CAPILLARY PERMEABILITY TO PLASMA PROTEINS

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ACCORDING to the classical hypothesis of Starling (1896) the exchange of water and small lipid-insoluble molecules across the capillary membrane is largely governed by the balance between hydrostatic and colloid osmotic pressures, the existence of the latter being dependent upon relative impermeability of the capillary membrane to plasma proteins. Starling's concept has been verified by direct experimental measurements (Landis, 1927; Pappenheimer and Soto-Rivera, 1948) and its essential features are no longer in dispute. In recent years, however, attention has been drawn to the fact that considerable quantities of plasma proteins pass through the capillary walls. Drinker and Field (1931) collected lymph from the cervical, leg and renal lymphatics, as well as from the thoracic duct, and found considerable concentrations of protein in all samples; they concluded that "the capillaries practically universally leak protein" and that this protein can only return to the blood stream via the lymphatic system. This concept of a continuous exchange of plasma proteins between plasma and extravascular compartments has been confirmed repeatedly with radioactively labelled plasma proteins (e.g., Wasserman and Mayerson, 1951; Yoffey and Courtice, 1956). ¹³¹I-labelled albumin turnover studies in the human subject indicate an overall exchange rate between intra- and extravascular pools of 117-234% (mean 140%) of the total plasma albumin per day; and the total amount of albumin in the extravascular pool is greater than that in plasma (Cohen, Freeman and McFarlane, 1961). Leakage of plasma proteins may be of importance in that it enables antibodies to reach the tissues, and certain hormones such as insulin to exert their direct effect on the tissues (Hechter and Lester, 1960). Other hormones (e.g., thyroxine and cortisol) are partly bound by plasma proteins, and many drugs are known to be bound by plasma albumin. There is also evidence that the presence of plasma proteins in the interstitial fluid plays a part in the maintenance of

normal tissue electrolyte content (Carey and Conway, 1954; Creese and Northover, 1961) and that the large extravascular reserve of plasma protein is drawn upon when protein is rapidly removed from the blood stream (Wasserman, Joseph and Mayerson, 1956; Cope and Litwin, 1962).

In this article the mechanism of protein leakage through capillary walls, the methods available for measuring the leakage, and the factors that control it will be reviewed.

Theoretical Considerations

The permeability of a membrane is difficult to define. Landis (1946) considered that, at the very least it should be defined in terms of volume or mass of substance passing through unit area, in unit time, under the influence of unit hydrostatic or unit osmotic pressure. In practice, however, it is usually not possible to measure all these variables, and when considering the permeability of a membrane to large molecules, like proteins, the ratio of the concentration of the particular substance on either side of the membrane (the filtrate/filtrand ratio) is an acceptable simplification.

All the available evidence suggests that plasma proteins, and other molecules of similar size, pass through the capillary membrane at rates inversely related to the size of the molecule (see Yoffey and Courtice, 1956; Landis and Pappenheimer, 1963). The similarity between capillary filtrates and those obtained by the use of inert artificial membranes led to the "Pore Theory" of capillary permeability. This postulates that the capillary membrane contains numerous minute holes, or pores, which allow rapid passage of small ions and lipid-insoluble molecules but restrict the rate of movement of larger molecules such as proteins.

Landis (1946) suggested that the capillary wall consists of a meshwork with pores of many different sizes, the diameter of the largest pores being at least 38 Å. A 'graded pore theory' such as this would satisfactorily account

for the inverse relationship between rate of passage and molecular size. Pappenheimer (1953), however, in a detailed critical analysis of the pore theory of capillary permeability, came to the conclusion that the facts could best be explained on the basis of "restricted diffusion" through an isoporous membrane; it was calculated that uniform cylindrical pores with a diameter of 60-90 Å and a population density of $1.2 \times 10^9/\text{cm}^2$ would account for the observed rates of passage of water and lipid-insoluble molecules of various sizes.

