shift local blood flow to meet metabolic requirements of the tissue cells (Table I). Volume flow through the microcirculation is modified by contraction or dilation of large muscular vessels primarily through the intervention of chemical mediators. Such principles, by virtue of their ability to modify directly the reactivity of the effector unit, represent the ultimate control of vascular smooth muscle behavior. Within the capillary bed proper, the blood is distributed by the action of the precapillary sphincters, a feature which is of major importance in transcapillary exchange since this determines the surface area available for blood-tissue interchange. Another structural element which has an important regulatory influence on capillary hemodynamics is the muscular venule. The resistance to the outflow of blood from the capillaries will determine to a large extent the mean capillary pressure.

Perhaps the single unique regulatory feature of the capillary system is the ebb and tide of flow by which blood is perfused through different capillaries and through varying numbers of capillaries. From a structural point of view, these vasomotor excursions can be traced back to several separate phenomena. The flow in a given arteriole and its entire hierarchy of branches can slow and even stop entirely, while an adjacent vascular unit shows no slowdown. This type of intermittency is encountered when the venules or venular arcades become narrowed, causing many capillaries to reverse their direction of flow in order to reach another effluent channel.

Most commonly, intermittency develops at the precapillary sphincters in a seemingly haphazard but consistent pattern. As a result of the opening and closure of these sphincters the flow through the capillary network is shifted from one vessel to another—a phenomenon referred to as "vasomotion." Most of the evidence indicates that the precapillary vessels are under the control of humoral agents—circulating substances as well as by-products of tissue activity. Mediators of this type have been studied extensively in relation to the genesis of tissue injury but we have only suggestive evidence as to which chemical agents are concerned with normal regulation of precapillary responses. Although oxygen tension may represent a possible feed-back circuit, the fact that the metabolism of neither the endothelial nor the smooth muscle cell is geared to oxidative metabolism (having

<table>
<thead>
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<th>Table I. Terminal vascular bed</th>
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<tr>
<td>I. Small arteries P_a P Q(volume flow)</td>
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<td>II. Arterioles r_a</td>
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<tr>
<td>III. Precapillary sphincters number of capillaries surface area</td>
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<td>IV. Capillary network P_v</td>
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<td>V. Collecting venules r_v</td>
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<td>VI. Muscular venules P_v</td>
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<td>VII. Veins Capacitance reservoir</td>
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little or no cytochrome oxidase) would suggest that such a mechanism would have to operate indirectly by way of some intermediate step. In view of the close interdependence between tissue blood flow and work performance, so clearly shown by skeletal muscle, it is likely that some small molecule or ion which is continuously in a state of flux either accumulates or fails to be removed when blood flow falls below a certain critical level. As repeatedly emphasized, the cardinal feature of local regulation is a shifting of the surface area across which blood-tissue exchange can occur. In this context, the continuous diffusion of a hypothetical substance would modulate the state of contraction of the precapillary smooth muscle cells until adequate numbers of capillaries are brought into the exchange system. Insofar as can be established, the endothelial wall is not directly concerned with moment-to-moment changes in exchange since there is no evidence that the fine capillaries are contractile in the true sense of the term. This facet of microcirculatory behavior comes closest to fulfilling the requirements of an independent activity directly influenced by tissue metabolism.

Much of the ebb and tide of flow within the capillary bed is a reflection of changes in the physical properties of the blood itself. The fact that the blood is a heterogeneous fluid mixture containing particulate elements creates a situation which by itself will influence flow through microscopic vessels. As has been reported, the aggregation of blood cells and the formation of sludgelike materials under abnormal conditions will profoundly affect blood flow. It is likely that under normal circumstances the physical attributes of the blood proper will affect primarily the outflow of blood by way of the venules. This would be manifested by short circuiting of certain pathways, increased venular resistance, and an inefficient distribution within the capillary bed proper.

The phenomenon of vasomotion is an integral aspect of blood tissue exchange bringing into play, as it were, the physical conditions commensurate with different physiologic requirements (Table II). It can readily be appreciated that flow through the majority of capillaries is not a steady state phenomenon but involves periods of complete stoppage interposed with periods of active circulation. The frequency with which the precapillary sphincters open and close will, therefore, determine the period of time and the surface area available for exchange under conditions of low hydraulic pressure as opposed to periods of comparatively high hydraulic pressure. These are precisely the conditions which should favor inward filtration of water as opposed to outward filtration on the basis of the colloid osmotic pressure of the blood. Vasomotor activity of the precapillaries becomes extremely rapid during conditions of lowered blood pressure (hemorrhage) when hemodilution can be demonstrated. In contrast, vasomotion is slowed or suppressed during conditions such as systemic infection where hemoconcentration occurs. Vasomotion is probably a balance between the myogenic response to fluctuations in pressure and changes in the smooth muscle cell itself through humoral and neurogenic stimuli.

