CAPILLARY PRESSURE AND CAPILLARY PERMEABILITY

EUGENE M. LANDIS

The Robinette Foundation, Hospital of the University of Pennsylvania, and the Department of Pharmacology, University of Pennsylvania

Until recently the capillaries were generally believed to be inert, thin-walled tubes serving to conduct blood through the tissues in whatever quantity the arterioles might supply. However, the monographs of Krogh (1922, 1929) and Lewis (1927) have summarized an impressive mass of evidence showing that the capillary vessels are independently contractile and capable of responding individually in a delicate manner to the circulatory needs of the immediately adjacent tissues. Even so, the great transporting medium, the blood stream, is still separated from almost all of the tissues it serves by a single layer of endothelial cells which form the walls of the capillary vessels. Obviously the interchange of substances between blood and the fluid bathing the tissues must depend fundamentally upon the properties of this membrane.

I. General nature of the capillary endothelium. The area of capillary wall available for fluid interchange is relatively enormous. Krogh (1922) estimates that if a man's muscles weigh 50 kgm. and his capillaries number 2,000 per square millimeter their total surface would be 6,300 sq. m. In the horse, dog and frog 1 cc. of blood is exposed in the capillary network to a filtering surface of 7,300, 5,600 and 2,700 sq. cm. respectively.

The capillary wall is also highly permeable since it permits fluid to pass much more easily than do other cellular membranes so far studied quantitatively. Strictly speaking, the permeability of a membrane must be defined in terms of units of volume or mass passing through unit area and thickness of membrane in unit time under the influence of unit hydrostatic or unit osmotic pressure. Using permeability so far as possible in this limited sense, the mesenteric capillary endothelium of the frog can be compared roughly with certain other cellular membranes. Lucké, Hartline and McCutcheon (1931) have shown that, under an osmotic pressure of one atmosphere, water passes through the membrane of the sea-urchin egg cell at the rate of 0.1 cubic micron per square micron of surface per minute. The membrane of the human erythrocyte is more

permeable (Jacobs, 1931); under an osmotic pressure of one atmosphere, water passes at the rate of 3.0 cubic micra (at 20°C.) per square micron of surface per minute. According to micro-injection experiments on single capillaries of the frog's mesentery (Landis, 1927b) a change in hydrostatic pressure of 5 cm. water modifies the filtration rate by 0.03 cubic micron per square micron of surface per second which corresponds to a filtration rate of 370 cubic micra per square micron of surface per minute under a pressure of one atmosphere. Thus fluid filters through the frog's capillary wall over 100 times more easily than through the membrane of the human erythrocyte and over 3000 times more easily than through the membrane of the sea-urchin egg cell. The importance of this high grade of permeability cannot be over-estimated in considering the physiology of the capillary network, one function of which is to distribute water and dissolved substances throughout the body efficiently and rapidly.

The significance of an extensive filtering area combined with great permeability is suggested by a calculation, which, on account of the assumption made, is admittedly more interesting than important. Assuming that the human capillary wall possesses a permeability to fluid similar to that of the frog's mesenteric capillaries, the total plasma volume of a man would be filtered through his calculated 6,300 sq. m. of capillary surface within 10 seconds at a capillary pressure of 10 mm. Hg if there were no force retaining fluid within the blood capillaries. Actually the vasomotor system normally prevents the entire peripheral vascular bed from opening simultaneously and, in addition, the colloidal constituents of blood plasma limit the loss of fluid from the blood stream. Only in widespread injury of the vascular endothelium would it be possible for fluid to leave the vascular system at such a rapid rate.

The movement of fluid between blood and tissue spaces varies in both rate and direction. Hydration, dehydration, change in posture and exercise affect the total volume and the water content of the blood but the variations are kept within safe physiological limits except under the most drastic conditions. Blood volume responds quickly to physiological needs and under pathological conditions shows great alterations, but the healthy organism strives to keep the general level constant (Erlanger, 1921).

Fluid absorbed from the gastro-intestinal tract dilutes the blood (Creveld and Feringa, 1921; Marx, 1925; Underhill and Sallick, 1925; Greene and Rowntree, 1927; Govaerts and Cambier, 1930; Bayliss and Fee, 1930; Rioch, 1930; Margaria, 1930; Farkas, 1932; Smirk, 1932;

Heller and Smirk, 1932a) during the period when the extra fluid is being transported throughout the body. Before diuresis begins some water passes into the tissues (Gömöri and Molnar, 1932; Heller and Smirk, 1932a) and, if excretion is delayed by administering pitressin (Heller and Smirk, 1932b), both hydremia and temporary storage in the tissues are accentuated. Limitation of water intake is accompanied by concentration of the blood (Underhill and Roth, 1922; Spencer, 1929; Kerpel-Fronius and Leövey, 1931) but the water content of the blood rapidly returns to normal when water is administered (Underhill and Kapsinow, 1922).

Muscular activity modifies the movement of fluid through the capillary wall; blood loses fluid rapidly during its passage through active muscle (Barcroft and Kato, 1915–16, and others) and lymph flows more rapidly from the region (White, Field and Drinker, 1933). During rest the loss of fluid from the blood ceases and lymph flow diminishes. Quiet standing diminishes blood volume (Thompson, Thompson and Dailey, 1927–28; Waterfield, 1931a; Youmans, Wells, Donley and Miller, 1933) and elevates the plasma protein concentration, while the lower extremities increase in volume (Waterfield, 1931b), owing to the extravascular accumulation of fluid which is filtered through the capillary wall. In the recumbent position this extravascular fluid is absorbed and blood volume returns to the earlier level. Under physiological conditions, therefore, fluid is moving at varying rates, at one moment inward, at another outward, through an extensive and highly permeable system of capillary walls. Nevertheless gross variations in blood volume and in the volume of tissue fluid are avoided.

To explain the equilibrium existing between blood and tissue fluid under these diverse conditions, the most attractive hypothesis is that advanced by Starling (1895–96). He pointed out that while the capillary endothelium is easily permeable to water and to solutions of most salts it is, in many tissues, relatively impermeable to the colloidal plasma proteins. The total osmotic pressure of the blood plasma amounts to approximately 7 atmospheres but is due almost entirely to substances which pass easily through the capillary wall. These crystalloids, being in a state of balance with the crystalloids in tissue fluid, cannot exert an osmotic pressure in the capillary and will not, under ordinary circumstances, influence the movement of fluid. The colloidal plasma proteins, on the other hand, are retained more or less completely by the endothelium and must therefore influence the movement of fluid through the capillary wall, though exerting a much smaller osmotic pressure,—found

by Starling to be about 30 mm. Hg. He suggested that although this colloid osmotic pressure is relatively insignificant, its order of magnitude is comparable to that of the probable capillary pressure. He postulated a balance between capillary pressure and the colloid osmotic pressure of the blood. In those areas where capillary pressure exceeds the colloid osmotic pressure of the blood, fluid will be filtered from the blood into the tissue spaces. In other areas where capillary pressure falls below the colloid osmotic pressure of the blood, fluid will be absorbed from the tissue spaces into the circulating blood.

This concept, in which physical forces become the prime agents activating the movement of fluid through the capillary wall, can be applied only if the endothelium of the capillary network acts like an inert membrane. From the morphological point of view it is not likely that a membrane having the structural simplicity of vascular endothelium could have a secreting function. The available evidence led Krogh (1929) to state, "When I review all the facts that have come to my notice I have no hesitation in saying that there is no trustworthy evidence of the capillaries having any power of hindering or favoring the passage by diffusion of all kinds of crystalloids through the endothelium." Recent chemical studies agree in demonstrating that at equilibrium electrolytes are distributed between blood serum and edema fluids in a manner which vigorously supports this view.

Mestrezat and Ledebt (1921) placed in the peritoneal cavities of animals collodion sacs filled with 0.5 per cent sodium chloride solution. After an interval of several days the fluid within the sacs resembled cerebrospinal fluid in freezing point, and in the content of chloride, sugar and protein, indicating that it is possible to obtain *in vivo* without "vital forces" an equilibrated dialysate which is superficially similar to at least one type of extravascular fluid.

Loeb, Atchley and Palmer (1922) compared ascitic fluid and blood, finding that the two fluids contained approximately equal amounts of HCO_3, Na, sugar, non-protein nitrogen and urea. The extravascular fluid differed from blood serum in its greater conductivity, its greater chloride and its lower potassium and protein contents. No new equilibrium was established when serum was dialyzed against the edema fluid through a simple collodion membrane. It was suggested that the relationship between serum and edema fluids results from a simple membrane equilibrium influenced in part by the amount of protein present.

Van Slyke, Wu and McLean (1923) recalculated the data of Loeb et al., expressing concentration in slightly different terms. The irregularity

of certain electrolyte ratios made it impossible to demonstrate quantitatively a Gibbs-Donnan equilibrium between blood serum and edema fluid. The agreement between the calculated and observed ratios for chloride, HCO_3 (arterial), and sodium seemed more than fortuitous and lent support to the concept that the capillary wall was a simple filtering membrane. This conclusion was verified by Hastings, Salvesen, Sendroy and Van Slyke (1925–27), who compared the electrolytes of edema fluid, ascitic fluid and blood serum. The HCO_3, Cl, Na, and H ratios approximated but still did not quite equal the ratios predicted on the basis of the Gibbs-Donnan equation. The K, Ca and Mg ratios departed widely from the predicted figure. Dialysis *in vitro* showed the same exceptions, however, and indicated that the discrepancies *in vivo* are to be attributed to physical factors inherent in the two solutions. Similar equilibria between plasma and edema fluid have been recorded by Muntwyler, Way and Pomerene (1931), Darrow, Hopper and Cary (1932b) and by Gilligan, Volk and Blumgart (1933) in various conditions. Schechter (1931) and Schechter et al. (1933) introduced into the peritoneal cavity solutions having an electrolyte composition more or less different from that of blood plasma and found that these extravascular fluids also attain eventually the pattern and distribution of electrolytes observed in spontaneously occurring edema fluids.

Greene and Power (1931) determined in dogs the distribution of electrolytes between arterial blood and an "*in vivo*" dialysate obtained through a collodion membrane. The distribution ratios thus obtained through a non-living membrane were then compared by Greene, Bollman, Keith and Wakefield (1931) with similar ratios between blood and extravascular fluids. The distribution of electrolytes in the system, blood plasma——capillary wall——extravascular fluid, is approximately the same as the distribution of these same ions in the system, blood plasma——collodion membrane——dialysate *in vivo*. The relative amount and the character of the protein present in the two solutions affects the distribution of the various ions between the serum and the transudate.

It cannot be said that the Gibbs-Donnan equilibrium holds accurately for any of these fluids but this is of no consequence in considering the properties of the capillary wall because those minor departures from theory observed in the case of edema fluids are also present in the ultrafiltrates or dialysates of plasma obtained *in vitro*. The essential point is that the electrolyte pattern observed when the capillary wall separates plasma and edema fluid is identical with the pattern observed when a collodion membrane separates the same two fluids. It can be concluded safely, therefore, that the normal capillary wall does not act differently from a collodion membrane in this respect.

It is generally agreed that the slight differences between electrolyte concentration on the two sides of the capillary wall depend upon the difference between the protein contents of the two fluids. The equilibrium between the electrolytes of plasma and extravascular fluid is independent of the location of the edema fluid and also independent of the underlying pathological process, whether mechanical or inflammatory, which leads to the accumulation of tissue fluid (Loeb et al., 1922; Hastings et al., 1925). The distribution of electroytes is the same at the height, during increase, and during disappearance of edema (Muntwyler et al., 1931). There is no evidence that the capillary wall possesses a special permeability which leads to the accumulation of chloride in the extravascular fluid. Although the physico-chemical laws expressed in the Gibbs-Donnan equation are concerned in determining the composition of a transudate while it is in equilibrium with the blood stream, they will not explain either the development or the absorption of the transudate (Greene, Bollman et al., 1931; Muntwyler et al., 1931). The discrepancies *in vivo* from the Gibbs-Donnan equation can be explained for a complex system such as blood on the basis of physical factors (e.g., activity coefficients of the ions) inherent in the two solutions, particularly since similar discrepancies are observed *in vitro* (Ingraham, Lombard and Visscher, 1933). Moreover, it has been pointed out (Greene, Bollman et al., 1931; Darrow, et al., 1932b) that it is difficult to obtain a sample of blood truly representative of that with which the particular transudate is in equilibrium. Greene, Bollman et al., (1931) mention that, in patients who had been taking ammonium nitrate, the nitrate content of the ascitic fluid might presumably lag behind that of serum, both when the amount in serum is increasing during administration and when the amount in serum is decreasing after administration has been stopped. With circulatory and chemical changes constantly taking place, large volumes of transudate probably cannot, except by chance, be in absolute equilibrium with any one blood sample.

From the physico-chemical standpoint the capillary wall can be regarded as an ultrafilter comparable to an artificial membrane impermeable to protein. It follows therefore that the osmotic pressure of the proteins must tend to absorb water from the tissue spaces, and that this absorbing force cannot be balanced by any other force than capillary blood pressure. Peters (1933) holds that the distribution of electrolytes

between blood and extravascular fluid supports Starling's theory just as adequately as the available physiological evidence.

Summary. The general properties of the capillary wall include 1, an enormous total area for interchange between the blood and tissue spaces; 2, permeability to fluid which is many times greater than that of certain cell membranes so far studied quantitatively, and 3, the physical characteristics of an inert (in the sense of non-secreting) membrane permeable to water and crystalloids but relatively impermeable to the plasma proteins. With this background it is justifiable,—or even obligatory,—to regard physical forces as important factors in the movement of fluid through the capillary wall. It is also necessary to examine critically so-called "changes in capillary permeability" in which these physical forces have not been carefully controlled.

II. PHYSICAL FACTORS AFFECTING THE MOVEMENT OF FLUID THROUGH THE CAPILLARY WALL. *1. Capillary blood pressure.* Blood flows past the highly permeable capillary wall under a hydrostatic pressure. Theoretically this capillary blood pressure would be expected to filter fluid from the blood through the capillary wall into the extravascular spaces. Capillary pressure interested early investigators of hemodynamics primarily because of its relation to the location of the peripheral resistance to blood flow. Fick (1888) placed practically the whole of the peripheral fall in blood pressure on the venous side of the capillary network. Since capillary pressure, according to some determinations, was extremely low, Krogh (1922) held that the peripheral fall in blood pressure must be situated primarily on the arterial side of the capillary network, a drop of a few millimeters of water pressure being sufficient to overcome the frictional losses of energy required to produce capillary blood flow. An intermediate view was expressed by Levy (1897) and by Dale and Richards (1919) who believed that the peripheral resistance was situated partly in the arterioles, and partly in the capillaries. This latter view postulates a gradient of pressure in the capillaries themselves. The validity of Starling's hypothesis depends, among other things, on the presence of such a gradient and on the demonstration that an excess of capillary pressure over the colloid osmotic pressure of the blood actually filters fluid from the capillary blood. The measurement of capillary blood pressure is of theoretical importance also in determining whether this force and the colloid osmotic pressure of the blood are in approximate balance.

a. *Methods of measuring capillary blood pressure.* Capillary blood pressure has been measured directly (Landis, 1926, 1930b) and, far more

frequently, indirectly. The many indirect methods of measuring capillary pressure are fundamentally similar; they consist in applying graded pressure to a tissue either by means of a transparent rigid plate, or by means of a capsule covered by a distensible, transparent membrane. They differ considerably in the arbitrary criterion taken to indicate a state of balance between intravascular pressure and external pressure. The criteria which have been used are extremely numerous, including, to mention only a partial list: 1, first perceptible blanching of the skin; 2, definite or even complete blanching of the skin; 3, appearance of capillary pulsation in a histamin flare; 4, blanching with only brief pressure by a jet of water; 5, return of skin color in a histamin flare to normal depth of color; 6, complete stoppage of flow in capillary vessels viewed under the microscope; 7, first perceptible modification of flow in single capillaries, and 8, the disappearance and reappearance of the spectroscopic bands characteristic of hemoglobin.

It is not surprising that little agreement exists in the results obtained in accordance with these various criteria. Table 1 collected by Strax and De Graff (1931) summarizes the capillary blood pressure measurements in man. The average normal values reported for a single tissue, skin, vary over a range so wide (1.5 to 71.0 mm. Hg) that it is impossible to draw any definite conclusion concerning the relation between capillary pressure and the colloid osmotic pressure of the blood. The same method, used by several investigators, yields values differing by several hundred per cent. This is to be expected from the subjective nature of the criteria adopted, particularly where fine gradations of skin color are concerned.

Danzer and Hooker (1920) and Liebesny (1923) found that external pressure blanches the skin by emptying the subpapillary venous plexus and not the capillaries. According to White (1924b) the pressure required to produce blanching has no relation either to capillary or to venous pressure, being occasionally even lower than venous pressure. Moreover variations from subject to subject are due largely to differences in normal skin resistance, a factor involved in all indirect methods. Blockage of circulation by long-continued external pressure has been criticized by Hill and McQueen (1928) and is undoubtedly responsible for some of the very high figures reported. On the other hand, mere modification of blood flow in a few capillaries, the criterion advocated by Hill (1920), can be produced by pressures below venous pressure (Landis, 1926).

The wide range of the indirectly determined estimates of capillary

blood pressure is doubtless due to errors which arise from the arbitrary adoption of different methods and criteria by almost every investigator.