Large molecules, like proteins, may traverse a porous membrane in one of two ways. They may be carried either by bulk-flow in a stream of other molecules (filtration) or by diffusion due to movement of the protein molecules amongst the other molecules. Both bulk-flow and diffusion contribute to the leakage of proteins from the vascular compartment, but the relative importance of these two mechanisms is uncertain, and may differ in different areas and at different rates of filtration. According to Pappenheimer (1953) the passage of protein molecules, whether by diffusion or bulk-flow, is restricted by at least two forces, namely viscous drag (or friction) between the molecules and the walls of the pores, and steric hindrance at the entrance to a pore (steric hindrance implies that the molecule can only enter a pore if it does not strike the edges of the pore). The magnitude of these forces is determined by the relationship between the size of the protein molecule and the size of the pore; the larger the molecule, the greater the resistance to its passage. Viscous drag and steric hindrance, therefore, determine the selectivity of protein leakage and account for "molecular sieving" through an isoporous membrane; the complex physical factors involved are discussed at length by Pappenheimer (1953) and Landis and Pappenheimer (1963).

It has been pointed out by Courtice and his colleagues (Courtice and Morris, 1955; Yoffey and Courtice, 1956; Courtice, 1961) that pores of the diameter suggested by Pappenheimer (1953) would not explain the escape of the large β -lipoprotein molecule into interstitial fluid. Similarly, the detailed studies of Grotte (1956) using dextran fractions of various sizes indicated the presence of 'pores' of at least 120 Å radius. Grotte postulates two different pore systems viz. capillary pores of relatively uniform size (40-60 Å radius) and capillary 'leaks' (radius 120-130 Å); an approximate ratio of capillary 'leaks' to capillary 'pores' was calculated to be 1:34,000. (Grotte,

1956; Areskog, Artusan, Grotte and Wallenius, 1964). Results similar to those obtained by Grotte (1956) have been reported by Mayerson, Wolfram, Shirley and Wasserman (1960). These authors, also, concluded that the data indicate two discrete sets of pores—a set of small pores allowing the passage of dextran molecules not greater than 250,000 M.W., and large pores permitting the passage of molecules of at least 412,000 M.W. An alternative explanation suggested is that molecules of molecular weight greater than 250,000 are transferred by a process called 'cytopempsis' (see below) rather than by passage through pores.

Both Grotte (1956) and Mayerson and others (1960) observed regional differences in capillary permeability, the hepatic capillaries being particularly permeable. It was suggested that large pores (or 'leaks') predominate in the liver and that regional differences are due to differences in the relative proportion of small pores and 'leaks'.

Pappenheimer (1953) considered the pores of the capillary membrane to be rigid structures. This concept may need to be modified since the observations of Shirley, Wolfram, Wasserman and Mayerson (1957) suggest that capillary distension produced by intravenous infusion of albumin greatly increases the porosity of the membrane. These authors attributed this phenomenon to stretching of the pores and concluded that the pores were not rigid structures.

The Anatomical Basis of Capillary Permeability

During the last decade, the electron microscope has revealed striking regional variations in the structure of capillaries (see Bennett, Luft and Hampton, 1959). The following section is a brief account of the electron microscopic structure of capillaries and summarises the attempts which have been made to correlate structure with function.

The capillary endothelium. The endothelium of capillaries may be fenestrated or non-fenestrated. Non-fenestrated endothelium is encountered in the capillaries of muscle, myocardium, lung and nervous system. In these capillaries, adjacent endothelial cells are separated by very narrow tortuous channels which measure some 100 Å in width. The cytoplasm of the endothelial cells adjoining these channels is condensed to form 'attachment belts' or 'desmosomes'. Fenestrated endothelium are of two types—the fenestrae may be intracellular or intercellular. Intracellular fenestrae measuring 300-600 Å in diameter, are found

in the endothelium of the glomerular and tubular capillaries of the kidney, in the intestine and in several endocrine glands. Rhodin (1962) showed that these fenestrae are not true pores but that they are closed by thin membranes which probably represent attenuations of the endothelial cells. Luft and Hechter (1957) showed that fresh ox adrenal-gland capillaries did not have intracellular fenestrations whereas if fixation was delayed for two hours, fenestrations were apparent. Moreover, it was found that if adrenal glands which had been left for two hours were perfused with warm ox blood, the fenestrations could be made to disappear. It is possible, therefore, that intracellular fenestrations only occur as a result of anoxia. Intercellular fenestrations up to several thousand Ångstrom units in diameter occur in the endothelium of liver and spleen capillaries. These are real pores and their presence may well explain the high protein content of hepatic lymph (Yoffey and Courtice, 1956).