Table II. Local regulatory influences

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<tr>
<th>Arteriolar tone</th>
<th>Primarily neurogenic—modified by chemical mediators</th>
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<tr>
<td>Precapillary sphincter tone</td>
<td>Primarily chemical—local and bloodborne agents Related to surface area and exchange</td>
</tr>
<tr>
<td>Capillary circulation</td>
<td>Permeability coefficient Parallel circuits Pressure (rV) Number (sphincter activity)</td>
</tr>
<tr>
<td>Venules</td>
<td>Resistance (rV) feedback for pC Rheologic factors</td>
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The selective reactivity of the different components of the capillary bed makes it possible for local blood flow to be modified in a highly specific manner. In conditions where blood flow is inadequate, by-products accumulate which put into motion an orderly set of events. Some of the precapillary sphincters open and increase the number of capillaries with an active flow of blood. Shortly thereafter the feeding arterioles dilate to increase the volume flow coursing through the capillary system. When the hyperemia is excessive, a resistance to outflow develops which in turn results in a further elevation of capillary pressure.

In situations where tissue requirements are met, the presentation of oxygen and other essential chemicals together with a washing out of accumulated products of metabolism removes vasoactive principles from the area and leads to a reversal of the sequence. The chemical agents responsible for these changes have not been identified. Some investigators favor by-products of anerobic metabolism (adenyl compounds, lactic acid). Others prefer some metabolite which is in a constant state of flux (potassium); still others emphasize neurogenic mechanisms via antidromic pathways. The fact that the same end result can be obtained with a whole family of chemical mediators suggests that no single system operates under all conditions and in different tissues.

The term "vasodilation" is used somewhat loosely with respect to the capillary bed. In actual fact, the true capillaries maintain a relatively fixed caliber despite wide excursions in total blood flow. In this sense the vasodilator aspect of reactive hyperemia, for example, refers to an increase in volume flow and surface area brought about by dilation of the muscular arterioles and precapillaries. There is no dilation of the capillaries per se. During this period there is an enhanced movement of materials from the blood into the tissue compartment which does not involve an increased permeability of the barrier.

In other situations, the vasodilation is accompanied by an increased permeability in the sense that materials normally retained by the capillary barrier now move into the tissues. Here, obviously, a change in the wall proper must be involved.

Capillary barrier

The actual barrier across which exchanges occur between blood and tissue consists of two principal components, a layer of endothelial cells interdigitated to form a continuous tube lining the interior of the vessel, and an outer investment of an amorphous fibrillar layer some 500 to 600 A thick referred to as the basement membrane. A number of distinguishing features should be singled out. Although the cell borders of adjacent cells seem to be in close contact (100 to 150Å), there is some question as to whether the endothelial tube is actually a continuous layer or may not have intercellular defects. The demonstration of attachment zones by electron microscopy is inconclusive since these are not regularly found between all endothelial cells and there is no indication that such structures are permanent. In fact, the ease with which adjacent endothelial cells can be caused to separate by chemical and physical factors clearly points to the unstable nature of intercellular attachments in endothelial membranes. Although the concept of an intercellular cement in morphologic terms has been dismissed by early electron microscopists, current studies reveal that the material between cells and the basement membrane is actually a continuum. A final structural consideration in relation to exchange across the capillary barrier is the existence of an endocapillary lining. Here again, electron microscopy at first rejected this possibility, but more recent evidence with special stains has demonstrated a thin lining material with the chemical characteristics of a polysaccharide protein complex. The mechanism by which water, dissolved materials, gases, proteins, etc.,
permeate this complex barrier is still an open question.