TABLE 1

Capillary pressure determinations in man (modified from Strax and De Graff, 1931)

		mm. Hg
I. Indirect methods:		
(a) With skin blanching:		
1. von Kries	1875	24–38
Natanson (v. Kries method)	1886	71
2. v. Basch	1900	25–30
3. von Recklinghausen	1906	55
Krogh and Rehberg (von Recklinghausen method)	1927	5–8
4. Basler	1912	7–9
Landerer (Basler method)	1913	17–25
Goldmann (Basler method)	1914	5–7
5. Marks	1920	6–20
6. Hill and McQueen	1921	10
7. Ariola	1925	10–14
8. Ellis and Weiss	1929	6–12
(b) With direct visualization of capillaries:		
i. Pressure applied by rigid surface:		
1. Lombard	1911–12	30–45
2. Guillaume	1924	18–28
3. Rajka	1926	1–2
4. Strax and De Graff	1931	18–29
ii. Pressure applied by elastic capsule:		
1. Krauss	1914	10
2. Danzer and Hooker	1920	20–24
Boas (Danzer and Hooker method)	1922a	20–30
3. Kylin	1921	13.6
Rominger (Kylin method)	1923	8
Liebesny (Kylin method)	1923	32.5
Nevermann (Kylin method)	1924	6–11
Grzechowiak (Kylin method)	1924	6–14
(c) Bleeding methods:		
1. Basler	1914	7.7–13.0
2. Weiss	1914	10
II. Direct methods:		
(a) Intubation, brief periods, Carrier and Rehberg	1923	3.3–5.5
(b) Intubation, long periods, Landis	1930b	12–32

Depending on selection of figures in table 1 capillary pressure in man seems to be far below or far above the colloid osmotic pressure of the plasma proteins and no conclusions can be drawn concerning the balance

between these two forces. Moreover, no indirect method can yield exact information concerning the existence or non-existence of a gradient of pressure in the capillary network itself. These difficulties led to direct determinations through minute cannulae inserted into single capillaries (Carrier and Rehberg, 1923; Landis, 1926).

A "direct" measurement of arterial or venous blood pressure requires that a cannula be inserted into the vessel and retained there long enough to secure complete balance between the blood in the vessel and the fluid in the manometer. A "direct" measurement of capillary pressure should have the same qualifications. Thus determining the pressure required to prevent bleeding after an incision is made in the skin is not strictly speaking a direct method, though often so termed. Basler (1914) and Weiss (1914) found that relatively low pressure sufficed to stop bleeding produced in this manner. There is no assurance that only capillaries have been incised, nor is it certain that applying an anticoagulant to the surface of the skin prevents clotting in the deeper parts of the puncture. Blood will finally cease flowing spontaneously without the application of any external pressure.

The first measurements of human capillary pressure by an intubation method were those of Carrier and Rehberg (1923) who observed the pressure at which blood would, or would not, flow into the tip of a pipette held in the hand and introduced into a capillary loop. The size of their pipettes restricted measurements to venous loops and the lack of rigid support for the pipette limited the period of observation to a few seconds. Kylin (1926) offered the objection that introducing a glass tube into the venous limb obstructs inflow from the arterial side. Under these circumstances, according to Krogh (1929), the venous limb and the minute cannula form a side tube to the nearest venule and the pressure measured is then that in the first net of venules instead of that at the top of the capillary loop. Of equal importance is the repeated observation (Landis, 1930b) that to draw blood rapidly into a fine micropipette requires a pressure approximately 5 to 10 mm. Hg lower than true equilibrium pressure. Pressure measurements should be made (Landis, 1926) only at true equilibrium when no fluid is moving through the tip of the pipette, since an orifice of 8 to 15 micra interposes considerable resistance to flow. Even pulsatile movement of the blood in the pipette is not evidence of equilibrium unless the corpuscles oscillate about the same point for 5 to 10 seconds without continuous movement either into, or out of, the pipette. Hence, it would seem that a true "direct" measurement of capillary pressure, like the "direct" measurement of arterial pressure,

should continue for a period which is long enough to ensure a complete balance of pressure between capillary blood and the fluid communicating with the manometer.

The direct micro-cannulation method used by Landis (1926, 1930a, 1930b) has the advantage of permitting *a*, repeated measurements over long periods of time, and *b*, pressure determinations in various parts of the capillary network and larger vessels. It is thus possible to follow variations in capillary blood pressure from moment to moment and also to determine the gradient of blood pressure in the capillary network itself. Micropipettes, their movement governed by a Chambers micromanipulator, are inserted into individual capillaries. The other end of the micropipette is connected with a water or mercury manometer and with a device for changing pressure within these pipettes and the manometer system. When equilibrium is established corpuscles oscillate freely with the pulse but move neither toward nor away from the tip of the pipette. Blockage of flow is to be carefully avoided to prevent the recording of erroneously high values. This procedure with due precaution fulfills the requirements outlined above for a true "direct" measurement and provides results which are most nearly free from criticism (Krogh, 1929; Strax and De Graff, 1931; Drinker and Field, 1933). Skin resistance and the danger of obstruction to flow are eliminated. When measurements are first made a transitory rise of pressure owing to stimulation of the axone reflex sometimes appears, but this lasts only a few minutes after which a lower, and presumably normal, capillary pressure can be measured repeatedly over extended periods. Ellis and Weiss (1929) have criticized the use of nail bed capillaries,—the only easily accessible ones in man,—on the basis of possible abnormalities because of exposure to light and variations in temperature. The direct method is not suited to clinical measurements since only a few capillaries can be pierced in the course of an hour and averages are unjustified unless large numbers of determinations have been made.

Fewer indirect determinations of capillary blood pressure have been made in lower animals and the results are discordant. Roy and Brown (1875) used a capsule with a distensible membrane and obstructed flow completely. They recorded relatively high pressures in the capillaries of the frog's web, tongue and mesentery. Hill (1921a, 1921b) used the same apparatus but regarded the true capillary pressure to be that pressure which, when suddenly applied, momentarily modified, but did not stop, capillary flow. He recorded pressures in the web, mesentery and tongue of the frog which were only one-third to one-sixth as great as

those recorded by Roy and Brown,—lower in fact than the venous pressures observed by direct methods (Landis, 1926). The wide discrepancy in the results obtained with the same apparatus, and in the same animal, emphasizes again the purely arbitrary nature of the criterion of balance between extravascular and intravascular pressures when measured indirectly. Micro-cannulation (Landis, 1926, 1931) indicated that average capillary pressure in the frog lies between these two extremes. This direct method, though carried out without obstruction to flow, has been criticized on the ground that the tissues investigated are exposed and abnormal. However, injury of the skin (Landis, 1930b) and tetanus of muscle elevates capillary pressure well above the normal level (Landis, 1931) so that the permanent effects of exposure cannot be very great.

Summary. The indirect methods of measuring capillary blood pressure have yielded figures which vary so widely that it is impossible to draw conclusions concerning either the absolute level or the gradient of capillary blood pressure. The direct micro-injection method, though technically difficult, yields more exact information because there is less doubt concerning the pressure required accurately to balance the blood pressure in single capillaries. The direct method also permits determining the gradient of blood pressure in the peripheral vessels.

b. *The average gradient of capillary blood pressure.* In agreement with Levy (1897) and Dale and Richards (1919) it was found in the mesentery (Landis, 1926), web and muscle (Landis, 1931) of frogs, in the mesentery of the rat and guinea pig (Landis, 1930a) and in the skin of man (Landis, 1930b) that the fall in blood pressure does not cease at the junction of the arterioles and capillaries but continues through the capillary network. In exposed tissues 20 to 30 per cent of the peripheral resistance to blood flow is situated in the capillaries. As shown in figure 1 the blood pressure decreases but slightly in the larger arteries; the gradient is steepest in the arterioles, but continues through the capillaries. The four curves are similar in form, differing, however, in the levels at which blood pressure is maintained.

A fall of pressure amounting to only a few millimeters of water is, in fact, not enough to produce the average rates of flow observed in the frog's mesentery. Cinematographic recording of the flow of an opaque substance through the frog's mesenteric capillaries indicated that the drop in capillary pressure cannot be less than 1.0 to 2.0 cm. of water and is considerably higher when allowance is made for theoretical difficulties encountered in applying Poiseuille's equation to the capillary circulation (Landis, 1933). The results of calculation and direct observation agree

in indicating that arteriolar capillary pressure is higher than venous capillary pressure by a significant amount.

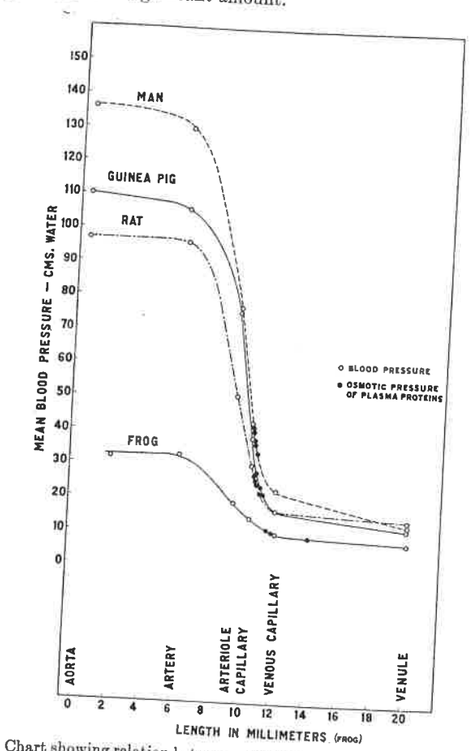

Fig. 1. Chart showing relation between capillary blood pressure and the osmotic pressure of the plasma proteins in four species.

In the frog, for instance, average arteriolar capillary pressure is 14 cm. of water while venous capillary pressure is 10 cm. of water. In man the arterial capillary pressure amounts, on the average, to 45 cm. of

water, venous capillary pressure to about 22 cm. of water. The blood colloid osmotic pressures of these two species show corresponding differences (table 2). The normal colloid osmotic pressure of frog plasma has been variously reported to range from 5.5 to 13.4 cm. of water while the colloid osmotic pressure of human blood amounts to about 36 cm. of water. The rat and guinea pig occupy an intermediate position with regard to both capillary pressure and the colloid osmotic pressures of

TABLE 2

Blood colloid osmotic pressure and capillary pressure (micro-injection determinations)

ANIMAL	COLLOID OSMOTIC PRESSURE OF BLOOD	AVERAGE BLOOD PRESSURE		TISSUE
		Arteriolar capillary	Venous capillary	
	cm. water	*cm. water*	*cm. water*	
Frog	5.5–6.0 (Krogh, 1922)	14.4	10.1	Mesentery (Landis, 1926)
	*6.8–13.4 (Churchill, Nakazawa and Drinker, 1927)	14.9	9.5	Muscle (Landis, 1931)
	†9.6–11.5 (White, 1924a) 11.7 (Landis, 1927b)	14.5	10.0	Skin (Landis; 1931)
Rat	22.0–26.5 (Landis, 1930a) 24.0–29.0 (Meyer, 1932)	30.0	17.0	Mesentery (Landis, 1930a)
Guinea pig	22.5–27.5 (Landis, 1930a) 24.0–25.0 (Kylin and v. Pein, 1931) 25.0–28.0 (Meyer, 1932)	38.5	17.0	Mesentery (Landis, 1930a)
Man	33.0–40.0 (Starling, 1895–6) 35.0–40.0 (Govaerts, 1924) 28.5–36.5 (Schade and Claussen, 1924) 33.0–40.0 (Verney, 1926) 29.5–39.0 (Krogh and Nakazawa, 1927) For others see Meyer (1932)	43.5	16.5	Skin, base of nail (Landis, 1930b)

* Normal frogs only.
† Cm. plasma.

their bloods. The gradient of capillary pressure in at least four species is such that on the average arteriolar capillary pressure is above the osmotic pressure of the plasma colloids while average venous capillary pressure is below the osmotic pressure of the plasma colloids (fig. 1; table 2). It is physically possible, therefore, that on the average, fluid is filtered from blood during its passage through the arteriolar portion of the capillary network while absorption takes place in the venous portion of the capillary network. Though this represents the average condition,

fluid movement in individual capillaries will diverge from the average in accordance with variations in capillary pressure, diameter and flow.

Summary. The peripheral fall in blood pressure does not cease at the junction of the arterioles and capillaries, but continues through the capillary network. In four species studied by the micro-cannulation method, average capillary pressure is approximately equivalent to the colloid osmotic pressure of the plasma proteins. Owing to the gradient of capillary pressure, under average conditions filtration is favored in the arteriolar portion of the capillary network, while absorption is favored in the venous portion of the capillary network.

TABLE 3

Variations in capillary pressure

	CAPILLARY PRESSURE					
	Arteriolar capillary			Venous capillary		
	Highest	Lowest	Average	Highest	Lowest	Average
	cm. water	*cm. water*	*cm. water*	*cm. water*	*cm. water*	*cm. water*
Frog, mesentery						
web, normal.	22.0	5.0	14.4	18.0	6.7	10.1
urethane	19.0	10.0	13.9	13.0	8.5	9.6
curare	20.5	10.0	14.5	15.5	8.5	10.0
web, hyperemia	26.5	14.0	19.5	17.5	15.0	16.5
muscle, normal	18.0	11.0	14.9	12.7	7.0	9.5
hyperemia	26.0	17.0	20.1	17.5	12.0	16.0
Rat, mesentery	34.0	22.0	30.0	20.0	15.0	17.0
Guinea pig, mesentery	49.0	31.0	38.5	19.5	13.0	17.0
Man, skin, normal	65.0	28.6	43.5	24.5	8.0	16.5
hyperemia	93.0	71.0		66.5	54.5	

c. *The variability of capillary blood pressure.* The capillary pressures recorded in table 2 and in figure 1 represent averages of numerous single determinations. Capillary pressure is, however, an extremely variable quantity, changing in the same capillary from moment to moment and differing widely in adjacent capillaries connected to the same arteriole (Roy and Brown, 1875; Landis, 1926). Table 3 shows that these variations, spontaneous or induced, are so large that blood pressure in an

entire capillary, or even in a whole network, may be at one moment above, at another below, the colloid osmotic pressure of the blood.

Arteriolar constriction increases the peripheral resistance and then capillary pressure becomes lower throughout the affected area, irrespective of capillary diameter. Pulse pressure in the capillary network decreases while the gradient of blood pressure becomes steeper in the arterioles and flatter in the capillaries. These changes were observed by Landis (1926) in the frog's mesentery after hemorrhage and during constriction produced by adrenalin. Raynaud's disease in man is a condition characterized by arterial spasm followed by arterial relaxation and reactive hyperemia. During spasm capillary pressure is low,—7 to 8 mm. Hg—and pulse pressure is small, while during arterial relaxation capillary pressure may reach 40 mm. Hg with a large pulse pressure (Landis, 1930c).

Dilatation of the arterioles shifts the peripheral fall of blood pressure toward the capillary network, elevates capillary pressure, and increases the pulse pressure in the capillary vessels. These effects were observed by direct measurement during hyperemia of the frog's mesentery (Landis, 1926), muscle and skin (Landis, 1931). In man cutaneous capillary pressure rises during hyperemia produced by heat (Goldmann, 1914; Danzer and Hooker, 1920; Lewis and Haynal, 1928; Landis, 1930b), histamin (Lewis and Haynal, 1928; Landis, 1930b) and acute inflammation (Landis, 1930b). In every instance blood flow becomes more rapid and pulse pressure increases. The appearance of capillary pulsation in normal individuals after heating the skin (Lewis, 1924) is in accord with these findings, the pulse penetrating even to the subpapillary venous plexus (Boas, 1922b). The changes in capillary pressure accompanying arteriolar constriction and dilatation verify the conclusions of Bayliss and Starling (1894) who pointed out the fallacy of arguing that capillary pressure must necessarily follow arterial pressure. Adrenalin elevates arterial pressure but lowers capillary pressure. Vasodilatation, if widespread, lowers arterial and capillary pressures but may elevate capillary pressure locally if systemic blood pressure is not reduced too greatly.

When capillary pressure is elevated by arteriolar dilatation, whether spontaneous or induced, the rate of capillary blood flow is increased, the relation between flow and pressure being often extremely close (Landis, 1926). Capillary blood flow, while usually constant, often shows rhythmic increase in velocity during cardiac systole (Hürthle, 1923). This pulse, like pulse pressure measured directly (Landis, 1930b), penetrates at times to the venous capillaries.

A rise of venous pressure elevates capillary pressure (Danzer and Hooker, 1920; Liebesny, 1923; Carrier and Rehberg, 1923; Lewis and Haynal, 1928; Landis, 1930b) even when the obstruction involves only a few veins or venules (Landis, 1926). If the veins of the upper arm are compressed by a pneumatic cuff of sufficient width capillary pressure equals or slightly exceeds the pressure in the cuff within 15 to 45 seconds. It is impossible for capillary pressure to be below venous pressure except for very brief periods. The effects of the Valsalva experiment on capillary pressure (Danzer and Hooker, 1920; Landis, 1930b) can be ascribed to the rise of venous pressure.

Likewise capillary pressure is high in dependent parts of the body owing primarily to the hydrostatic pressure of the blood in the vertically placed veins. Carrier and Rehberg (1923) and Landis (1930b) found that when the hand is above the base of the heart capillary pressure remains at a low but constant level in all positions. The discrepancy in the absolute pressures observed is to be ascribed to the brief periods of cannulation used by Carrier and Rehberg. Both sets of figures agree in showing that when the hand is dropped below the heart the increase of capillary pressure is almost identical with the theoretical increment due to the hydrostatic pressure of the column of venous blood. Thus according to Landis (1930b) if the hand is held quietly 30 cm. above the base of the heart capillary pressure in the arteriolar and venous capillary limb falls below the colloid osmotic pressure of the blood. If the hand is 40 cm. below the heart, pressure, even in the venous capillary, is above the colloid osmotic pressure of the blood.