Palade (1953 and 1956) and Moore and Ruska (1957) demonstrated that the endothelial cells of non-fenestrated endothelia contained numerous pinocytotic vesicles which measured some 200-600 Å in diameter. These authors also noted invaginations of the cell membrane both on the luminal and outer aspect of the endothelial cells (*caveolae*). It was suggested by Palade (1953) that this system of vesicles and caveolae might act as a transport mechanism, the caveolae being nipped off to form vesicles and the vesicles discharging their contents on the outer surface of the endothelial cell after they had migrated across the endothelial cell cytoplasm. This method of transport was referred to as *pinocytosis* by Palade and, more correctly, as transport by *cytopempsis* by Moore and Ruska. The existence of such a transport system is supported by the observations of Wissig (1958) who showed that ferritin molecules injected intravenously were incorporated in pinocytotic vesicles and finally appeared in the pericapillary space and basement membrane. Palade (1960) made similar observations using intravenous colloidal gold. Further support for transport by cytopempsis was obtained by Alksne (1959) who showed that under the influence of histamine, a substance known to increase vascular permeability to plasma proteins (*vide infra*), the incorporation of colloidal gold and mercuric sulphide particles into pinocytotic vesicles was much increased. Florey (1964) who studied the perfused heart showed that colloidal ferric hydroxide particles entered

the caveolae and became incorporated in vesicles. It seems likely that transport by cytopempsis would require energy and it is surprising, therefore, that Florey (1964) was totally unable to influence the incorporation of colloidal ferric hydroxide into pinocytotic vesicles by the addition of respiratory inhibitors to the fluid perfusing the isolated heart or by gradually cooling the perfusion fluid. Nor did these procedures alter the number of pinocytotic vesicles. He concluded, therefore, that it seems unlikely that the vesicles are being actively formed and destroyed and that they are probably more permanent structures than had previously been thought. There is still no direct proof that transport by cytopempsis occurs.

The basement membrane. The basement membrane forms a continuous coat of moderate electron density some 200-500 Å thick. It does not represent condensed 'cement' substance, for when a capillary is damaged and the endothelial cells retract from it, the basement membrane remains behind as a distinct layer. Palade (1953) regarded the basement membrane as a felt of fine fibrils whose meshes are filled with an amorphous matrix. It has been claimed that the basement membrane may act as a filter. There is no experimental proof for this, except perhaps in the case of glomerular basement membranes. Farquhar, Wissig and Palade (1961) showed that the main filtration barrier to ferritin molecules in the rat kidney was the basement membrane and that in rats with aminonucleoside nephrosis ferritin molecules penetrated the basement membrane more speedily.

The adventitial layer. This layer forms the outer coat of capillaries and consists of fusiform cells (*pericytes*) together with collagen and reticulin fibres. It may be complete, as in the capillaries of the brain and spinal cord, or incomplete, as in the capillaries of cardiac and skeletal muscle, liver and kidney (Bennett and others, 1959). There is no evidence that the adventitial layer contributes in any way to the 'semi-permeability' of the capillary membrane.

Two conclusions can be drawn from the foregoing electron microscopic observations:

1. Although functionally the capillary membrane behaves as a porous membrane, electron microscopy has failed to show the existence of pores except in the liver and spleen. It may be, of course that in the living capillary such pores do exist but until techniques are devised for obtaining the requisite high magnification

for studying living capillaries this question cannot be settled.

2. Cytopempsis as a mechanism of transport across the capillary wall remains unproven. It is possible, however, as suggested by Mayer-son and his colleagues (1960), that macromolecules are transported in this way.