On a broad conceptual level, the original proposal by Starling\textsuperscript{18} is probably correct; the net movement of water across the barrier will depend upon the balance between the hydraulic force of the blood and the osmotic pressure of the plasma proteins. Such an exchange involves both diffusion and a bulk movement of water through aqueous channels or pores.\textsuperscript{4} Two pathways for the bulk movement of water have been suggested: (1) the hydrophilic matrix which is present between the endothelial cells and is continuous with the basement membrane\textsuperscript{16}; and (2) the attenuated portions of the endothelial cells.\textsuperscript{1} Deuterium-labeled water apparently diffuses freely across the surface of endothelium with great rapidity.\textsuperscript{19} Evidence on the exchange of ions and small water-soluble molecules likewise favors diffusion as the ultimate factor in this form of transcapillary exchange.\textsuperscript{20} The fact that ions and small molecules which do enter cells and those which are known not to penetrate cells traverse the capillary barrier with equal facility raises some question as to whether the endothelial cell proper is the pathway for such movement. There is a possibility that a portion of the endothelial cell surface may behave differently, that is, the attenuated extensions of the cell in which the opposite cell membranes appear to have fused into a series of diaphragm-like structures.\textsuperscript{21} Experiments in which the permeability to small molecules was increased by chemical mediators\textsuperscript{22} likewise show a uniform enhancement of the passage of such materials irrespective of whether they do or do not enter cells—pointing to an intercellular locus of action of such agents.

Exchange studies of radioactive solutes indicate that substances up to the molecular size of inulin diffuse freely, while larger molecules encounter increasing resistance to passage across the capillary wall.\textsuperscript{4} Plasma proteins for the most part are retained within the bloodstream, although there is evidence that the venules may normally contain a limited number of larger pores or "fenestellae," as termed by Landis,\textsuperscript{23} through which bulk movement of plasma may occur. Thus, the leakage of plasma proteins is a flow-dependent phenomenon activated by the blood pressure. It is obvious that defects of this kind involve two components—the spacing between otherwise tightly joined endothelial cells and the porosity of the outer basement membrane. Factors which lead to an increased outward movement of plasma into the extravascular compartment probably involve both of these structural features. The behavior of gases suggests that they permeate the capillary wall by virtue of their lipid solubility across the cell surface proper.

**Endothelial vesicles**

The cytoplasmic vesicles prominently seen in endothelial cells are believed by some investigators to be concerned with exchange processes across the capillary wall.\textsuperscript{24} Such a concept has not been universally accepted, particularly with respect to the movement of water and small molecules. Actually, the electron microscope evidence on this function deals only with the incorporation of colloidal particles into such vesicles (cytopempsis), a phenomenon which may have a bearing on the movement of colloids. It is possible that a vesicular type of uptake may include lipoprotein complexes which have an affinity for cell surfaces.\textsuperscript{25} In this context the phenomenon of vesiculation at the electron microscope level is analogous to that of phagocytosis as seen with the light microscope. Differences exist in terms of the size of the particles which then introduces surface factors into the picture. Phagocytized particles are believed to be incorporated into digestive vacuoles, "phagosomes," whereas materials in the endoplasmic vesicles are believed to be transported across the cell cytoplasm and discharged on the other side. It is interesting to note that specialized endothelial
cells, the Kupffer cells of the liver which are a part of the reticuloendothelial system of phagocytes, have an unusually prominent complement of cytoplasmic vesicles.

**Intercellular concept**

Chambers and Zweifach\(^\text{16}\) expressed the belief that it was difficult to conceive how the endothelial cells themselves could be freely permeable to ions, electrolytes, and some colloids to account for transcapillary exchange and yet maintain their own integrity. Generally speaking, except for liver and kidney in which the vessels have a specialized function, the endothelial lining is continuous even where the wall may be thinned to several hundred Angstrom units. In other cellular membranes which have highly selective permeability properties, as in the case of frog skin and toad bladder, the intercellular boundaries show the presence of specialized tight junctions.\(^\text{3}\) Similar desmosomes have been described in some capillary vessels, but not in all and not uniformly. Majno\(^\text{2}\) has shown that these structural configurations do not, in fact, seal the intercellular space and may be breached by various chemical mediators.

The increased prominence of vesicles in endothelial cells during tissue injury\(^\text{20}\) has led some investigators to suggest that these vesicles are the apparatus responsible for moving from the lumen to the exterior of the vessel. This concept has not withstood close scrutiny as a generalized mechanism for blood-tissue exchange. Emphasis is currently shifted to the separation of endothelial cells and the movement through such defects of plasma and cells into the subendothelial space limited only by the basement membranes. The relative rapidity with which such intercellular defects appear and are sealed off makes it probable that a similar mechanism may be operating under normal circumstances to a much more limited degree and in a much more subtle fashion.