Local heating produces hyperemia and elevates capillary pressure (Danzer and Hooker, 1920; Lewis and Haynal, 1928; Landis, 1930b), while cold diminishes capillary pressure during the first few minutes (Danzer and Hooker, 1920; Landis, 1930b), though when reactive hyperemia sets in capillary pressure may rise (Landis, 1930b). Diurnal variations in capillary pressure may or may not exist (Danzer and Hooker, 1920; Kylin, 1926). Innervation affects capillary pressure which rises when the axone reflex is stimulated (Landis, 1930b, 1931). In hemiplegia blood flow is rapid in the affected extremity and capillary pressure high (Weiss and Ellis, 1931).

Summary. Capillary pressure is extremely variable; its changes cannot always be predicted by measuring arterial pressure. The height of capillary pressure depends upon arterial tone, freedom of venous outflow, posture and temperature,—to mention only those factors which have been studied in detail. Blood pressure in an entire capillary, or

even in a whole network, may be at one moment far above, at another far below, the colloid osmotic pressure of the blood, favoring massive filtration or massive reabsorption, respectively, over large areas of endothelium.

d. *Capillary blood pressure and fluid movement.* The indecisive results of older experiments on the qualitative changes in fluid movement produced by changes in arterial pressure have been reviewed by Oehme (1928). Elevating arterial pressure for very brief periods of time by compressing the aorta is not accompanied by loss of fluid from the blood, according to Tani (1924), but Adolph and Lepore (1931) were able to detect an increase in the water content of the tissues. Lymph flow is not increased by elevating arterial pressure until very high levels are reached, when arteriolar resistance appears to break down (Haynes, 1932a). Scott, Rabinowitz and Rupp (1923) state, on the other hand, that elevating systemic blood pressure by injecting adrenalin increases the concentration of Congo red in the plasma, and conclude that fluid leaves the blood stream, the colloidal dye leaving more slowly than fluid. The frequent independence of arterial and capillary pressures probably explains the varying results.

Active hyperemia elevates capillary pressure and would therefore be expected to facilitate filtration. Stimulating the lingual nerve produces active hyperemia of the tongue, but edema appears regularly only in the presence of hydremic plethora (Starling, 1894). It must be remembered, however, that tissue volume must be increased by 10 per cent before edema is grossly detectable (Drury and Jones, 1927). The active hyperemia accompanying heating of the skin favors the passage of dyes from the blood stream (Okuneff, 1924; Anitschkov, 1924; Hudack and McMaster, 1932) but damage to the capillary wall is also a possible factor. Nerve section produces more general staining by intravenously administered dye (McMaster, Hudack and Rous, 1932) but does not affect lymph production in the dog's leg (Haynes, 1932a). Vasodilator drugs increase the conjunctival edema produced by mustard oil only when they also raise capillary pressure; the vasodilator drugs lose their effect on fluid movement when systemic blood pressure falls (Hirschfelder, 1924). The active hyperemia which accompanies functional activity is complicated by metabolic factors and will be considered in a later section.

Arteriolar constriction produced by adrenalin or by cocaine diminishes the conjunctival edema produced by mustard oil (Hirschfelder, 1924). The loss of fluid in paraphenylenediamine edema is diminished by a drop

in systemic blood pressure or by the administration of adrenalin (Tainter and Hanzlik, 1924). The injection of pituitrin, which increases vascular tone in mammals, diminishes lymph flow and delays the exit of salt solution from the blood stream according to Bayley et al. (1925). Hemorrhage which reduces capillary blood pressure (Landis, 1926) withdraws fluid from the tissue spaces of the dog at the rate of 0.25 cc. per kilo of body weight per minute corresponding to a (calculated) fall in capillary pressure of 28 cm. water (Adolph, Gerbasi and Lepore, 1933). The effects of arterial tone on fluid movement are therefore not absolutely uniform, but in general vasodilatation appears to favor filtration while vasoconstriction appears to hinder filtration.

The qualitative effects of elevating venous pressure, and therefore capillary pressure, are more uniform. Lymph flow from the thoracic duct increases when abdominal venous pressure is raised (Starling, 1894). Similarly subcutaneous lymph flows more rapidly during venous congestion (White, Field and Drinker, 1933) and when the limb is dependent. Venous congestion elevates the protein and hemoglobin concentration of the blood (Yamaguchi, 1927a, b; Plass and Rourke, 1927) roughly in proportion to the venous pressure (Landis, Jonas, Angevine and Erb, 1932). Venous congestion, according to McMaster, Hudack, and Rous (1932) increases also the amount of dye passing into the tissue spaces after intravenous injection. Postural increase of venous pressure concentrates the plasma proteins generally (Thompson, Thompson and Dailey, 1927–28; Waterfield, 1931) and particularly locally in the vessels of dependent tissues (Youmans et al., 1933). The volume of the leg increases owing to the accumulation of fluids in the tissue spaces (Waterfield, 1931b). Partial obstruction of the vena cava leads to ascites even in the presence of normal lymphatic drainage (Bolton, 1924). Perfusing the dog's leg with defibrinated blood produces edema if venous pressure is above 10 mm. Hg; at venous pressures below this no true edema develops though a small amount of fluid leaves the blood (Bornstein and Budelman, 1930). Loss of fluid from blood by filtration is detected consistently therefore when capillary pressure is elevated by raising venous pressure. These observations show, however, only a qualitative relationship between hydrostatic pressure and filtration. Other things remaining constant it would be expected, in the presence of an inert capillary wall, that filtration must be directly proportional to the hydrostatic pressure exerted upon the capillary blood.

Micro-injection experiments on single capillaries in the frog's mesentery (Landis, 1927b) indicate that in this animal and tissue, when the hydrostatic pressure falls below 9 cm. of water, fluid moves from the extravascular spaces into the blood. When capillary pressure is above 12.5 cm. of water fluid moves from the blood to the tissue spaces. The rate of absorption and the rate of filtration are roughly proportional to the difference between capillary pressure and 11.5 cm. of water. When the rate of filtration or absorption is charted against capillary pressure a straight line can be drawn through the points, indicating that the rate of fluid movement, when studied in single capillaries, is directly proportional to hydrostatic pressure.

In normal human subjects Mende (1919) observed the effect on limb girth of raising venous pressure by means of a narrow rubber cuff inflated to various pressures. He concluded that a venous pressure of 50 cm. was required to produce the first measurable filtration of fluid. This method of identifying increase in limb volume is so rough that small accumulations of fluid might easily have been overlooked. Drury and Jones (1927) measured the rate of filtration in the lower extremities by means of a water plethysmograph during venous congestion. They found that the rate of filtration was roughly proportional to the increase in venous pressure. They were not able, however, to measure filtration during the first ten minutes of venous congestion on account of the time required for the congested veins to fill completely with blood. Krogh, Landis and Turner (1932) used a "pressure plethysmograph" by means of which volume changes due to vascular tone were eliminated during the time that limb volume was being measured. In this way small accumulations of fluid were estimated and filtration rates were measured even during the first minutes of venous congestion. No filtration of fluid could be detected by this method until venous pressure was above 15 cm. of water. Later observations by Landis and Gibbon (1933) with still another type of "pressure plethysmograph" yielded essentially the same result. When venous pressure in the forearm was elevated to various levels above this so-called "margin of safety" the rate of filtration was directly proportional to the increase in venous pressure, at least up to the highest pressure tested, 80 cm. of water. The change in the rate of filtration accompanying unit rise (1 cm. of water) in venous pressure amounted to between 0.0023 and 0.0028 cc. per minute per 100 cc. of forearm when the congestion periods were thirty minutes long (Krogh et al., 1932; Landis and Gibbon, 1933) and to 0.0033 cc. per minute per 100 cc. of forearm when the congestion periods were ten minutes long (Landis and Gibbon, 1933).

Summary. The movement of fluid from blood to tissue spaces varies

considerably with circulatory adjustments and particularly with capillary pressure. High arterial pressure and active hyperemia usually, but not always, increase the filtration of fluid. Elevating venous pressure is always associated with increased filtration, the rate of filtration being proportional, within certain limits, to the venous pressure.

2. *The colloid osmotic pressure of the blood.* Though Graham (1861) mentioned that the plasma colloids might exert an osmotic pressure in the vascular system, it remained for Starling (1896) to measure the magnitude of this force in the blood plasma. This subject, reviewed in detail by Meyer (1932), will be considered here only in its relation to the movement of fluid and dissolved substances through the walls of the systemic capillaries.

The balance between colloid osmotic pressure and capillary blood pressure (Landis, 1926, 1930a, c) offers presumptive evidence that the plasma proteins aid in controlling fluid movement. The association of a low colloid osmotic pressure of the blood with certain forms of edema occurring as a result of disease in man (Krogh, 1922; Govaerts, 1924; Schade and Claussen, 1924; and others) also suggests, but does not prove conclusively, that movement of fluid through the capillary wall is related to the colloid osmotic pressure of the blood. In dogs Leiter (1928, 1931) showed that chronic hypoproteinemia produced by plasmapheresis leads to the accumulation of extravascular fluid with outspoken edema when the plasma protein falls to 3 per cent or less. The relation between hypoproteinemia and edema was verified in plasmapheresis by Shelburne and Egloff (1931), Lepore (1931, 1932), Darrow, Hopper and Cary (1932a, b), Weech, Snelling and Goettsch (1933), and in experimental malnutrition by Kohman (1920), Frisch, Mendel and Peters (1929), Shelburne and Egloff (1931), and Weech, Snelling and Goettsch (1933). Even in the presence of a low plasma protein, however, edema cannot develop without an adequate supply of salt and water (Leiter, 1928; Fahr, Kerkhof and Giere, 1931; Weech, Snelling and Goettsch, 1933). Clinical experience in the treatment of edema has shown empirically that a physical "tendency toward edema" can be neutralized by restricting the intake of salt and water or by increasing the excretion of water and salt by means of diuretics. Plasmapheresis also increases lymph flow considerably (Field and Drinker, 1931a) and a low plasma protein favors the movement of dye into the tissue spaces (Smith and Dick, 1932).

Drinker (1927) observed that the addition of relatively large quantities of horse serum to the perfusing fluid prevents subcutaneous edema from

appearing in the perfused leg of the frog. He concluded that the force which retains fluid within the blood vessels is associated with the protein, but found no evidence that the favorable effect of serum is due to the colloid osmotic pressure of the perfusing fluid. The large amount of protein required in Drinker's experiments may, however, be related to the greater permeability of the capillary walls of the frog, particularly after perfusion (Conklin, 1930b) of the skin vessels. Leakage of protein would diminish the effective colloid osmotic pressure to a point considerably below the colloid osmotic pressure measured *in vitro*. Under these conditions higher concentrations of protein would be required to prevent edema. Kitmura (1927) states that the effect of colloids upon the accumulation of edema fluid in the perfused frog's leg depends upon whether the colloid is, or is not, retained in the blood vessels.

Abnormal filtration can be prevented in mammals by injecting acacia, even though the proteins are reduced. Fahr and Kerkhof (1933) produced hypoproteinemia by plasmapheresis but prevented edema from appearing by substituting gum acacia for the missing protein. Though edema is produced by lowering the protein content of the blood, it is the low colloid osmotic pressure of the blood and not the loss of protein as such that is responsible for the edema.

The addition of plasma protein in the form of blood transfusions can aid in producing diuresis and subsidence of the edema accompanying nutritional hypoproteinemia (Landis and Leopold, 1930), though it is usually of no value in nephrosis due to the copious albuminuria characteristic of the latter condition. Hartman and Senn (1932) raised the colloid osmotic pressure of the blood in nephrosis by intravenous injection of gum acacia and observed subsequent diuresis and subsidence of edema. Weech, Goettsch and Reeves (1933) failed to obtain a similar effect with serum transfusions in edematous dogs, the amount of serum transfused being, however, too small to raise plasma albumin concentration to anything approximating normal value. Hyperproteinemia diminishes for a time the total amount of dye leaving the circulation (Smith and Dick, 1932) but this is ascribed to binding of dye by protein.

The observations so far cited provide qualitative evidence that the plasma proteins are concerned with the movement of fluid through the capillary wall under abnormal conditions. Krogh, Landis and Turner (1932) studied quantitatively in normal subjects the effect on fluid movement of changing the colloid osmotic pressure of the blood. Quiet standing increases the amount of protein in the circulating blood since protein-poor fluid is filtered from the blood into the dependent tissues.

By comparing the filtration produced in the forearm by a given venous pressure while the subject stood and reclined it was possible to determine the effects which measured changes in colloid osmotic pressure exert on filtration rate. A unit rise (1 cm. water) of venous pressure increased filtration by average values between 0.0023 and 0.0033 cc. per minute per 100 cc. of forearm. In six experiments a unit rise (1 cm. water) of colloid osmotic pressure diminished filtration by 0.0027 to 0.0045 cc. per minute per 100 cc. of forearm.

Summary. The available evidence, direct and indirect, indicates that the colloid osmotic pressure of the blood retains fluid within the vascular system and acts quantitatively in opposition to capillary pressure. In accord with physical principles the effects of capillary pressure and colloid osmotic pressure are opposite in sign but have the same order of magnitude.

3. *Impermeability of the capillary wall to plasma proteins.* To use the term "permeability" in accordance with the definition given on page 404 requires under the simplest possible conditions information concerning at least four quantities,—mass, area, time and pressure. When the permeability of the capillary wall is studied many additional factors affect the movement of substances. So complicated are the forces involved that it is doubtful whether use of the term "capillary permeability" has ever been based on completely adequate information. Thus alterations in the vitality of the capillary wall, internal and external hydrostatic or osmotic pressures, changing area, reabsorption, and staining affinities have each, at one time or another, obscured a complete understanding of the true properties of the endothelium itself.

It is generally agreed that crystalloids pass through the capillary walls with ease and, with greater or less rapidity, reach an equal concentration inside and outside the endothelial barrier separating blood and tissue fluid. When concentration is thus equalized crystalloids can no longer influence the movement of fluid through the capillary wall, though they do affect fluid movement temporarily before this equalization of concentration is reached. Under conditions of equilibrium, however, the transfer of fluids through the endothelium will depend in part upon the colloids inside and outside the capillary. The colloid osmotic pressure of blood when measured *in vitro*, is determined with an artificial membrane wholly impermeable to proteins. To apply these measurements to biological problems requires specific information concerning the permeability of the capillary wall to the plasma proteins.

During inflammation the endothelium permits leucocytes to pass;

yet potential fissures, if present in the capillary wall, play no part in the filtration of fluid or dyes under ordinary circumstances. Krogh (1929) describes the retention of dialyzed and filtered India ink within capillaries while plasma is completely filtered off after the application of urethane. Ink particles are retained also after chemical and mechanical injury of the endothelium (Landis, 1927a), indicating that even the damaged capillary wall can hold back particles having an average diameter of 200 millimicra. Florey (1926a) perfused the intestinal blood vessels of the dog with potassium ferrocyanide and iron ammonium citrate, fixing the tissue immediately afterward by perfusing with formalin and HCl. Prussian blue was distributed equally through the endothelial cells except for the nuclei. During inflammation the perfusion of starch and fixation with formalin and iodine showed starch within the cytoplasm of the endothelial cells, but the deposit was more copious on the inner side. Both substances passed into and through the capillary wall diffusely, without evidence of microscopically visible fissures or pores. Whatever may be the mechanism by which leucocytes pass through the capillary wall, it appears in the light of present information to have no direct relation to the normal filtration of fluid and dissolved substances.

The permeability of the capillary wall to protein could be defined easily and exactly if a true capillary filtrate were obtainable. The three fluids which can be distinguished are *a*, blood plasma within the capillary; *b*, tissue fluid bathing the external surface of the capillary, and *c*, lymph collected from small or large lymphatic ducts. Normal tissue fluid exists in very small amounts and consists probably of the original capillary filtrate mixed with capillary filtrate which has been modified by partial reabsorption. Lymph consists of tissue fluid which, after bathing the cells of the tissue, passes through the lymphatic endothelium and usually through lymph glands, all involving possible modifications in composition (Starling, 1909). The inaccessibility of the essential capillary filtrate and the minute size of the capillaries require that information concerning endothelial permeability be gathered primarily by indirect methods. Tissue fluid offers the nearest approach to capillary filtrate but reabsorption often plays a part in determining its composition and the amount of tissue fluid is normally so small that its analysis has so far not been accomplished. Endothelial permeability to protein has been perforce studied indirectly by analysis of *a*, edema fluid; *b*, blood collected under varying conditions, and *c*, lymph.

The concept of fluid balance proposed by Starling (1896) and elaborated

by Schade (1927) was used by Drinker and Field (1931) to explain the relation between capillary filtrate, tissue fluid and lymph. To use the words of the last-mentioned authors, a possible mechanism of lymph formation is . . . "that the filtrate from the blood capillaries to the tissue spaces contains water, salts and sugar in the concentrations found in the blood, together with serum globulin, serum albumin and fibrinogen in low concentration, lower probably than that of tissue fluid and lymph; that water and salts are reabsorbed by the blood vessels and the protein enters the lymphatics together with water and salts in the concentration existing in the tissue fluid at the moment of lymphatic entrance." Except for protein and the substances combined with protein (calcium and total phosphorus) the concentrations of the constituents investigated are nearly the same in plasma and subcutaneous lymph (Heim, 1933). Lymph also reflects very rapidly changes in the diffusible constituents of serum (Arnold and Mendel, 1927; Heim and Berg, 1933). The difference between normal tissue fluid and true capillary filtrate is due therefore primarily to reabsorption of water and crystalloids with simultaneous concentration of the protein in the extravascular fluid. The analysis of extravascular fluid, which has accumulated when reabsorption is completely prevented, should provide the most accurate estimate of the amount of protein leaking through the capillary wall.