Methods of Assessing Capillary Permeability

It is extremely difficult, if not impossible, to obtain a true sample of normal capillary filtrate, and for this reason the methods available for measuring capillary permeability to plasma proteins are indirect.

An early technique that has been used extensively measures the local accumulation in the tissues of proteins labelled with a dye or with ^{131}I iodine. Plasma albumin binds vital dyes such as Evans' blue, trypan blue or pontamine blue, and in animals with recently injected dye in their blood an intradermal injection of a substance that increases capillary permeability results in local 'blueing' of the skin due to increased leakage of dye-stained protein (Rocha e Silva and Dragstedt, 1941; Menkin, 1940; Miles and Miles, 1952). Dye containing ^{32}Br may also be used (Cope and Moore, 1944) and vascular permeability in normal and oedematous brain tissue has been investigated with fluorescein-labelled proteins (Klatzo, Miquel, and Otenasek, 1963). These methods, however, are not quantitative, and may be misleading. Measurement of the amount of dye in tissues is made difficult by the need to remove blood from the tissue without also removing tissue fluid (Cope and Moore, 1944), while the 'skin-blueing' method requires that the injection of the test substance does not alter blood flow in the local vascular bed (Miles and Miles, 1952).

Landis, Jonas, Angevine and Erb (1932) compared blood samples taken simultaneously from the brachial veins of congested and control arms and showed that the permeability of the capillary wall to protein varies with the degree of venous congestion. Under standard conditions it may be possible to gain some information about capillary permeability by this method but, as Landis and his colleagues emphasized, "caution must be used in extending conclusions based on observations involving high grades of venous congestion to considerations of normal capillary permeability".

Drinker and his colleagues believed that the protein concentration of lymph and of tissue fluid in any area is approximately the same (Drinker and Field, 1931; Drinker, Field, Heim

and Leigh, 1934; Drinker and Yoffey, 1914). It is now recognized, however, that the protein concentration in the lymph draining from an area does not necessarily reflect the permeability of the capillaries in that area, since the protein concentration in interstitial fluid, and therefore in lymph, might increase as a result of increased absorption of water at the venous end of the capillary without any change in capillary permeability. Conversely, a decreased amount of protein might be found in the lymphatic trunk, in the presence of increased capillary permeability if the blood flow were sufficiently reduced (Cope and Moore, 1944; Yoffey and Courtice, (1956). Measurements of the total amount of protein drained from a given area might be considered a better index of permeability but alterations in haemodynamics, and particularly in the number of capillaries being perfused at the time make this, too, an unreliable method.

While the measurement of total protein concentration in interstitial fluid or lymph is of no value in determining capillary permeability useful information may be obtained by measuring the relative concentrations of proteins of different sizes. Thus, an increase in the size of the pores reduces molecular-sieving, and leads to a relative increase in the amount of large proteins in the filtrate. It was early recognized that not only albumin but also globulins and fibrinogen pass through the capillary wall, and that for most regions capillary permeability to albumin was greater than that to globulins (Drinker and Yoffey, 1941). Perlmann, Glenn and Kaufmann (1943) examined lymph proteins by Tiselius electrophoresis and found the same four electrophoretic components as are present in serum. The albumin/globulin ratio in lymph exceeded that of plasma and moreover, it was shown that the distribution of proteins in lymph changed when capillary permeability increased following burns; the injury permitted both an increased passage of plasma proteins and a decrease in the differential permeability to albumin. Courtice and Morris (1955) and Courtice (1961), using paper electrophoresis, confirmed that the albumin/globulin ratio of lymph was greater than that of plasma, and demonstrated that even the largest protein, namely β -lipoprotein (Molecular weight 1,300,000), escapes into the tissue fluid.