The demonstration that the increased permeability resulting from histamine, bradykinin, or serotonin is accompanied by the separation of the endothelial cells\(^\text{7}\) suggests that the relative imperviousness of the venular capillary wall to protein under normal conditions resides within the endothelial cell surface. Some colloidal material is undoubtedly moved through the endothelial cell proper in vesicles. We have no firm basis for determining the relative magnitude of the exchange of proteins and colloids through each of these mechanisms. Renkin\(^\text{27}\) has calculated that vesicular transport could account for the movement of large macromolecules across the capillary wall in skeletal muscle.

Plasma proteins traverse the capillary barrier to a limited, barely measurable extent. If one were to assign this phenomenon to a vesicular transport mechanism, it would indicate that vesicle exchange is a comparatively slow process. Whether vesicle movement occurs with equal facility in both directions remains largely speculative. Actually one cannot with any assurance attach significance to the movements of denatured proteins, such as ferritin, via the endothelial vesicle system as providing evidence for the movement of plasma proteins across the capillary wall. In contrast to the vesicle concept of protein passage into the tissue compartment, the evidence of Witte\(^\text{28}\) with fluorescent-labeled proteins indicates that these substances leave the vessel only when an active flow is present. Obviously, in this context, protein is moved across the wall through pores by the hydraulic pressure of the blood. Perhaps the strongest argument in favor of the bulk movement of plasma proteins by way of the intercellular route is the demonstration with radioisotopes that the protein in the edema fluid during inflammation has essentially the same concentration as that of plasma.\(^\text{29}\) Under normal conditions, the limited loss of protein can be conceived to occur through a continuously changing population of temporary imperfections between contiguous endothelial cells. Such defects may be more numerous in the venules.
as shown by Landis with high-speed motion pictures of the leakage of blue dye-protein complexes.

The original concept of transcapillary exchange by way of intercellular pathways envisaged a cement material as the binding factor whose physicochemical properties were the determining factor in the selectivity of the process. Electron micrographs show the endothelial cells to be closely interdigitated and separated on the average by from 100 to 200 Å, a space not visible with the light microscope. The fact that some doubt exists concerning the existence of a cement substance does not detract, however, in any way from the intercellular concept of capillary permeability. Increasing attention is being directed at the basement membrane in relation to permeability phenomena. It should be pointed out, however, that the basement membrane materials and the attenuated interendothelial cellular material are, in fact, a continuous phase of the same structure elements. Factors which result in a separation of endothelial cell surfaces also affect the adhesion of the cell to the basement membrane. There is no valid reason to believe that reactions which alter the basement membrane will not have a comparable action on the intercellular component as well.

Capillary basement membrane

The physical appearance of the capillary basement membrane, as manifested by the electron microscope (thickness, density, structural configuration) does not reflect its functional capacity to serve as a filter. Serial sections reveal that the thickness of the basement membrane varies considerably along the length of selected vessels, as well as in different capillary vessels. Frequently, vessels with the thickest basement membranes, such as the venules, are more permeable to dyestuffs than are the capillaries. Despite the fact that injury reactions are associated with marked increases in the perviousness of the vessel wall, the basement membrane shows no obvious structural impairment.

The chemical make-up of the basement membrane is not known. It has the appearance of an amorphous matrix containing occasional fibrils. Recent work on kidney glomeruli indicates that these membranes have an amino acid content reminiscent of collagen. It has been proposed that the membrane is a mucoprotein formed by the endothelial cells and epithelial elements. Others believe the membrane has a mucopolysaccharide matrix which contains protein-coated fibrils and in effect forms aqueous pores that serve a filtration function.

Vessels with a clearly defined basement membrane have a limited permeability to protein. In contrast, structures such as lymphatic capillaries or the sinusoids of the liver and spleen are not encased in a continuous basement membrane and are collectively much more permeable to plasma proteins. On the other hand, as mentioned previously, histamine or bradykinin causes a local increase in permeability to plasma proteins manifest on the ultrastructural level only by a separation of endothelial cells. Although this does not eliminate completely the possible effect on the basement membrane, it casts doubt on its contribution as a barrier to dissolved substances. More likely, the basement membrane filters off cellular elements and colloidal aggregates. Cochrane, in experiments on antigen-antibody complexes, showed that anaphylaxis led to localization of the complexes in the subendothelial spaces through a separation of the endothelial cell junctions. Under such conditions plasma proteins leak into the tissue compartment. Here, evidently, the basement membrane can filter off large macromolecules but not the smaller proteins.

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