In advanced nephrosis and malnutrition the colloid osmotic pressure of the blood is apt to be lower than capillary pressure. Reabsorption by purely physical forces is then impossible and the edema fluid thus produced should, in the absence of secretory activity on the part of the capillary wall, resemble the original capillary filtrate. The proteins of edema fluid are physically similar to those of blood plasma (Cavett and Gibson, 1931). If the protein content of edema fluid is expressed in terms of percentage of plasma protein the efficiency of the capillary wall in retaining plasma protein can be estimated. The objection may be raised that in edema the vascular endothelium is abnormal, but capillary injury has thus far been found always to be associated with increased capillary permeability. The protein content of the edema fluid would then be, if anything, greater than that of normal capillary filtrate. It is also true that the plasma proteins are reduced in nephrosis and malnutrition so that less protein would be expected in the edema fluid, but this error can be avoided by comparing the protein content of edema fluid with the corresponding plasma protein.

Beckmann (1921) found that subcutaneous edema fluid, in cases of "tubular nephritis" and amyloid kidney, contains under 0.1 per cent of

protein. Vančura (1931) observed in nephrosis 0.14 to 0.49 per cent protein. The colloid osmotic pressure of certain edema fluids is too small to measure accurately (Schade and Claussen, 1924). Landis and Leopold (1930) examined the ascitic fluid in a case of malnutrition and found 0.04 per cent protein while Meyer and Friedheim (1931) found in nephrosis from 0.15 to 0.27 per cent protein. The protein in peritoneal fluid remains low while fluid is moving into and out of the blood stream (Schechter, 1931). Landis et al. (1932) stated that the subcutaneous edema fluid of a nephrotic patient contained 0.09 per cent protein with a plasma protein of 3.7 per cent, indicating that the capillary wall retained over 95 per cent of the blood protein.

In chronic plasmapheresis also the edema fluid contains less than 0.25 per cent protein and at times less than 0.1 per cent (Leiter, 1928; Shelburne and Egloff, 1931). In another series of experiments ascitic fluid contained between 0.10 and 0.75 per cent protein with an average of 0.36 compared to an average serum protein of 5.88 per cent,—showing nearly 95 per cent retention (Greene et al., 1931).

Venous congestion also reduces to a minimum the absorption of fluid from the capillary filtrate since capillary pressure is raised above the colloid osmotic pressure of the plasma proteins. According to Beckmann (1921) edema fluid removed from patients with cardiac decompensation contains from 0.1 to 1.0 per cent protein with an average of 0.4 per cent. Landis et al. (1932) found edema fluid produced by local venous obstruction contained 0.29 per cent protein with a plasma protein of 6.64,—nearly 95 per cent of the blood protein being retained.

Inflammatory conditions and, to a less extent, cardiac decompensation generally produce edema fluids with a higher content of protein, the subcutaneous edema fluid containing in general less than collections in the serous cavities. Damage of the capillary wall is held to be responsible for the high protein content of inflammatory exudates. It is likely, therefore, that the lowest figures obtainable in studies of transudates (during their formation and before reabsorption begins) represent most nearly the protein content of normal capillary filtrate. At least these studies of edema fluid indicate that the capillary wall can, and in the absence of injury often does, retain approximately 95 per cent of the plasma protein.

Capillary permeability to protein has been estimated also by observing modifications in the concentrations of erythrocytes and blood proteins under various conditions. Such studies are made difficult, however, by the constantly varying diameter, pressures, and flow in the vessels which form the capillary network. To reduce the number of variables Landis

(1927b) studied, by a micro-injection method, the relation which capillary blood pressure bears to the direction and rate of fluid movement through the walls of single capillaries in the frog's mesentery. In this tissue, when capillary pressure exceeds 12.0 cm. of water, filtration occurs, the rate of filtration being proportional to the difference between capillary pressure and 11.5 cm. of water. When capillary pressure is below 9.0 cm. absorption occurs. Since neither absorption nor filtration occur with capillary pressures in the vicinity of 11.5 cm. of water, this figure represents the effective colloid osmotic pressure of frog's blood in the mesenteric capillaries. This value, determined *in vivo*, agreed approximately with the colloid osmotic pressure of frog's plasma measured *in vitro* by White (1924a). Much lower (and occasionally much higher) colloid osmotic pressures have been reported for frog's plasma by Krogh (1922) and by Churchill, Nakazawa and Drinker (1927) explaining (vid. inf.) the variable and often high rates of lymph formation in this animal.

According to Yamaguchi (1927a) the increase in plasma protein relative to erythrocytes during venous congestion in dogs and man indicates that the capillary wall of mammals is only slightly permeable to protein. The fluid lost from the blood stream of men during venous congestion produced by quiet standing was stated to be practically protein-free by Thompson, Thompson and Dailey (1927), while Waterfield (1931a) concluded that only globulin was held back, the albumin leaking through the capillary wall. Landis, et al. (1932) observed in human subjects that at very high venous pressures (80 mm. mercury or more) considerable protein passes through the walls of the capillaries in the forearm, though at lower venous pressures the capillary wall remains relatively impermeable to protein. This last observation and the use of different methods of determining blood volume may explain the discrepancy in findings during quiet standing.

If large amounts of protein were lost through the normal capillary wall it would be expected that raising colloid osmotic pressure by a given amount should affect the rate of filtration very much less than changing venous pressure by a similar amount. In observations on man Krogh, Landis and Turner (1932) found it difficult to associate the quantitatively similar effects of changing venous pressure and colloid osmotic pressure with any considerable leakage of proteins through the human capillary wall. Landis, Jonas, Angevine and Erb (1932) elevated venous pressure to 20, 40, 60 and 80 mm. of mercury and calculated from hematocrit determinations and analyses of plasma protein the amount of fluid and

protein lost during filtration. At venous pressures up to 60 mm. of mercury the amount of protein in the capillary filtrate was calculated to range from 0.0 to 0.7 per cent with an average of 0.3 per cent. It was concluded that during mild venous congestion the capillary wall retains approximately 95 per cent of the blood protein.

Analyses of lymph represent a third source of information concerning capillary permeability to protein. The mechanism of lymph formation has been reviewed recently by Drinker and Field (1933). Since lymph represents the original capillary filtrate modified by more or less reabsorption of fluid, caution must be used in estimating from analyses of lymph the constitution of the original capillary filtrate and therefore the true permeability of the capillary wall to protein.

Starling (1894), on the basis of analyses of lymph in dogs, stressed the differences in the permeability to protein exhibited by the capillaries of the limbs, intestine and liver. Regional differences exist also in the capillaries of the frog. Freund (1922) found the capillaries of the frog's hind limb, including chiefly muscle, are impermeable to protein under normal conditions though they become permeable after the injection of arsenic. According to Pak (1926) the capillaries of the hind leg of the frog retain Congo red and permit ammonium chloride, urea, glucose and certain alkaloids to pass with great ease. While micro-injection measurements of filtration and absorption (Landis, 1927b) indicated that the capillaries of the frog's mesentery are practically impermeable to protein, Churchill, Nakazawa and Drinker (1927) found simultaneously that subcutaneous lymph in the frog contains normally from 0.29 to 2.17 per cent of protein derived from leakage of plasma protein through the permeable cutaneous capillaries. This cutaneous lymph has an average osmotic pressure of 4.2 cm. water compared to 7.1 cm. for the blood serum. Since the average cutaneous capillary pressure is between 10 and 14 cm. water (Landis, 1931), fluid must be filtered throughout the entire capillary network of the skin. Lymph should therefore be produced in large amounts and, in the absence of reabsorption, its protein content measures directly the permeability of the cutaneous capillaries to protein.

Isayama (1924a, b) dissected out the lymph hearts of frogs and estimated, from temporary changes in the erythrocyte count of the blood, that in twenty-four hours a volume of fluid equivalent to 50 times the blood volume may pass out of the blood capillaries. Essentially similar findings were reported by Ito (1926). Conklin (1930a) collected lymph from the crural sacs and found that fluid leaves the blood at rates cor-

responding to the filtration of seven to forty times the calculated blood volume in twenty-four hours. Curarization, which stops the lymph hearts, produces edema and elevates body weight by 10 to 32 per cent in six hours. When edema is produced by injecting Ringer's fluid into the circulation the skin absorbs most fluid,—indicating, like the studies of lymph, that the cutaneous capillaries of the frog retain less fluid than capillaries elsewhere. The combination of highly permeable cutaneous capillaries with lymph hearts and rapid circulation of body fluids represents, therefore, a specialized mechanism, which must be kept in mind in studies of fluid balance in amphibians.

The easy passage of proteins through the cutaneous capillary walls of the frog was demonstrated by Conklin (1930b). Intravenous injection of large quantities of Ringer's fluid produces a copious flow of protein-containing lymph and the blood protein may be reduced eventually to very low levels. Hemoglobin and hemocyanin pass easily, though egg albumin and gelatin pass with difficulty and then only after the endothelium has been rendered abnormally permeable by the injection of Ringer's fluid. These findings amply verify the statement of Drinker (1927) that the capillaries of the frog's foot may "leak protein-containing fluid at all diameters."

With such rapid movement of fluid from blood, through the capillary wall, into the lymph spaces it is entirely justifiable to assume that capillary filtrate, tissue fluid and lymph are practically identical under normal conditions (Drinker, 1927) since there is little or no opportunity for reabsorption of fluid from the original capillary filtrate. But this relation between capillary filtrate and lymph may well be limited to certain animals and tissues. If available data be accepted the same condition does not exist in the mesentery of the frog nor in the limbs of mammals, where protein is retained more completely and where reabsorption takes place.

Drinker and Field (1931) called attention to the high and variable concentration of protein in mammalian lymph, concluding that this protein must have passed through the capillary wall in order to reach the lymphatics. The presence of blood protein in lymph makes it unlikely that the capillary endothelium is totally impermeable to the plasma proteins, but it does not rule out the possibility that the original leakage of protein is extremely slight. It is also conceivable, though far from likely, that the tissue cells or lymphatics fabricate proteins which find their way into lymph.

The importance of the colloid osmotic pressure of the blood in determining the rate and direction of fluid movement depends upon the degree to which protein is retained by the capillary endothelium. If the capillary filtrate contains very small amounts of protein compared to the blood plasma the effective colloid osmotic pressure of the blood will be equal to the colloid osmotic pressure measured *in vitro*. On the other hand, if large amounts of protein are lost in the capillary filtrate the concept of a balance between capillary pressure and the colloid osmotic pressure of the blood becomes untenable.

The passage of protein through the capillary wall in immunologically detectable amounts has been demonstrated under normal and experimental conditions. Field and Drinker (1931a) injected sterile horse serum intravenously and demonstrated its presence in the cervical lymph within one to two hours by a precipitin reaction. Serum injected subcutaneously found its way rapidly into the lymphatics. The protein passes slowly through the capillary wall, and once outside the capillary it enters the lymphatics almost at once, the lymphatic endothelium being presumably freely permeable to protein. When horse serum is injected subcutaneously no absorption of foreign protein through the capillary wall is detected during periods up to an hour. This indicates either that the capillaries of the subcutaneous tissues are permeable to protein in one direction only or that extraneous physical forces deter protein from entering the blood stream. After plasmapheresis, however, when the plasma protein is reduced, and blood pressure lowered, foreign protein placed in the subcutaneous tissues can be detected serologically in the blood though entrance *via* lymphatics is avoided (Field and Drinker, 1931b). Hence Field and Drinker conclude that the capillary wall permits protein to pass in either direction as an inert membrane should, providing extraneous physical factors do not prevent such passage. This passage of protein takes place under exceptional circumstances; under normal conditions the capillary wall is not concerned with the removal of protein from the tissue spaces. Selective removal of protein from the tissue spaces by lymphatic endothelium has been suggested (Peters, 1933) but for this no direct evidence is available at present.

Qualitative passage of protein through the capillary wall into the lymph having been demonstrated, the amount of leakage of protein must be considered because of its relation to the effective colloid osmotic pressure of the blood. In considering the high and variable protein content of mammalian lymph Drinker and Field (1931) suggested that tissue fluid and lymph are identical on account of the ease with which large molecules and even particles enter the lymphatics. Motion or

massage causes the lymphatic wall to lose its anatomical integrity and to become continuous with the tissue spaces.

Churchill, Nakazawa and Drinker (1927) point out that in the frog the effective colloid osmotic pressure for restoring fluid to the capillary blood is the difference between the colloid osmotic pressure of the blood and that of subcutaneous lymph. This conclusion is justifiable for the cutaneous capillaries of the frog where fluid moves from blood to lymph channels rapidly with little or no reabsorption (Isayama, 1924; Ito, 1926; and Conklin, 1930a). This concept was applied by Loewen, Field and Drinker (1931) to the dog. The colloid osmotic pressure of the blood amounted to 37.7 cm. of water compared to 16.6 cm. water for cervical lymph. It was held that the effective colloid osmotic pressure for returning water to the blood is the difference between the colloid osmotic pressure of the blood and the lymph from the area under observation. This difference amounts to 21.1 cm. water, considerably less than 35–37 cm. water,—the colloid osmotic pressure of blood when measured *in vitro*. However, reabsorption is not absent nor is lymph commonly produced in mammals at a rate comparable to its flow in the frog. Assuming the correctness of the direct capillary pressure determinations in mammals, reabsorption by purely physical means would be almost impossible and fluid should be filtered constantly and rapidly from the cervical capillaries of the dog, whereas massage is usually required to obtain any lymph during rest.

If the effective colloid osmotic pressure of the blood were merely the difference between the colloid osmotic pressures of blood and lymph a paradoxical situation would result. During rest lymph flows slowly and contains much protein, a low effective colloid osmotic pressure being associated with marked reabsorption of fluid. During muscular activity it is generally agreed that lymph flows more rapidly and contains less protein, a high effective colloid osmotic pressure being associated with less absorption of fluid. The true effective colloid osmotic pressure of the blood is the difference between the colloid osmotic pressures of the capillary filtrate and blood plasma. This should be a fairly constant figure for any one tissue and animal except when injury of the endothelium permits large amounts of protein to pass. It was in this sense that the term "effective colloid osmotic pressure" was used in studies of fluid movement during inflammation and injury of the frog's mesenteric capillaries (Landis, 1927b).

Krogh, Landis and Turner (1932) found that no filtration of fluid could be detected in the human forearm until venous pressure was

elevated to 15 cm. water. They found it difficult to associate this so-called margin of safety with the very low effective colloid osmotic pressure that must result from the general presence of an extravascular fluid containing from one-third to one-half as much protein as blood. From the filtration-absorption concept adopted by Starling (1896), Schade (1927), and Drinker and Field (1931) it follows that tissue fluid must vary from a true capillary filtrate with low protein content just outside the filtering capillary areas to a concentrated fluid containing more protein near the absorbing areas. . Lymph, being composed partly of the latter type of tissue fluid, must usually contain more protein than true capillary filtrate. It is doubtful whether analyses of normal lymph can in general provide definite information concerning the average protein content of the tissue fluid surrounding the capillary wall and particularly concerning the concentration of protein in the original capillary filtrate. The protein in lymph must vary widely depending, among other things, on the rate of filtration and the relative amount of absorption. The slower the filtration and the more complete the reabsorption, the more will the composition of lymph differ from that of the capillary filtrate and from that of average tissue fluid. The more rapid the filtration and the less complete the reabsorption, the more closely will both tissue fluid and lymph resemble the fluid filtered through the capillary wall.

In order to determine from analyses of lymph the protein content of the original capillary filtrate, it is necessary to collect lymph *a*, without reabsorption, and *b*, without injury of the capillary wall. Both of these factors, if present, will tend to produce extravascular fluid which contains more protein than does the filtrate passing originally through the normal capillary wall. Results obtained from studies of lymph can be brought into general agreement with those obtained from analyses of edema fluid and blood, when allowance is thus made for the high protein concentration sometimes, but not always, observed in lymph. The permeability of the lymphatic endothelium must also be remembered for its possible importance in determining the composition of lymph (McMaster and Hudack, 1932a, b; Peters, 1933).

The composition of subcutaneous lymph has been studied recently during sterile inflammation, extreme venous congestion, plasmapheresis (Field and Drinker, 1931c), muscular activity, rest and mild venous congestion (White, Field and Drinker, 1933).

Immersing the leg of a dog in hot water increases the flow of lymph and the protein content of the lymph rises to 4 per cent or more. This leakage of protein is obviously due to capillary injury. Ligation of all

the leg veins increases the rate of lymph flow and the protein in lymph simultaneously decreases, but 1.02 per cent is the lowest figure reported. Such complete venous ligation not only raises venous pressure to extremely high levels, but stops blood flow. Reabsorption is impossible, but anoxemia makes the capillary wall abnormally permeable to protein (Landis, 1928). Marked venous congestion of the human forearm also produces a capillary filtrate containing considerable protein (Landis et al., 1932).

Acute plasmapheresis increases the flow of cervical lymph and lowers its protein concentration to between 0.86 and 1.25 per cent (Field and Drinker, 1931c), the lymph protein percentage tending to follow variations in plasma protein percentage. Lymph collected after acute plasmapheresis contains considerably more protein than does edema fluid removed during chronic plasmapheresis. As Field and Drinker (1931c) mention, reabsorption is eliminated and the lymph flows so rapidly that it must resemble the original capillary filtrate quite closely. The higher protein content may, however, be due to capillary damage with increased permeability owing to rapid protein depletion. Whipple, Smith and Belt (1920) describe a shock-like state following rapid plasmapheresis. Death was produced within 1.5 hours and was ascribed to tissue injury. Conklin (1930b) found also that extensive flushing with Ringer's fluid rendered the vascular endothelium of the frog more permeable to colloidal substances. Acute plasmapheresis is accomplished by a few large injections of Ringer's fluid or salt solution in a relatively short time, while in chronic plasmapheresis numerous smaller injections are made over a period of days. This may be responsible for the greater protein leakage in the acute experiment.