Hardwicke and Squire (1955), investigating glomerular permeability, performed simultaneous quantitative analysis of urine and serum in patients with proteinuria and expressed the

results in terms of the separate clearances of albumin, α_1 , α_2 , β and γ globulins. The clearances of the four globulin fractions were then expressed as a percentage of the albumin clearance, and in this way it was possible to classify proteinuria according to its selectivity. It was argued that if tubular reabsorption of protein is non-selective (and evidence to support this was produced) then the degree of selectivity of the proteinuria reflects changes in glomerular permeability. The available evidence suggests that the lymphatic membrane readily allows the passage of all plasma proteins and, indeed, even larger particles such as red cells (for review see Yoffey and Courtice, 1956 and Mayerson, 1963). It seems likely, therefore, that protein reabsorption into lymphatics is non-selective with regard to molecular size, and that measurement of differential protein 'clearance' into tissue fluid on lymph might provide a good index of capillary permeability.* The technique of paper electrophoresis is not ideal for this purpose, however, since the electrophoretic components, apart from albumin, are not homogeneous with regard to molecular size (β -globulins, for example, include siderophilin of molecular weight 90,000 and β -lipoprotein, of molecular weight 1,300,000). Immunological methods have allowed more precise measurements of the renal clearance of a number of individual proteins in patients with proteinuria (Soothill, 1962; Squire, Hardwicke and Soothill, 1962); similar methods may be used in analysing tissue fluids.

The development of gel-filtration techniques, using 'Sephadex' (Porath and Flodin, 1959 and Flodin, 1962) has provided a relatively simple method of separating proteins according to their molecular size. Hardwicke (1965) has used this technique to measure differential protein clearances into urine. The method may also be used for measuring differential clearances of plasma proteins into oedema fluid and ascites (Jones and Peters, 1965).

After an intravenous injection of ^{131}I -labelled albumin, plasma radio-activity falls rapidly at first, because labelled albumin is being removed by diffusion into the extravascular space as well as by catabolism. Later, when mixing of labelled albumin in the plasma and extravascular pools is complete, the rate of fall in plasma radioactivity is reduced, since diffusion from plasma is now balanced by the return of labelled albumin from extravascular sites via the lymphatics. The shape of the plasma radioactivity curve may, therefore, provide

*Capillary porosity is, strictly, a more accurate term.

some indication of the rapidity of mixing, and of the relative quantities of albumin in the intravascular and extravascular compartments. A mathematical analysis widely used for these purposes is that described by Matthews (1957). Results obtained by this method of analysis agree well with those derived by other techniques (Cohen and others, 1961), but there is no proof that intercompartment transfer rates derived in this way are an indication of capillary permeability, and the dynamics of plasma/extravascular exchange are analysed in terms of the total amount of protein present in each compartment rather than in terms of protein concentration.

Much useful information has resulted from the use of polydisperse macromolecules other than plasma protein,—in particular from studies with dextrans. Glomerular permeability has been investigated by measuring the clearance of dextran fractions of different mean molecular size. Brewer (1951), Wallenius (1954) and Wasserman, Loeb and Mayerson (1955) determined plasma/lymph concentration ratios for dextrans of different molecular weight in an attempt to measure capillary permeability. Later, (Mayerson and others, 1960) the method was improved by infusing dextran fractions and ^{131}I -labelled serum albumin simultaneously. "Steady state" lymph/plasma concentration ratios for each dextran fraction could then be related to the ratio for labelled albumin and a coefficient obtained which referred the permeability of a capillary bed with respect to a given molecular weight of dextran to its permeability with respect to albumin. Grotte and his colleagues have also made extensive studies of capillary permeability using dextran fractions (Grotte, 1956; Areskog and others, 1964). Dextran fractions of sufficiently uniform molecular size for studies of this nature are difficult to prepare, and the methods used by these authors for estimating the molecular size and concentrations of dextrans in the biological fluids are tedious. Recently, Brooks, Davies, Graber and Ricketts (1960) have succeeded in labelling dextran with radio-iodine, thus enabling small quantities to be measured accurately; while gel-filtration techniques, using 'Sephadex', allow the distribution of molecular sizes present to be determined. These recent developments eliminate the need to prepare dextran fractions of 'narrow' molecular weight distribution and enable more precise work to be done with dextran (Hardwicke, Hulme, Jones and Ricketts, 1964).