During walking the lymph from the feet of dogs contains on the average 1.0 per cent of protein, but 0.5 per cent is not uncommon (White, Field and Drinker, 1933). It is impossible to state that reabsorption has been entirely avoided, nor is there any definite knowledge, as Drinker and Field (1933) mention, of the exact line of demarcation between normal and abnormal capillary permeability. It is conceivable that even in normal muscular activity temporary asphyxia or compression of turgid capillaries by contracting muscle fibers might modify capillary permeability so that more protein leaks through the endothelium than would pass through the same region during rest.

In man (Drinker and Field, 1933) subcutaneous lymph obtained during rest contained 0.69 per cent protein while walking reduced it to 0.49 per cent. Lymph obtained by massage of resting tissues may contain up to

4.5 per cent protein, this higher content being explicable on the basis of reabsorption.

Elevating venous pressure slightly by inflating a pneumatic cuff at the base of the dog's leg increases lymph flow and diminishes the protein concentration. The lymph contained in one observation 0.21 per cent protein and in another 0.78 per cent (White, Field and Drinker, 1933). Thus when capillary pressure is elevated slightly, with little or no local asphyxia, the protein content of lymph may be extremely low,—much lower than that observed ordinarily during rest or even during exercise. Such moderate elevation of capillary pressure limits reabsorption, but still is not so likely to produce anoxemia. Under such conditions lymph would be most apt to resemble capillary filtrate and would most nearly reflect the permeability of the normal capillary wall. These findings compare favorably with the very slight protein loss described for human capillaries by Landis et al., (1932) when venous pressure is raised but slightly.

It seems very likely that reabsorption and endothelial injury explain why lymph contains under certain conditions only 0.21 per cent protein and under other conditions over 5.0 per cent. If this reasoning is correct the available studies on lymph agree with the studies on edema fluid and blood in showing that the capillary endothelium can, and often does, retain 95 per cent of the plasma protein. The effective colloid osmotic pressure is then very slightly less than the colloid osmotic pressure of the blood measured *in vitro*.

The fact that small amounts of protein are found in edema fluid and in lymph obtained during slight venous congestion invites inquiry into the manner in which protein leaks through the capillary wall. Protein might pass in very low concentration through the entire endothelial surface or unmodified plasma might leak through a few capillaries which are abnormally permeable owing to trauma, or to a natural process of ageing. If the first possibility were correct lymph would probably contain more albumin than globulin owing to the smaller molecular weight of albumin. If the latter condition existed the albumin-globulin ratio of lymph would tend to resemble that of blood. Loewen, Field and Drinker (1931) found that the specific colloid osmotic pressure of subcutaneous lymph per gram of protein is higher than that of plasma and suggested that this might be due to a greater proportion of serum albumin in lymph. Wells (1932) on the other hand found in nine experiments that the albumin-globulin ratios of serum and of lymph from the mesenteric lacteal vessels of dogs are approximately similar. The ratios agreed

satisfactorily with direct estimations of colloid osmotic pressure. The capillary filtrate produced in the human forearm by marked venous congestion contains both albumin and globulin (Landis et al., 1932). Weech, Goettsch and Reeves (1933) also found that the albumin-globulin ratios of serum and subcutaneous lymph are mutually dependent variables. Pathological collections of fluid, on the contrary, frequently show a higher specific colloid osmotic pressure than blood indicating a preponderance of albumin (Peters and Van Slyke, 1931; Meyer, 1932). Nothing final can be said concerning the manner in which protein passes through the normal and injured capillary wall. If the albumin-globulin ratios of lymph are significant, proteins may, under normal conditions, leak through relatively few pores large enough to permit both albumin and globulin to pass in the ratio existing in blood. Pathological increase in capillary permeability, however, may be accompanied by leakage of more albumin than globulin.

The loss of fluid from the blood stream which accompanies quiet standing increases not only the concentration of blood protein but also the concentrations of cholesterol, phosphatides, and compounds of saturated and slightly unsaturated fatty acids, showing that not only protein but also other substances are retained by the capillary wall (Man and Peters, 1933). Though substances other than protein affect the colloid osmotic pressure of the blood, their significance in this respect is limited (Kylin and v. Pein, 1931; Fishberg, 1929; Macheboeuf and Sandor, 1931; Meyer, 1932; Achard, Grigaut and Codounis, 1930).

Summary. The physical factors involved in the movement of fluid and dissolved substances through the vascular endothelium are so complex that changes in capillary permeability should be described only after careful control of the forces known to influence the movement of substances through an inert membrane. Ever varying capillary pressure and rate of blood flow in the units of the capillary network add further complexity. Analyses of edema fluid, blood and lymph indicate that the capillary wall is usually relatively impermeable to protein. In many tissues the endothelium normally retains at least 95 per cent of the total plasma protein. Generalizations should not be made to apply to all capillaries since regional differences in permeability exist. Lymph resembles the original capillary filtrate most closely when reabsorption and capillary injury have been completely avoided. The leakage of protein through the capillary wall in many tissues is so slight that it is justifiable to assume that normally the effective colloid osmotic pressure of the plasma proteins in the capillary network is practically the same as the colloid osmotic pressure of the plasma when measured *in vitro* with a membrane which is totally impermeable to protein.

4. *Diffusion and the permeability of the capillary wall to electrolytes.* The exchange of highly diffusible solutes to which the capillary wall is permeable need not follow the current of water during either filtration or absorption. When hypertonic solutions of electrolytes are introduced intravenously the electrolyte diffuses through the capillary wall toward the tissue spaces even while fluid is moving toward the blood. This is fortunate since (Peters, 1933) if diffusion of solutes followed the current of solvent only, the establishment of electrolyte and osmotic equilibrium among body fluids would be much slower than it is. Thus after glucose solutions are introduced intraperitoneally water and electrolytes pass into the injected fluid while glucose diffuses into the blood simultaneously (Clark, 1921; Schechter, 1931). On account of the time required for the diffusion of electrolytes, fluid movement through the capillary wall is modified temporarily (White and Erlanger, 1920; Weed and McKibben, 1919; Kubie, 1928; Kinsman, Spurling and Jelsma, 1928, and others) but the effect is transient, disappearing when the concentration of electrolytes is once more equal inside and outside the capillary wall. The time required to restore equilibrium depends upon the rapidity with which the substance diffuses through the capillary wall. Diffusion is doubtless aided by a current of water moving in the same direction. Whether diffusion can be hindered appreciably by fluid moving through the capillary wall in the opposite direction is not known though from rough calculation it seems unlikely.

The independence of fluid movement and the diffusion of electrolytes is perhaps best illustrated by the behavior of certain dyes which have been used extensively to investigate the resistance which the capillary wall offers to the passage of substances whose molecular size lies between those of plasma protein and crystalloids. The passage of dyes can be followed easily since they are usually visible in low concentration. Interpretation of results, on the other hand, is often difficult owing to complicating factors such as electrical charge, selective staining, adsorption, toxicity, decolorization or deposition in the tissues. Dyes are, moreover, foreign substances and many are collected selectively by cells whose function it is to rid the body of extraneous materials.

Schulemann (1917) showed that those acid dyes which diffuse slowly into gelatin do not show, after subcutaneous injection, any great degree of general vital staining while those diffusing rapidly show conspicuous vital staining. He concluded that dyes pass into the blood stream

from the subcutaneous tissues by diffusion and that their relative diffusibility through the capillary endothelium is the same as that through gelatin.

The rate at which dye solutions pass through the capillary wall has been referred to various chemical and physical properties of the dyes used (Wittgenstein and Krebs, 1926; Shimidzu, 1922; Pohle, 1924). With any single suitable dye, however, the state of the capillary wall itself is usually taken to be the chief factor in determining the rate of passage. Rogowicz (1885) observed that a dye introduced into the saphenous vein passes into the tissues more rapidly whenever active hyperemia is induced by stimulation of vasodilator nerves or by division of vasoconstrictor fibers. Krogh (1922) states that two relatively indiffusible dyes, brilliant vital red and Chicago blue VI B, pass very slowly through the normal capillary wall, but with the production of hyperemia or stasis the vessels are quickly surrounded by a deeply stained zone. Likewise the active hyperemia resulting from heating of the skin (Okuneff, 1924) permits in the affected area a more conspicuous staining of the tissues after intravenous injection of trypan-blue. Anitschkov (1924) attributed this effect to local dilatation of the capillaries, with increased permeability due to stretching, a suggestion originally made by Krogh (1922). Dyes follow the current of fluid under these conditions.

When dye solutions are injected through micro-pipettes into single capillaries of the frog's mesentery, vessels of like diameter, even though they arise from the same arteriole, permit pigment to appear outside the endothelium after periods of time which differ widely in various capillaries (Landis, 1927b). These variations in the rate of passage of dye solutions depend primarily upon the level of capillary pressure existing in each vessel and very little, if at all, upon the diameter of the capillary. At a given pressure solutions of various dyes must be perfused through single capillaries for different periods of time before the pigment appears outside the endothelium. This was related to differences in the colloidal properties of the dyes used (Landis, 1927b).

Vital red HR injected in relatively small quantity into the blood stream of the frog leaves some mesenteric capillaries and fails to leave other capillaries in the same region. In those capillaries where no dye passes the pressure is generally below 11 cm. of water, while in those where dye passes rapidly the capillary pressure is almost always over 14 cm. of water. Diverting the flow of an arteriole into a single capillary makes dye pass quickly through the endothelium, though under normal

pressure conditions none has passed. It was also noted that after some delay considerable dye leaves the smaller venous capillaries and the smallest venules, so that finally the connective tissue surrounding these vessels is deeply stained. This passage of dye from venules was ascribed by Landis (1927b) to selective "vital staining" of the connective tissue. The relation between capillary pressure and the passage of dye-stained fluid from capillaries was taken to be corroborative evidence that capillary pressure influences the movement of fluid through the endothelium. In such cases diffusion of dye is aided by a current of fluid passing in the same direction.

Certain dyes pass through the walls of veins before any visible passage through the capillary endothelium can be detected (Frölich and Zak, 1924; Runge, 1927). Rous, Gilding and Smith (1930) injected acid vital dyes intravenously and studied the staining of tissues about the capillaries and veins. Highly diffusible dyes escape so rapidly from the capillaries of mammalian muscle that the tissue surrounding the arterial end of the capillary is colored even before the venous end is reached by the dye-stained blood. Less diffusible dyes emerge all along the muscle capillaries, but in greater amount toward the venous end. Poorly diffusible dyes at first fail to appear outside the arteriolar portion of the capillary network but escape in increasing amount in the venous portion. Eventually in all cases the tissue becomes colored evenly. The greater accumulation of poorly diffusible dyes in the vicinity of the venous capillaries and venules is but little affected by the changes of circulation and fluid movement which accompany muscular activity (except tetanus), plethora, severe hemorrhage, nerve section, shock, dehydration and injections of epinephrin and pituitrin.

Capillary pressure and fluid movement do not especially favor the passage of dye through the venous capillaries, since in this region blood pressure is lower and filtration much less likely than in the arteriolar capillaries. Moreover, dyes pass through the endothelium even when intravascular pressure is reduced nearly to zero. Rous, Gilding and Smith (1930) developed the hypothesis that the endothelium of the capillaries serving certain organs is relatively impermeable near the arterioles and becomes increasingly permeable as the venules and veins are approached. Anatomical and physiological reasons were advanced to indicate that this gradient of capillary permeability ensures equal distribution of diffusible substances to the tissues. They pointed out that the absence of a demonstrable gradient of permeability in the liver and bladder of mammals and in the muscles of birds is associated with an

anatomical arrangement of capillaries which in itself ensures such a uniform supply of the diffusible constituents of the blood (Smith and Rous, 1931a).

Under normal circulatory conditions, the gradient can be demonstrated only by means of moderately or poorly diffusible dyes; highly diffusible dyes like phenol red and patent blue V pass so rapidly through the entire endothelial surface that no difference in the rate of diffusion can be observed. Smith and Rous (1931a) state that the most highly diffusible material used, phenol red, spreads through water at the same rate as dextrose and through gelatin more than three times as slowly, lagging therefore far behind many substances used by the tissues, since the rate at which dextrose passes through the endothelium is slow compared to that of the salts. Patent blue V which, according to their tests, "most nearly approaches a normal foodstuff in diffusibility" passes out at once everywhere along the entire capillary wall and the field is obscured. Colored substances of simple constitution were either not sufficiently intense in hue for their escape from the vessels to be followed or else they proved toxic. The gradient is therefore demonstrable only with dyes whose diffusibility is much less than that of the blood constituents concerned in nutrition. To what extent observations with poorly diffusible dyes can justifiably be applied to the highly diffusible constituents of blood is still a matter of inference and conjecture.

Rous believes that the gradient of permeability is based upon anatomical differences along the capillary wall because local differences in the escape of dyes are still demonstrable despite great alterations in the circulatory state. Complete denervation does not obliterate the gradient, though widening its scope. Hesselmann (1932), on the other hand, found in urethanized frogs that sympathectomy obliterates all trace of the gradient and believes it to be functional in origin depending on innervation.

Though the deeper staining about the venous capillaries occurs in spite of drastic variations in capillary pressure it is much influenced by capillary pressure (McMaster, Hudack and Rous, 1932). Nerve section induces hyperemia and increases blood flow. After an intravenous injection of dye, denervated muscles are equally and evenly stained at a time when the control muscles still show the barring of color characteristic of greater escape of dye in the venous portion of the capillary network. Prior to diffuse staining, barring occurs also in denervated muscles but the bars of color are deeper and broader with a light general staining which the control muscle lacks entirely. Thus a generalized staining is finally superimposed upon the local, more intense staining about the venous end of the capillaries.

Elevating venous pressure increases the escape of dye through the capillary wall. When venous congestion has persisted for some days even the veins become more permeable than usual. It was concluded that the gradient of permeability exists independently of variations in hydrostatic pressure, though raising venous pressure extends the scope of the gradient and accentuates local differences in permeability. If venous pressure is raised in the ear of the mouse so high that capillary pressure approaches the arterial pressure, dye escapes from the greatly distended capillary network without a trace of the gradient observed under ordinary conditions.

Rous and Smith (1931) repeated in modified form the experiment of Landis (1927b) on the frog's mesentery, injecting larger quantities of vital red HR intravenously. Landis injected only enough dye to color the plasma definitely while Rous and Smith used amounts great enough to render the corpuscles invisible. The patchy appearance of dye outside certain arteriolar and venous capillaries, found by Landis to be associated with higher capillary pressure by direct measurement, was ascribed by Rous and Smith to injury, since such "escape of stain in rapid and disorderly fashion from isolated capillary segments" was more frequently noted after prolonged irrigation of the frog's mesentery. Capillary pressure was not measured, however, and a much larger amount of dye was injected by Rous and Smith. This may explain the fact that the escape of dye about the venous capillaries occurred simultaneously with its passage from the true capillaries in the studies of Rous and Smith, while delayed somewhat in those of Landis. The amount of dye injected clearly conditions the extent and the rate of staining (Smith and Rous, 1931a).

The extent of the visible gradient of permeability and the intensity of staining are increased by diminishing the plasma colloids and are decreased by raising the concentration of the plasma proteins. In the first instance generalized staining with poorly diffusible dyes occurs in addition to the usual evidence of a gradient. The influence of plasma protein on the escape of dye from the blood is ascribed to adsorption of dye by protein (Smith and Dick, 1932).

An increased escape of dyes everywhere along the capillary over and above the localized staining described above accompanies hyperemia (with probable increase in capillary pressure), venous congestion (McMaster, Hudack and Rous, 1932), and capillary pressures above cer-

tain levels (Landis, 1927b). This general escape is probably due to the passage of a dye-containing filtrate of plasma. The staining about the further portion of the capillaries occurs even during the intravenous injection of hypertonic glucose solution (Smith and Dick, 1932) which is known to withdraw fluid from the tissues. Rous, therefore, holds this localized staining to be independent of fluid movement and to be due to diffusion which might well occur against a current of fluid moving inward through the capillary wall if the results of Ingraham, Lombard and Visscher (1933) and of Schechter (1931) may be cited in this regard. However, the filtration of dye-stained fluid is often superimposed upon this pure diffusion (Landis, 1927b; McMaster, Hudack and Rous, 1932).

Evidence has already been cited to indicate that the gradient of permeability influences but little the distribution of dyes which are similar in their diffusibility to the crystalloidal constituents of blood plasma. Whether or not blood proteins escape most readily through the further portion of the capillary there is at present no way of telling. In any case the total amount of protein passing through the capillary wall is small (vid. sup.). Tests with methemoglobin, Congo red and protein coupled with azo dyes yielded only an equivocal coloration (Smith and Rous, 1931b).

The evidence given above concerning the impermeability of the capillary wall to protein indicates that in most tissues the plasma proteins pass through the vascular wall only in relatively small concentration under normal conditions. In order essentially to modify the balance between capillary pressure and the colloid osmotic pressure of the blood, permeability must be increased sufficiently to permit plasma protein to pass freely. Thus the gradient of permeability, which has so far been demonstrated only by dyes, can play only a small rôle in the relation which fluid movement bears to the balance between capillary pressure and the colloid osmotic pressure of the plasma proteins. Landis (1928) in micro-injection experiments in the frog's mesentery found that increasing the hydrogen ion concentration of the irrigating fluid increases slightly the rates of filtration and of absorption which accompany a given difference between hydrostatic and colloid osmotic pressure, but does not modify the effective colloid osmotic pressure of the plasma protein until injury supervenes, when the effective colloid osmotic pressure of the blood is reduced. Only with conspicuous injury can the absorption of fluid be abolished, but absorption is slightly hastened by minor injury which is insufficient to reduce the effective colloid osmotic

pressure of the plasma protein. The greater permeability to dyes, if not great enough to allow the proteins to pass, can merely facilitate reabsorption since, for a given difference between capillary pressure and the colloid osmotic pressure of the blood, more fluid will be reabsorbed in unit time. Free diffusion, on the other hand, will be facilitated by greater permeability however small.

Peters (1933) points out that Rous' objection to the acceptance of the Starling concept fails to take into account that Starling was dealing with the forces that determine the passage of protein-free filtrate as a whole, and which hold back protein, not with processes which determine the diffusion of single solutes to which the vessel walls are permeable. He cites the experiments of Smith and Dick (1932) who showed that modifying water balance by changing the protein and electrolyte content of serum influences but little the distribution of dyes. According to Peters (1933) this at once establishes clearly the irrelevancy of Rous' experiments to water exchange and the Starling theory. Such gradients as Rous demonstrated "can at most equalize the distribution of nutrient materials of large molecular size as he has suggested but cannot appreciably influence the exchange of water or electrolytes."

Summary. The exchange of diffusible solutes, to which the capillary wall is more or less freely permeable, need not follow the current of water during either filtration or absorption. When the electrolyte equilibrium is disturbed, fluid movement is modified temporarily until diffusion equalizes the concentration and the osmotic pressure of the electrolytes inside and outside the capillary. The rates at which certain poorly diffusible dyes pass through the various portions of the capillary network indicate that the capillary wall becomes increasingly permeable to dyes toward its venous extremity. The greater passage of dyes through venous capillaries is independent of capillary pressure and fluid movement and is presumably due to pure diffusion. Yet elevating capillary pressure increases the passage of dyes everywhere along the capillary so that under appropriate conditions the filtration of dye-stained fluid may be superimposed upon pure diffusion of dye, and may even obliterate all evidence of local differences in endothelial permeability. This gradient of permeability tends therefore to equalize the distribution of poorly diffusible dyes but, in view of the available evidence, cannot appreciably modify the exchange of water or electrolytes.

5. *Tissue pressure and the movement of fluid through the capillary wall.* The pressure under which blood flows through the capillary network is but one point in the difference between the hydrostatic pressures inside

and outside the capillary wall. If the fluid filtered by an excess of capillary pressure over colloid osmotic pressure passed into a space which could expand easily without distention, a high venous pressure should produce filtration indefinitely at a constant rate. Observation shows, however, that this is not the case (Drury and Jones, 1927; Landis and Gibbon, 1933). In the tissues, and to a lesser extent in the serous cavities, the space available for accommodating extravascular fluid is limited; the tissue elements must be separated and further filtration of fluid is opposed by the pressure required to distort the tissues.

The external force required to depress the skin has been used to identify various stages of pre-edema and edema (Gildemeister and Hoffmann, 1922; Schade, 1926; Kunde, 1926; Meyer and Holland, 1932) but does not measure tissue pressure in absolute figures. Landerer (1884) was the first to estimate tissue pressure directly by introducing a fine needle or cannula into the cutaneous or subcutaneous tissues. He concluded that in rabbits tissue pressure is normally equivalent to about 5 to 7 cm. water with wide variations in different parts of the body and in different tissues. In man tissue pressures up to 55 cm. water were found, intracutaneous pressures being usually two to three times greater than the pressure in subcutaneous tissues. Venous congestion elevated tissue pressure conspicuously but the duration and the grade of venous congestion are not recorded.

Hajen (1927) measured the pressure required to form a cutaneous wheal, but this procedure separates the tissue elements far more suddenly and widely than does normal filtration. Drury and Jones (1927) observed that at a given venous pressure the rate of filtration, measured by a simple plethysmograph, is greater from the tenth to the twentieth minute of congestion than it is from the twentieth to the thirtieth minute. They were, however, unable to measure the volume of fluid filtered during the first ten minutes of congestion due to the limitations of the method used. According to Krogh, Landis and Turner (1932) an accumulation of fluid in the tissue spaces diminishes or even abolishes the filtration usually observed with venous pressures of fifteen to thirty centimeters water. The possible importance of lymphatic drainage and tissue pressure were both considered in the discussion of these results, but the limitations of the earlier pressure plethysmograph precluded any definite decision concerning the importance of tissue pressure. Later observations (Landis and Gibbon, 1933) with an improved plethysmograph indicated that tissue pressure is the more important. Filtration rates measured during the first few minutes of congestion are

uniformly higher than those observed during succeeding periods even when congestion continues during the entire period over which the accumulation of extravascular fluid is measured. Likewise the filtration rates observed in the forearm over ten and thirty minute periods of congestion are considerably higher than those reported for the leg by Drury and Jones who measured filtration only after venous congestion had been present for ten or more minutes. This discrepancy would be expected if a gradual increase of tissue pressure accompanied the accumulation of extravascular fluid.

According to Landis and Gibbon (1933) tissue pressure reduces filtration most rapidly during the first thirty minutes of venous congestion; at the end of this period the rate of filtration is often less than one-quarter that observed during the first five or ten minutes. When sufficient fluid has accumulated in the tissue spaces low venous pressures fail to produce further filtration. With higher venous pressures the filtration rate is decreased by an amount which is equivalent to a tissue pressure of 35 cm. of water. This figure was obtained indirectly and represents only the extent to which the effectiveness of a given capillary pressure is diminished when large amounts of extravascular fluid are present. In part this reduced rate of filtration is explained by the greater concentration of plasma protein owing to loss of fluid from the blood trapped in the congested vessels. The colloid osmotic pressure of blood removed from the veins of the foot during quiet standing is from 24 to 64 per cent greater than normal (Youmans, Wells, Donley and Miller, 1933).

A high tissue pressure increases also the rate at which extravascular fluid is removed from the tissue spaces (Krogh, Landis and Turner, 1932; Landis and Gibbon, 1933). It is impossible to state whether this fluid is removed *via* blood capillaries or lymphatics, though indirect results indicate (Krogh, Landis and Turner, 1932) that small accumulations are reabsorbed by the capillaries while larger accumulations are removed primarily through lymphatic channels.

In the human being tissue pressure helps to maintain normal blood volume against considerable hydrostatic disadvantage. Thus in the erect position, and particularly in quiet standing, when the veins are not emptied by muscular contraction, the capillary pressure in the dependent tissues is much higher than the colloid osmotic pressure of the blood. Yet normal individuals fail to show edema in the dependent tissues even though the standing position is assumed for relatively long periods of time. Filtration, though present, is reduced conspicuously long before

limb volume has increased by 10 per cent, which, according to Drury and Jones (1927), is the change required to produce pitting edema. The dangers of reducing blood volume too greatly are obvious. Quiet standing brings the vasular system very near to temporary failure and frequently produces fainting even of normal subjects (Turner, Newton and Haynes, 1930; Hamilton, Lichty and Pitts, 1932). Tissue pressure, by limiting the amount of fluid which is temporarily lost by filtration, reduces the need for cardiovascular readjustment during prolonged standing.

The earlier measurements of tissue pressure in man show little agreement, varying from 55 (Landerer, 1884) to 13 cm. water (Gildemeister and Hoffmann, 1922). According to more recent observations by Meyer and Holland (1932) normal cutaneous tissue pressure amounts to approximately 7 cm. water while subcutaneous tissue pressure is considerably less, ranging from 2 to 4 cm. water. While Landerer, and Gildemeister and Hoffmann both found tissue pressure increased during elevation of venous and capillary blood pressure, Meyer and Holland (1932) found no change when the extremity was placed below heart level. Using Landis' (1930b) figures for capillary pressure, Meyer and Holland (1932) have calculated that in man, when tissue pressure is allowed for, arteriolar capillary blood pressure exceeds the sum of the effective colloid osmotic pressure of the blood and tissue pressure by 50 cm. water. Venous capillary blood pressure, on the other hand, falls below the sum of the colloid osmotic pressure and tissue pressure by 220 mm. water. Krogh, Landis and Turner (1932) on different grounds suggested also that on the average in resting tissues the tendency toward reabsorption is greater than that toward filtration.

Equations have been used to clarify the manner in which capillary pressure, colloid osmotic pressure and tissue pressure influence fluid movement (Iversen and Johansen, 1929; Meyer and Holland, 1932; Weech, Snelling and Goettsch, 1933). At equilibrium with no fluid movement capillary blood pressure (CP) will be balanced by tissue pressure (TP) and the effective colloid osmotic pressure of the blood which consists of the total blood colloid osmotic pressure (COP_B) minus the colloid osmotic pressure of the extravascular fluid (COP_T).

$$CP - TP = COP_B - COP_T$$

The last quantity (COP_T) ranges from very low values around filtering areas of capillary wall to high values in regions where low capillary pressure has allowed reabsorption to take place. The total colloid osmotic pressure of the blood is, in fact, the only force which is relatively constant, the other forces varying widely with circulatory adjustments. These variations, however, in general act between themselves to prevent excessive filtration of fluid through the capillary wall.

Whatever may be the importance of tissue pressure in limiting undue filtration under ordinary conditions, the mere existence of edema shows in itself that the power of the tissues to resist accumulation of tissue fluid is limited. Landerer (1884) believed that all forms of edema were to be explained by reduced elasticity of the tissues. In determining the modulus of normal and edematous tissues he failed to take in account that a given mass of edematous tissue contains fewer connective tissue fibers and more fluid than the same volume of normal tissue. It would be expected, therefore, that under a given force edematous tissue would stretch more easily. Bönniger (1905) tested the elasticity of the skin taken from cadavers and found no evidence that the elasticity of tissue was diminished in edema. In fact the skin removed from an edematous extremity shortened more than did skin taken from a normal extremity. Bönniger observed also that the tissues are very imperfectly elastic so that after stretching they fail to return immediately to their original dimensions though tension is removed. Therefore a relatively low tissue pressure acting for a long time may gradually stretch the tissue, the elasticity of which delays, but cannot prevent, the appearance of edema.

Additional evidence of the ease with which the tissues stretch was given by Iversen (1928) who found in studies on ascites that intraabdominal pressure is reduced almost to atmospheric pressure after relatively little fluid is removed. After stretching, the tissues of the abdominal wall are capable of accommodating a considerable volume of fluid without great increase in extravascular pressure.

Few measurements of tissue pressure in edema are available. The tightness of the skin in certain massive edemas suggests that the tissue pressure is quite high under certain conditions. Yet Holland and Meyer (1932) failed to find the slightest evidence of such an increase in edema. It is a clinical truism that certain forms of edema appear first in the loose tissues of the orbit and face, but the looseness of the tissues is not the primary cause for the appearance of the edema since the relaxed abdominal skin of multiparae is not usually edematous (Fishberg, 1930). If, however, physical conditions allow filtration to exceed absorption conspicuously over long periods of time the loose tissues will show pitting edema before the more compactly constructed tissues. Weech, Snelling and Goettsch (1933) observed that in experimental animals

nutritional edema is apt to be correlated with less reduction of plasma protein than is edema due to plasmapheresis. Change in the elasticity of the tissues is suggested in order to explain this difference.

Summary. Tissue pressure modifies the movement of fluid through the capillary wall and normally prevents excessive filtration. Direct measurements show little agreement concerning the absolute level of normal tissue pressure. Plethysmographic studies of filtration indicate that tissue pressure modifies the effect produced by a given difference between capillary pressure and colloid osmotic pressure, particularly when that difference acts over brief periods of time. Direct measurements of tissue pressure and clinical experience indicate that when the tendency toward excessive filtration persists over long periods of time, the importance of tissue pressure is much less, presumably because the tissues are imperfectly elastic.

6. *Other factors possibly influencing the movement of fluid through the capillary wall.* The preceding sections of this review deal primarily with certain effects which a few of the more thoroughly studied physical factors exert on the movement of fluid and dissolved substances through the capillary wall. Enough evidence has accumulated to indicate that normally the movement of fluid through the capillary wall depends fundamentally upon capillary blood pressure, the colloid osmotic pressure of the plasma proteins and the retention of proteins by the capillary wall. Abnormality in one factor must be balanced by compensatory changes in the others if a normal balance between filtration and reabsorption is to be maintained. This does not mean, however, that all or even most of the observed facts can be explained in terms of the few and relatively simple forces already considered. On the contrary, it is to be expected that other forces, both fundamental and conditioning, will be recognized as knowledge increases.

The relation between lymph flow and tissue function has for a long time directed attention to influences, chemical or physical, originating in the tissues. Tissues differ with reference to their normal water content; according to recent studies (Skelton, 1927) half the body water is found in muscle and one-fifth in skin. The tissues vary, too, in their rate of yielding water to the blood stream during dehydration or after hemorrhage, and in their rate of receiving water from the blood stream during hydremic plethora (Skelton, 1927; Adolph and Lepore, 1931). Though the liver and intestines respond most quickly, it is muscle, because of its greater mass, which gives up more total fluid than any other tissue during fluid deprivation and takes up by far the greater

part of water added to the blood stream (Skelton, 1927). The mean arterial blood pressure is the only factor measured which varies in parallel with this muscle hydration (Adolph and Lepore, 1931). Blood pressure is more important than blood dilution in regulating the water content of tissues since infusions of gelatin and acacia produce dilution of the blood persisting for a longer time than the variation in muscle water. During hemorrhage, also, the changes in tissue water are initiated by alteration of blood pressure. Clamping the dorsal aorta modifies muscle water in accord with the change of mean arterial blood pressure. Adolph and Lepore (1931) found that increasing mean arterial blood pressure by 20 per cent raises the water content of muscle between 1 and 2 per cent. They conclude that changes in capillary blood pressure which accompany sudden changes in blood volume are important elements in controlling the initial exchange of fluid between blood plasma and tissues.

The state of extravascular fluid is also intimately concerned with the presence of free and bound water in relation to the colloidal constituents of the tissues. Peters (1933) has discussed the nature of interstitial and serous fluids, concluding that the existence of lymph, a fluid similar to blood serum and different from intracellular fluid, shows the tissue spaces between the capillaries and lymphatics must contain some fluid similar to both serum and lymph. In addition edema fluid is for the most part situated in spaces which are histologically demonstrable between the connective tissue fibrillae. Slight pressure on the skin displaces this fluid and, after external pressure is removed, the depression in the skin disappears when the fluid filters back to its usual situation. Fluid does not flow from a needle inserted into a block of swollen gelatin but edema fluid flows freely from a needle inserted under the skin. Were the capillary filtrate removed from the circulating blood by swelling of tissue colloids its withdrawal from the tissues should be far more difficult. The gradual transition from normal amounts of tissue fluid, through stages of pre-edema to outspoken edema make it reasonable to infer that such fluid is nothing more than an augmentation of normal tissue fluid. Peters (1933) suggests that the accommodation of this undifferentiated capillary filtrate by tissue cells would disturb the intracellular electrolyte balance which is highly complex and presumably of functional significance. Recent evidence, too, agrees in showing that relatively little of the water in the living organism is closely bound to colloids.

The free water in blood is practically equal to the total water being only 2 per cent less (Hill, 1930). In frog's muscle very little bound

water is found (Hill, 1930) and in mammalian muscle at least 94 per cent of the total water is capable of diluting electrolytes (Moran, 1930). Hetherington (1931) concludes from vapor pressure measurements that practically all of the water in the body is free and available to take part in osmotic interchanges between blood, tissues and cells. Even colloidal solutions such as gelatin, gum acacia, casein or starch show little or no detectable hydration (Grollman, 1931; Greenberg and Greenberg, 1932).

According to Fischer (1921) swelling of tissues and edema is to be ascribed to the accumulation of acids resulting from disturbance of circulation or to local injury. This concept, based on the effects of large changes in hydrogen ion concentration on swelling of colloids outside the body, has been destructively criticized by Schade and Menschel (1922) and by Schade (1927). Lucké and McCutcheon (1926a, b) found that the unfertilized eggs of Arbacia do not swell in acid solutions except after injury or death. In general death is accompanied by irreversible gelation of the cells.

Connective tissue is in contact with both capillaries and body cells and, of all tissues, is most likely to be concerned with the movement of fluid through the capillary wall (Schade and Menschel, 1923). The amount of water in connective tissue depends upon mechanical pressure, hydrogen ion concentration, and salts, in order of importance. The collagenous fibers and the so-called ground substance, the two components of connective tissue, react differently to certain of these forces and the net change in tissue volume depends upon the algebraic sum of the effects on the two components. According to the summary given by Schade (1927) if pH changes from 7.35 to 5.90 the volume of connective tissue increases by 15 to 20 per cent. If the concentration of sodium chloride changes from 0.5 to 1.0 per cent swelling amounts to between 3 and 9 per cent. If all the connective tissue in the body were to swell 10 per cent, approximately one liter of water might be retained. This quantity is, however, relatively small compared to the volume of the extravascular fluid required to produce edema. Moreover to obtain even this slight change requires that the electrolyte balance shift well beyond the ordinary range of physiological variation.

Del Baere (1931) made incisions into the skin and determined the pressure required to balance what he termed the swelling pressure of the tissues. Since these observations apply to injured tissue in which fluid balance is influenced not only by leakage through the tissue spaces but also by filtration and reabsorption from presumably dilated and injured capillaries, it is doubtful whether the absolute figures are significant.