Grotte, Juhlin and Sandberg (1960) have used

TABLE 1
SUBSTANCES WHICH INCREASE VASCULAR PERMEABILITY TO PLASMA PROTEINS

<i>Amines</i>	
Histamine	Lewis (1927), Gaddum (1948), Spector and Willoughby (1957), Majno and Palade (1961).
5-Hydroxytryptamine	Rowley and Benditt (1956), Majno and Palade (1961).
<i>Peptides</i>	
'Leukotaxine'	Menkin (1956), Duthie and Chain (1939), Cullumbine and Rydon (1946), Spector (1951).
Bradykinin	Holdstock, Mathias and Schachter (1957), Rocha e Silva (1955).
Kallidin	Hilton and Lewis (1955), Werle (1955).
Substance P.	Euler and Gaddum (1931), Pernow (1955).
Substance U.	Beraldo (1955).
Pepsitensin	
Pepsitocin	Croxatto (1955).
Pepsanurin	
Kinin	Holdstock, Mathias and Schachter (1957).
Angiotensin	Giese (1964).
<i>Proteins</i>	
Permeability Factor (Dilution)	Wilhelm, Miles and Mackay (1955), Mill, Elder, Miles and Wilhelm (1958), Stewart and Bliss (1957).
Permeability Factor (Age).	Miles and Wilhelm (1955).
Permeability Factor (Native)	Elder and Wilhelm (1958).
Permeability Factor formed by interaction of guinea-pig tissue with serum.	Mill (1964).
Lymph Node Permeability Factor	Walter and Willoughby (1965).
Kallikrein	Frey, Kraut and Werle (1950), Werle (1955).
Renin	Winternitz, Mylon, Waters and Katzenstein (1940).
	Masson, Plahl, Corcoran and Page (1953), Asscher and Anson (1963 a and b), Giese (1963).

solid spherical particles (radius 300-700 Å) of methylmethacrylate, marked with a fluorescent dye, to determine the maximum particle-size that can cross the 'blood-lymph barrier' at different sites in the body.

It is evident that there is no satisfactory method of measuring capillary permeability in normal subjects. Apparently satisfactory techniques of collecting normal extracellular fluid have been described in animals (Creese, D'Silva and Shaw, 1962) but not in man. In oedematous subjects, however, samples of extracellular fluid are easier to get. Quantitative analysis of the proteins present in such fluid by the more precise methods now available will probably be useful.

The Regulation of Capillary Permeability with Respect to Plasma Proteins

The factors which account for changes in capillary permeability have been studied mainly in relation to the inflammatory reaction. This subject has been extensively reviewed by Spector (1958). An embarrassingly large number of substances have been described that could produce the increase in capillary permeability which is observed in the inflammatory reaction. The accompanying table lists the naturally occurring substances known to increase vascular permeability to plasma proteins. It is difficult

to prove that any of these substances are involved in the inflammatory reaction. Some light has been cast on the problem by Sevrin (1957) who showed that the reaction to injury is a double phenomenon. An immediate increase in capillary permeability lasting for less than 10 minutes (which can be suppressed by antihistaminics) is followed by a delayed increase in permeability which begins about one hour after injury and which is unaffected by antihistaminics. Spector and Willoughby (1959) clearly demonstrated the participation of histamine in the early stages of inflammation by showing that previous body depletion of histamine by administration of compound 48/80 (a powerful histamine liberator) delayed the onset of increased capillary permeability caused in rats by the intrapleural injection of turpentine. There is some evidence from the work of Spector (1956) and Spector and Willoughby (1960) that activation of globulin-peptide systems such as the kallikrein-kallidin system might be involved in the delayed increase in permeability.