Meyer (1932) states that even the filtration produced by venous congestion should be ascribed to changes in the tissues rather than to distortion of the balance between capillary blood pressure and the colloid osmotic pressure of the blood. The rates of filtration observed by Landis (1927b), Krogh, Landis and Turner (1932) and Landis and Gibbon (1933) are directly proportional to capillary or venous pressure respectively. Moreover, independent changes in venous pressure and colloid osmotic pressure modify the filtration rate by similar amounts (Krogh, Landis and Turner, 1932). It would be an extraordinary coincidence if this relationship, which accords with physical principles, were due to some undefined change in the tissue associated with anoxemia or with the retention of metabolic products. Moreover White, Field and Drinker (1933) have shown that elevating venous pressure increases the flow of lymph from the congested region. If the change in water distribution were due to swelling of the tissues this fluid should not be free and would not flow from the part through the lymphatic vessels.

Aldrich and McClure (1923, 1924) found that wheals produced by the intradermal injection of physiological salt solution disappear more rapidly from edematous skin than from normal skin. This was taken to show that edematous tissues exhibit a heightened affinity for water. Salt solution in 20 per cent and 4 per cent strengths disappears with equal rapidity (Chevallier and Stiffel, 1925). Elevating the limb prolongs, and lowering the limb shortens, the time required for the wheals to disappear (Guggenheimer and Hirsch, 1926). Wheals of normal salt solution and of paraffin oil behave similarly with respect to their rates of disappearance from normal and edematous tissue (Govaerts and Bernard, 1927). Posture should not change the affinity of tissue for water. Paraffin cannot be bound by tissues nor can it be absorbed by the capillaries. Separation of the tissue elements in pre-edema or edema opens up channels in the tissues, and it is through these that salt solution or oil filters after intradermal injection. The rapid disappearance of cutaneous wheals in edema is therefore primarily mechanical in origin.

From the evidence at hand it is unlikely that binding of water by tissues plays an essential rôle in determining the distribution of fluid between blood and tissue spaces. Those effects which have been observed occur slowly and are too small to explain the modifications of fluid balance observed under physiological conditions. It is conceivable, however, that swelling of tissue colloids plays a rôle in the pathogenesis of certain rare intracellular edemas.

The stimulation or section of nerves modifies the rate at which fluid and dissolved substances pass through the capillary endothelium (Asher, 1922; Kajikawa, 1922; Yamamoto, 1924; Fleiderbaum, 1931; Hesselmann, 1932). Such procedures, however, alter capillary blood pressure, capillary diameter and blood flow and it is impossible to state whether the effects on diffusion, absorption and filtration are due to intrinsic change in capillary permeability or to changes in circulation. Since the latter are known to modify the interchange of substances between the blood and tissue spaces, it is essential that they be carefully controlled before a change in capillary permeability is postulated.

Certain hormones have been studied with reference to their effects on capillary permeability and fluid balance. Pituitrin, first studied by Krogh and Harrop (1921b) does not prevent edema from appearing in the frog's leg during perfusion (Drinker, 1927) nor does it keep protein from leaking through the mammalian capillary wall when the blood pressure is abnormally low (Blalock, Wilson, Weinstein and Beard, 1933). It does not prevent the local edema which follows the conjunctival installation of mustard oil (Saxl and Donath, 1925). The flow of lymph from the thoracic duct, however, is decreased after pituitrin injections (Bayley et al., 1925; Petersen and Hughes, 1925) and pitressin diminishes the flow from the leg lymphatics (Haynes, 1932b). In these last observations the capillary wall was normal and circulatory effects can explain the modification of lymph flow.

The usefulness of epinephrine and ephedrine administered hypodermically in the treatment of certain forms of localized clinical edema remains unexplained. According to Tainter (1926) the gross edema of paraphenylenediamine, which is due primarily to endothelial injury, can be prevented by the slow intravenous injection of epinephrine or by continued stimulation of the cervical sympathetic nerve. Moderately large and repeated doses of nicotine, strychnine, picrotoxin and santonin have the same effect, by increasing the output of epinephrine from the adrenal glands. It is suggested that edema is less owing to reduced blood flow incident to vasoconstriction. Thus the action of adrenalin in paraphenylenediamine edema may be due to a reduction of capillary blood pressure similar to the local action described by Hirschfelder (1924). Yet epinephrine added to cocaine and saligenin increases their tendency to cause local edema (Hirschfelder, Backe and Jennison, 1925). This effect of relatively large local dosage may possibly be attributed to injury of the endothelium from prolonged vasoconstriction and anoxemia. The observations of Freeman (1933) on vasoconstriction and

shock are relevant in this regard. More recently the hormones of the adrenal cortex have been shown in the intact animal to modify fluid balance after hemorrhage (Swingle et al., 1934) but the exact mechanism is not yet clear (Britton and Silvette, 1934). Previous thyroidectomy and hyperthyroidism modify the rate at which edema develops in the perfused surviving limbs of mammals (Sato, 1928a, b, c).

The effects of calcium on capillary permeability and fluid balance are difficult to interpret on account of the conflicting nature of results obtained under different circumstances. Earlier work on the effects of calcium was reviewed in detail by Loeb (1923) who concluded that its effect on endothelial permeability cannot be very striking. Hamburger (1922) observed that calcium contracts the vessels in a perfused limb, and that this vasoconstriction is released by potassium. Schmidt (1921), however, described dilatation and diminished sensitivity of vessels to adrenalin following the use of a perfusion fluid containing calcium. According to Lipschitz and Schmitt (1932) the subcutaneous administration of calcium chloride inhibits inflammatory reactions while intravenous injection of a similar amount has a very uncertain effect. The confusing results are in all probability due to varying dosage and circulatory effects.

Summary. The available evidence indicates that swelling of the tissues accounts for relatively little retention of fluid. Bound water is not present in sufficient quantity to modify the balance between the capillary blood and the tissue fluid appreciably. Extravascular fluid produced by the physical forces considered in previous sections rests in the interstitial spaces in free form. Innervation, hormones and calcium affect the movement of fluid and dissolved substances through the capillary wall, but their action cannot be ascribed definitely to changes in capillary permeability since the observations are complicated by possible modifications of blood flow and particularly of capillary blood pressure.

III. Complex changes in capillary pressure and permeability.

1. *Temperature.* Though fluid movement is conspicuously modified by heat or cold there is as yet no direct evidence that these changes are due to modification of capillary permeability *per se*, unless the change in temperature is great enough to injure the endothelium. Slight changes in capillary permeability due to temperature variations are by no means ruled out, but even if present they would have little effect on the concurrent processes of filtration and reabsorption since, all other factors remaining constant, more rapid filtration in one area would be balanced by more rapid reabsorption elsewhere. Only if capillary permeability is

increased to the point where protein passes with ease will absorption cease. Thus excessive heat injures the capillary wall and produces edema, but this is the usual effect of tissue damage and not a specific effect of temperature.

Bazett (1927) mentions the common knowledge that the digits swell during warm weather and shrink during cold weather. This change in volume is partly due to the amount of blood in the vessels though the rate of change is too slow to be explained satisfactorily on this basis alone. Local heat dilates the superficial vessels and blood flow is much increased. Average capillary pressure in the skin of the finger under normal conditions amounts to 32 mm. Hg in the arteriolar limb and 12 mm. in the venous limb. When skin temperature is elevated to 42°C. capillary pressure rises to 60 and to 45 mm. in the arteriolar and the venous limbs respectively (Landis, 1930b). The excess of capillary blood pressure over the colloid osmotic pressure of the blood must lead to the filtration of fluid which presumably passes on into the lymphatic vessels.

Local heat also increases the total filtering area by dilating capillaries previously closed or only partially open. Both factors or either factor singly, would tend to increase the rate of filtration at any given venous pressure. It is impossible to estimate the relative importance of these two possibilities from the data at present available.

Drury and Jones (1927) found with a simple plethysmograph that a given venous pressure applied when the foot was immersed in water at 42° filtered fluid from two to five times as rapidly as the same venous pressure at 16°. Landis and Gibbon (1933) with a pressure plethysmograph found that the filtration produced by venous pressures from 30 to 60 cm. water was twice as great at 45° as at 15°C.

These results have been interpreted (Bazett, 1932) by assuming a linear relationship between the rate of edema formation and the difference between capillary pressure and the osmotic pressure of the plasma proteins—a relationship demonstrated by experiment (Landis, 1927; Krogh, Landis and Turner, 1932; Landis and Gibbon, 1933). The results imply that with a sufficiently high local temperature filtration predominates, and continual lymphatic drainage takes place.

The general effects of temperature on fluid movement are less uniform and clear. Hamilton and Barbour (1925) studied the effect of cold on the transport of fluid from the blood to the tissue spaces. When anesthetized dogs were kept lying on slabs of ice for twenty to fifty minutes immediately before they were killed, more water was found in the subcutaneous tissue and muscle of the cooled side. Barbour and Hamilton

(1925) postulated, therefore, that exposure to cold produces anhydremia because fluid is diverted to the cooled skin, subcutaneous tissues and muscles as a result of arteriolar constriction, capillary dilatation from anoxemia, and increased permeability. In plethysmographic studies lowering the temperature of the forearm to 14.5° Centigrade did not increase tissue volume (Drury and Jones, 1927; Landis and Gibbon, 1933). Bazett (1927) points out that the generalization made by Barbour and Hamilton seems unwarranted for no control observations were made to determine the effect of gravity. Moreover, ice might well be an excessive stimulant producing the effects of slight frostbite rather than those of simple cold. Lewis (1930) postulated that the reactive dilatation which comes on when the skin is cooled below 15° Centigrade is due to an axone reflex stimulated by injury and the secondary release of H-substance in the cooled skin. Excessive cooling can produce blistering and all the evidences of local injury (Lewis and Love, 1926). The blister fluid obtained from these areas contains protein in a concentration approaching that of blood, indicating endothelial damage. Excessive cold, while diminishing capillary pressure temporarily, increases capillary pressure during the period of reaction (Landis, 1931).

Excessive heat leads to the formation of a blister with fluid rich in protein and produces the inflammatory changes secondary to tissue injury. The exudate contains certain substances arising from injury of tissue and the blister fluid when injected beneath normal skin produces there both vascular dilatation and increased capillary permeability (Lewis and Grant, 1924).

Heat increases the rate at which dyes pass through the capillary wall (Okuneff, 1924; Hudack and McMaster, 1932) though the staining of the tissues does not become uniform until the capillary wall is damaged (Hudack and McMaster, 1932). Injury due to heat increases lymph flow and the pressure in the lymphatic vessels may reach 120 cm. water (Field, Drinker and White, 1932). The protein content of such lymph approaches that of blood owing to endothelial injury.

The striking effect of lesser changes of temperature on the filtration produced by venous pressures of 30 cm. water or more is of particular interest with regard to the appearance, or the accentuation of certain forms of edema in response to climatic changes. Frequently patients with mild edema complain that the swelling of the lower extremities is greater during warm weather than during cold. Castellani (1931) in a recent review of minor tropical diseases mentions two types of heat edema. The milder form is "extremely common all over the tropics,

and Europeans on their way to the East frequently develop it as soon as the boat reaches the southern portion of the Red Sea and Aden." The feet and legs swell slightly and pitting occurs without any evidence of renal or cardiac abnormality. In more severe form heat edema was observed by Castellani in Europe and America during a heat wave. The edema comes on suddenly, lasts as long as the high temperature persists and then disappears. This type of edema involves the lower extremities, pits slightly on pressure and, like the first variety, is not accompanied by abnormal renal or cardiac function.

In a warm environment, according to Lewis and Pickering (1931) the cutaneous vessels of the upper extremities dilate in order to promote the loss of heat. Gibbon and Landis (1932) found that immersing the forearms in warm water produces in the lower extremities a maximal vasodilatation which is usually comparable in degree to that obtained by spinal anesthesia. During such vasodilatation the total area of capillary wall available for filtration in the extremities must be increased. In the erect posture venous pressure in the lower extremities reaches very high levels due to the hydrostatic pressure of the column of venous blood. Thus high venous pressure and greater filtering area favor the filtration of fluid. According to de Almeida (1920) high temperature increases the rapidity with which local edema is produced by venous congestion in the frog. Heat edemas may be at least partially due to physical effects similar to those exerted by local heat on the filtration of fluids through the normal capillary wall.

Summary. The effects of heat on fluid movement through the capillary wall are explicable on the basis of *a*, capillary dilatation which increases the area available for fluid movement; *b*, rise in capillary pressure which favors filtration, and *c*, injury by which heat, like other noxae, increases capillary permeability to colloids and consequently lowers the effective osmotic pressure of the plasma proteins. The effect of temperature on the permeability of the capillary wall to fluid alone has not been ruled out but, on theoretical grounds, other factors remaining constant, cannot be expected to influence conspicuously the balance between blood and tissue fluid.

2. *Tissue function in relation to capillary pressure and permeability.* The effects exerted on local blood flow and capillary diameter by products of metabolism have been reviewed in detail by Lewis (1927) and Krogh (1929). Secretory activity (Asher, 1908) and muscular contraction (Barcroft and Kato, 1915–16) are accompanied by a conspicuous increase of blood flow through the active tissues. Even temporary

anemia of the tissues produces reactive hyperemia (Lewis and Grant, 1924). The number of open capillaries in exercising muscle is much greater than in resting muscle (Krogh, 1919; Martin, Woolley and Miller, 1932) and the surface available for filtration is proportionately increased. Arteriolar dilatation and the opening of previously closed capillaries are generally ascribed to action of metabolic products (Asher and Barbera, 1898; Harris, 1922; Lewis and Grant, 1925). While there is not complete agreement concerning the specific metabolic product which produces vasodilatation (Krogh, 1929), the relation between tissue activity and hyperemia is not questioned.

Many observations have shown also, that tissue activity is accompanied by a shift in the equilibrium between the circulating blood and tissue fluid. It is an old observation that though lymph can be obtained only with difficulty from resting muscle, it flows freely during and after a series of contractions. Physiological activity increases the flow of lymph, usually but not always, from salivary glands (Asher and Barbera, 1898; Bainbridge, 1900; Moussu, 1900; Carlson, Greer and Becht, 1907); from the liver (Asher, 1899) and from the kidney (Schmidt and Hayman, 1929–30). Muscular activity also increases lymph flow. Barcroft and Kato (1915–16) compared the hemoglobin content of blood before and after its passage through contracting muscle and found that the blood loses fluid at the average rate of 1.0 cc. per hundred grams of tissue per minute. During exercise the muscles become heavier so that the rate of lymph flow must be something less than this. White, Field and Drinker (1933) cannulated the lymphatic vessels and found that muscular activity increases the flow of lymph but the lymph produced per gram of tissue cannot be computed from their data.

Capillary blood pressure rises following tetanus of muscle. In resting frog's muscle average arteriolar capillary pressure is 14.9 cm. water while average venous capillary pressure is 9.5 cm.; during the hyperemia which follows tetanus average arteriolar capillary pressure is 20.1 cm., and average venous capillary pressure 16.0 cm., without significant change in arterial or venous pressures (Landis, 1931). Pulse pressure in the capillary network is increased to several centimeters of water during this period of hyperemia. The conspicuous increase in capillary pressure must favor the movement of fluid toward the tissues.

It is unfortunate that there are no direct estimates of the amount of lymph produced per gram of active tissue. According to the indirect determinations of Barcroft and Kato (1915–16) filtration during muscular activity exceeds the possible filtration to be expected from a simple rise of

capillary blood pressure. Landis and Gibbon (1933) found in the human forearm that a venous pressure of 80 cm. of water causes fluid to accumulate in the tissue spaces at a rate of only 0.20 cc. per minute per hundred cc. of tissue, while Barcroft and Kato computed that in contracting muscle blood loses fluid at the rate of 2 cc. per minute per hundred grams of functioning tissue. Thus during muscular activity fluid leaves the blood at least several times more rapidly than it does under a venous pressure of 80 cm. water during rest. This suggests that some other factor is concerned in producing the high rate of lymph flow characteristic of functional activity of tissues.

Because of the close relation between tissue activity and lymph flow Asher and Barbera (1898) postulated that metabolic products must change the osmotic relationship between lymph and blood. Barcroft and Kato (1915–16) considered the formation of lymph in activity to be related to *a*, increased capillary pressure (following Starling, 1896) and increased metabolism (following Asher and Barbera, 1898). According to Barcroft and Kato the different points of view stressed by Starling and Asher, while frequently thought to be antagonistic, are really not in any true conflict. Metabolic products produce dilatation of the arterioles in active organs and cause local increase of capillary blood pressure with greater lymph flow. It is reasonable to suppose that functional activity, through the production of osmotically active substances, causes fluid to move toward the tissues by raising temporarily the osmotic pressure of the extravascular fluid, and possibly by increasing the permeability of the vessels. Barcroft and Kato were able in a few instances to show that if blood flow is constant and metabolism variable, the loss of fluid from the blood changes with metabolism. Given a constant metabolism, however, the loss of fluid from the blood changes with blood flow. They conclude that functional activity increases filtration *a*, directly, by altering the osmotic properties of the system, and *b*, indirectly, by inducing vasodilatation and increased capillary pressure.

This view explains why lymph flow during muscular activity exceeds the filtration produced during rest by a simple rise in capillary blood pressure. Muscular activity is accompanied by the production of osmotically active substances, which are diffusible and which, by reason of their smaller molecular size, have an osmotic pressure greater than the parent substances from which they were derived. According to Hill and Kupalov (1930) the frog's sartorius muscle, when completely fatigued, has an osmotic pressure greater than normal by an amount, which is equivalent to 0.35 per cent of NaCl solution. This, of course,

represents an extreme condition following anaerobic contraction. The change in the vapor pressure of the circulating blood during exercise shows that significant local changes in osmotic pressure in contracting muscle are at least within the range of possibility. According to Margaria (1930) severe muscular exercise raises the vapor pressure of human blood from the equivalent of 0.9447 gram of NaCl in 100 grams of water to the equivalent of 1.048 grams of NaCl in 100 grams of water.