Little is known about the mode of action of substances which increase vascular permeability to plasma proteins. Nearly all these substances share in common the property of producing contraction of smooth muscle cells. It is tempting

ing to suggest, therefore, that they might act by producing contraction of endothelial cells with the consequent appearance of gaps between the cells or enlargement of already existing pores. This suggestion was originally made by Zweifach (1953) who studied the effect of histamine on the capillaries of the mesoappendix of the rat. Majno and Palade (1961) showed that under the influence of histamine and 5-hydroxytryptamine, large gaps appeared between the endothelial cells through which mercuric sulphide particles rapidly escaped. These findings support the view that the increase in vascular permeability produced by histamine and 5-hydroxytryptamine might be due to contraction of endothelial cells. This may not be the sole mechanism whereby these substances act. Thus, Alksne (1959) showed that histamine produced increased pinocytotic activity in the endothelial cells. Moreover, histamine produces dilatation of terminal arterioles which raises hydrostatic pressure and increases capillary filtration of proteins. The dilatation of the terminal arterioles may also increase the number of perfused capillaries and so enlarge the surface area available for transfer of plasma proteins.

The mode of action of angiotensin on vascular permeability has recently been studied by Giese (1964). He showed that angiotensin infusion in the rat produced an alternating pattern of constriction and dilatation in the mesenteric arteries similar to that observed by Byrom (1954) in severe experimental hypertension. He noted that carbon particles were invariably deposited in the dilated segments. The 'stretched pore' phenomenon might, therefore, be involved in producing the increase in permeability. Alternatively, the increase in permeability might be due to anoxia consequent on the arterial constrictions since anoxia is known to increase vascular permeability to plasma proteins (Landis and others, 1932) and it is also known to produce intracellular fenestrations (Luft and Hechter, 1957). There are no data published on the mode of action of any of the other substances which increase

Capillary Permeability in Disease

In view of the difficulties inherent in the measurement of capillary permeability it is, perhaps, not surprising that data relating to changes in permeability in disease are relatively scanty, and, in many instances, probably unreliable. There is little doubt, however, that changes in vascular permeability do occur. They are particularly well documented follow-

ing injury, be this due to direct trauma, thermal and chemical burns, exposure to irritant gases (see Yoffey and Courtice, 1956; Florey, 1962) or irradiation (Wish, Furth, Sheppard and Storey, 1952). Similarly, there is little doubt regarding the significance of increased vascular permeability in the pathogenesis of allergic oedema (Florey, 1962), or of increased glomerular permeability in the pathogenesis of the nephrotic syndrome (Squire, Hardwicke and Soothill, 1963). Increased permeability to proteins has also been postulated in post-decompression shock (Brunner, Frick and Bühlmann, 1964) and in high-altitude pulmonary oedema (Singh, Kapila, Khanna, Nanda and Rao, 1965), while profound changes in capillary permeability have been demonstrated in occasional cases of idiopathic oedema (Clarkson, Thompson, Horwith and Lucky, 1960; Weinbren, 1963).

In other conditions, increased capillary permeability is more doubtful. Some authors have postulated a generalized increase in capillary permeability in acute glomerulo-nephritis, but Warren and Stead (1944) found the protein content of the oedema fluid to be no higher than in cardiac failure, and the periorbital distribution of oedema may be explained on other grounds (Burch, 1940). Excessive protein leakage has also been reported by several authors in the later stages of normal pregnancy, and in toxæmia of pregnancy. (Szontagh, 1949 and 1950; Herold, 1950; Burger, 1951; Herold and Brautigam, 1955; Friedberg and Lutz, 1963).

Schurmann and MacMahon (1933) postulated that leakage of plasma proteins into the medial muscle coat of arteries was responsible for the appearance of fibrinoid necrosis in hypertensive disease. Some support for this view was obtained by Asscher and Anson (1963a) who showed that renal cortical extract induced both leakage of plasma proteins and fibrinoid necrosis when injected into nephrectomized and renal-hypertensive rats. Since fibrinoid necrosis is commonly considered to be the histological hallmark of malignant hypertension, it is possible that the transition from the benign to the malignant phase is determined by a change in endothelial permeability to plasma proteins.

These few examples are intended to illustrate both the variety of disorders which may be associated with alterations in vascular permeability, and the paucity of information available. The methods used in many instances do not allow anything other than tentative conclusions to be drawn, and it is clear that further progress in this field must await the develop-

ment of reliable techniques of measuring capillary permeability in the human subject.

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