Since these osmotically active substances diffuse from muscle into the extravascular fluids, and then into blood, it is logical to suppose that fluid will be withdrawn from the blood stream until diffusion restores the osmotic equilibrium which usually obtains between the diffusible constituents of blood and tissue fluid. No change in capillary permeability is required since this movement of fluid is due solely to temporary inequality of osmotic pressure inside and outside the capillary wall.

Shimizu (1931) observed in animals that muscular activity of mild grade had no uniform or conspicuous effect on the lactic acid content of blood. The amount of lactic acid in lymph, however, was always increased. He concludes that in dogs during muscular exercise, lactic acid is produced in the muscles, diffuses into the lymph spaces and finally reaches the circulation.

The movement of fluid toward functioning tissues might conceivably be concerned also with a change in the permeability of the capillary wall itself. This is suggested by the relatively high protein content of lymph collected from dogs during walking (White, Field and Drinker, 1933). According to Lazarus-Barlow (1894) simply stopping blood flow produces little transudation into the tissue spaces, but when accompanied by muscular activity it causes obvious edema. The lymph then becomes abnormally rich in protein, indicating that capillary permeability is increased.

Under normal conditions the glomerular filtrate produced in the kidney is nearly or quite free of protein (Wearn and Richards, 1924). Stoppage or even reduction of renal blood flow produces a transient albuminuria, which is not accompanied by any microscopically visible pathologic change (Starr, 1925a, b). Apparently temporary asphyxia increases the permeability of the glomerular tuft so that protein escapes from the plasma when blood flow is reëstablished.

Metabolism of adjacent tissues might modify endothelial permeability through 1, lowered oxygen tension; 2, increased carbon dioxide tension, or 3, local increase in acidity. From micro-injection experiments Landis (1928) concluded that, after three minutes' anoxemia, fluid filters through

the frog's capillary wall four times more rapidly than normal. After a period of oxygen lack the capillary wall, normally impermeable to protein, permits protein to pass and the effective osmotic pressure of the plasma proteins is reduced to one-half normal. The movement of fluid through the asphyxiated capillary wall is still directly proportional to the difference between capillary pressure and the effective osmotic pressure of the plasma proteins, indicating that the endothelium acts merely as a passive filter, though more permeable than normal. When blood flow is resumed the capillary wall rapidly recovers its impermeability to protein and the rate of fluid movement also returns practically to normal. This indicates that the effects of oxygen lack, if sufficiently brief in duration, are almost completely reversible.

Exposing the frog's mesentery to Ringer's fluid half saturated with carbon dioxide does not modify fluid movement; complete saturation increases the rate of fluid movement very slightly, but the wall still remains normally impermeable to protein. Increasing the hydrogen ion concentration within physiological limits produces almost no change in fluid movement until, at a pH of 4.0, the characteristic effects of injury appear.

Though brief, complete lack of oxygen increases capillary permeability conspicuously and reversibly it is still doubtful whether the oxygen tension in functioning tissues ever becomes low enough to be of importance. Anoxemia would have to occur in spite of increased blood flow and the opening of many new capillaries (Krogh, 1929). The possible effects of oxygen lack on capillary permeability must, however, be kept in mind on account of the evidence that the reactions of larger vessels (Adler, 1921) and of the capillaries themselves (Heimberger, 1926–27; Goldschmidt and McGlone, 1932) are modified by their oxygen supply.

There is little information concerning the importance of long-continued, mild oxygen lack. Bolton (1903–16) concluded that the edema of passive congestion, which follows ligation of the vena cava must be caused in large part by endothelial injury resulting from reduced blood flow, since in chronic experiments capillary blood pressure is not elevated except for a brief period immediately after the veins are ligated. In cardiac decompensation the edema fluid sometimes, but far from always, contains more protein than extravascular fluid rising from mechanical causes. This is possibly related also to capillary damage following long-continued, mild anoxemia.

Lymph collected from the subcutaneous lymphatics of walking dogs

contains from 1.52 to 0.5 per cent of protein (White, Field and Drinker, 1933). The protein content of this lymph is considerably greater than that ordinarily found in extravascular fluid or lymph produced by simply elevating capillary blood pressure. Moreover, lymph collected during exercise ordinarily contains red cells and this suggests also that the capillary wall is in some manner modified by muscular activity. Cohnheim (1867) observed in the frog's web that severe venous congestion produces capillary dilatation and, after a period of hours, extravasation of red cells, singly or in the form of small hemorrhages. Yet when venous congestion is relieved the closely packed cells within the capillaries are rapidly washed out and circulation continues quite normally in spite of the fact that orifices large enough to admit red cells had previously appeared in the capillary wall. Cohnheim expressed the belief that under pressure erythrocytes may escape through preformed stomata which close when pressure is reduced to normal. Turner (1933) observed that red cells escape sometimes directly into lymphatics, more often into the tissue spaces, during maximal venous obstruction combined with exercise. Drinker and Field (1933) found that venous pressure fluctuates during muscular activity; the pressure in the veins at the knee of the dog may be doubled when the leg muscles contract, falling instantly to the original value or lower when the muscles relax. The capillaries in the foot are subjected to a steady, high venous pressure when the individual stands quietly, and to a fluctuating pressure when he walks or runs. Microscopically it may be observed that circulation is much modified during tetanus of muscle when groups of capillaries are obviously distended, probably from pressure exerted by the muscle fibers on the small venules draining the region under observation (Landis, 1931). Blood will frequently spurt from such capillaries into the venules when the muscle relaxes.

If India ink be introduced under a pressure of 50 to 60 mm. Hg into single capillaries of the frog's mesentery some of the pigment escapes from weak spots in the capillary wall, collecting outside the vessel not uniformly, but in discrete collections. Yet afterward blood flows through such a vessel quite normally without undue loss of fluid, in spite of the fact that previously the wall had permitted the passage of India ink, to which even the damaged capillary wall is impermeable (Landis, 1934). Evidence is accumulating (Drinker, 1934) to show that activity may, in fact, produce temporary openings in the capillary wall through which erythrocytes may pass into the extravascular tissue. Apparently these

openings can disappear without modifying the normal permeability of the capillary wall under ordinary conditions since in some experiments mentioned by Drinker blood flow continues without microscopic evidence of any distinct rupture of the endothelium. The relation of capillary permeability to mild, long-continued oxygen lack and to these temporary openings will probably explain certain perplexing anomalies of fluid movement during tissue activity.

Summary. Functional activity of the tissues produces hyperemia and with it a rise in capillary blood pressure. The increased flow of lymph which accompanies tissue activity is probably too great to be explained on the basis of a simple rise in capillary pressure. It is likely that osmotically active substances produced in the course of tissue metabolism are concerned with this copious flow of lymph. The accumulation of carbon dioxide and changes in hydrogen ion concentration within physiological limits have little, if any, influence on capillary permeability, certainly not enough to lower the effective colloid osmotic pressure of the plasma proteins to any measurable extent. Lack of oxygen, if extreme, can produce a temporary increase of permeability which is great enough to reduce the effective colloid osmotic pressure of the blood to half its normal value. There is less information concerning the effects on capillary permeability of mild anoxemia persisting over long periods of time. Openings appearing temporarily in the capillary wall may explain certain anomalies of fluid movement observed during muscular activity.

3. *The effects of injury on capillary pressure and permeability.* The effectiveness with which the plasma proteins retain water within the capillaries depends upon the vitality of the endothelium. Injury increases capillary permeability and reduces correspondingly the effective colloid osmotic pressure of the blood. It is well known that tissue damage influences the movement of fluid through the capillary wall in a complex manner, depending, among other things, on the grade of damage and the concomitant changes in blood flow, capillary pressure and capillary permeability.

The injury that is produced when a single capillary is pierced by a micro-pipette is extremely slight, but nevertheless is often followed by measurable changes in blood flow and capillary pressure. While measuring capillary blood pressure in man Landis (1930b) observed that piercing the skin with a micro-pipette, 4 to 8 micra in diameter, usually produced slight dilatation of the nearest capillary loop, a local reaction previously described by Heimberger (1925). When capillary

pressure was then determined repeatedly at frequent intervals, the level of pressure in most instances remained unaltered, but in approximately one-third of the measurements it rose by 2 to 6, or even 16 mm. of Hg after the first reading, reaching a maximum during the first or second minute. The time relations of this brief increase in pressure are similar to those of the normal reflex flare to pin prick described by Cotton, Slade and Lewis (1916–17). Thus the minute trauma produced by piercing a single capillary loop sometimes stimulates the axone reflex, producing local vasodilatation and a transient rise in capillary blood pressure. The direct injury involved is so slight, however, that no local wheal or visible edema develops. Similar transient changes in capillary pressure were observed following the insertion of a micro-pipette into single capillaries of the frog's web (Landis, 1931), the maximum pressure in this situation being 0.5 to 4.5 cm. of water above the original readings. This circulatory reaction to minimal trauma illustrates the extraordinary sensitiveness of the peripheral circulation to what may be termed the slightest possible mechanical injury.

If a single capillary in the frog's mesentery be compressed gently by means of a minute glass rod the effect of local injury on the permeability of the endothelium becomes apparent (Landis, 1927a). Colloidal dye solutions pass freely through such an injured area long before they can be detected outside normal areas of endothelium in the same capillary. The colored fluid does not spurt from a single point as it should if the endothelium were ruptured, but filters out uniformly along the whole damaged section. India ink introduced intravenously flows past the normal section of capillary but the carbon particles accumulate in dense masses on the inner surface of the injured endothelium. When mechanical injury is severe blood corpuscles and ink are commingled in a solidly packed collection indicating that endothelial permeability is maximally increased and that whole plasma has filtered through the damaged section of capillary wall. In this instance the permeability of the capillary wall increases without change in diameter. The leakage of plasma and of dye-stained fluid, with consequent packing of corpuscles, is not produced by a rise in capillary blood pressure *per se* since fluid is retained in the undamaged portion of the same capillary. Hydrostatic pressure is the same in the injured and normal portions of a single capillary, but plasma leaks only from the injured segment of endothelium. Moreover, if blood pressure is elevated in a normal capillary the corpuscles move together as fluid is filtered from the trapped blood, but this filtration ceases when the proteins are concentrated sufficiently to balance

the higher capillary blood pressure (Landis, 1927a, b). If the endothelium retains protein the corpuscles are, therefore, never tightly packed since some plasma remains within the capillary. Thus mechanical injury of single capillaries evidently produces filtration of whole plasma primarily because of increased capillary permeability.

Injury which, instead of being limited to a minute area, affects large portions of the peripheral vascular system, initiates a series of events which are fundamentally similar in their development. The effects of widespread injury are more difficult to analyze, however, because of added factors such as capillary dilatation, rise of capillary blood pressure, and changes in blood flow. Small amounts of harmful substances introduced intravenously, or applied to a tissue externally, produce simply vasodilatation, increased rate of blood flow and usually a rise of capillary blood pressure. This was described in detail for urethane (Krogh and Harrop, 1921; Krogh, 1922; Landis, 1927a), and in part for formaldehyde (Jacobj, 1923). In acute experiments circulation continues and edema is not conspicuous. The reaction to more severe injury begins also with vasodilatation, ascribed to direct injury of the contractile elements of the capillary and arteriolar walls (Gelpke, 1921; Jacobj, 1923), and increased blood flow. This is followed more or less rapidly (depending on the grade of injury) by microscopically visible concentration of the red cells, slower flow, and finally complete stoppage of circulation due to complete loss of plasma through the damaged endothelium (Krogh and Harrop, 1921a; Gelpke, 1921; Jacobj, 1923; Herzog, 1925; Landis, 1927a).

The development of true stasis is the surest sign of increased capillary permeability (Krogh, 1922). The escape of plasma can be followed microscopically from the first visible concentration of cells through the period of sluggish flow when the viscosity of the concentrated blood impedes venous outflow, to the final stage when the capillaries are filled completely with solid cylinders of tightly packed cells. Stasis ordinarily begins in the venous capillaries but the column of packed and immobile cells grows longer as new erythrocytes are added to it on the arterial side until the entire capillary network, and the smaller arterioles likewise, are involved. The term stasis has been used by Elliott (1921), Lennartz (1921) and Stegemann (1924) merely to designate cessation of flow without reference either to escape of fluid or to change in the ratio of corpuscles to plasma. In experiments dealing with capillary permeability, however, Krogh's use of the word has been adopted by Herzog (1925), Florey (1926b) and Landis (1927a); in each case the important

feature is the concentration of the red cells to which stoppage of flow is secondary. To avoid confusion, it is in this latter sense that the word is used in this paper.

Capillaries injured to the point where stasis occurs permit proteins (Landis, 1927b), colloidal dyes (Krogh, 1922; Herzog, 1925; Landis, 1927b; Menkin and Menkin, 1930) and colloidal starch (Krogh, 1922) to pass but still retain India ink quantitatively (Krogh, 1922; Herzog, 1925; Landis, 1927a). Krogh (1922) placed the size of the pores in damaged endothelium between 5 and 200 millimicra. The increased endothelial permeability of injury reduces the effective colloid osmotic pressure of the plasma conspicuously and increases by five to seven times the rate at which fluid filters through the capillary wall under the influence of a given difference between the effective colloid osmotic pressure of the blood and hydrostatic pressure (Landis, 1927b). Stickiness of the endothelium accompanies injury (Krogh, 1922; Herzog, 1925; Landis, 1927a) and affects not only the distribution of erythrocytes but of platelets (Landis, 1927a) which at times form colorless thrombi large enough to stop blood flow.

Increased endothelial permeability, though often accompanied by marked dilatation (Krogh, 1929) occurs also in constricted capillaries when highly injurious substances are applied to the vessels (Ricker and Regendanz, 1921; Landis, 1927a). Stasis often appears and resolves spontaneously without measurable change in capillary diameter (Landis, 1927a; Florey, 1926b). It is therefore primarily injury, and not stretching of the wall, which increases capillary permeability. It is logical, however, to suppose that injury sufficient to devitalize the endothelium might also diminish or even abolish the power of the contractile elements to maintain normal capillary tone.

The increased transudation through the walls of injured capillaries, though fundamentally dependent on greater capillary permeability, is related also to capillary blood pressure. The rate at which blood plasma leaves the injured capillary is greater during cardiac systole, when capillary pressure is high, than during diastole, when capillary pressure is slightly lower (Landis, 1927a). If systemic blood pressure is low stasis is absent or develops very slowly. Moreover, the development of stasis may be delayed or stopped at any moment if capillary pressure is reduced by blocking the arteriole supplying the injured region. Stasis develops more rapidly in a capillary network with rapid blood flow where capillary pressure is high than in a capillary network showing sluggish flow (Landis, 1927a).

Capillary pressure changes conspicuously as stasis develops. If dilute urethane be applied to the mesentery of the frog the capillaries dilate, capillary pressure rises slightly during hyperemia, but stasis does not occur. If a more concentrated solution is applied blood flow, at first rapid, becomes gradually more and more sluggish. When the corpuscles begin to concentrate in the venous capillaries and venules, capillary blood pressure rises quite suddenly to levels approaching arteriolar pressure. This striking rise in capillary pressure is ascribed to blockage of the venous capillaries by abnormally viscous, concentrated blood (Landis, 1927a). The transudation of fluid is favored by the higher filtration pressure and stasis, once begun, advances very rapidly. When the entire capillary network is blocked by cells in stasis capillary pressure is again low because solid plugs of cells in the finer arterioles interpose a block to arterial pressure. Thus while high capillary pressure does not in itself produce stasis, it favors the rapid development of stasis when the endothelium is injured. Resolution of stasis is favored by the lower capillary pressure observed during the later stages of injury.

Stasis develops rapidly or slowly depending upon the nature and the concentration of the injurious substance. The intravenous injection into a frog of gold or platinum salts is followed within a few minutes by conspicuous arteriolar dilatation, the opening of many new capillaries, and striking capillary dilatation. In a few minutes more capillary blood flow becomes slow, the corpuscles are concentrated and stasis develops in the turgid capillary network (Heubner, 1907; Gelpke, 1921). Eventually the capillary wall loses its continuity so that large or small hemorrhages appear. The whole series of events requires but 5 or 6 minutes and the more rapid the advance of stasis, the less likely is one to observe the original vasodilatation and the increased blood flow. Generally speaking, hyperemia with rapid blood flow is physiological and easily reversible; hyperemia with slow blood flow is pathological and return to normal conditions is difficult or even impossible.

If injurious chemical substances are applied externally in different concentrations to the frog's tongue or web the various stages of the reaction to external chemical damage may be dissociated. Urethane in dilute solution produces merely vasodilatation, but in concentrations toxic to other living cells also increases capillary permeability conspicuously (Landis, 1927a). According to Jacobj (1923) formaldehyde applied to the frog's web in concentrations less than 0.05 per cent does not change the peripheral circulation. An 0.05 per cent solution produces slight constriction which soon gives way to dilatation; 0.25 per

cent produces only dilatation and increased blood flow without any evidence of stasis. Stronger solutions after the period of rapid flow produce progressive slowing of flow with eventual stoppage in stasis. Formaldehyde in 1, 4, 16, 30 and 40 per cent strengths produces conspicuous stasis in 60, 55, 37, 18 and 3 minutes respectively. In each concentration the first effect is dilatation of all the vessels large and small. Jacobj ascribes this dilatation to paralysis of the contractile elements since they fail to react to sympathetic stimulation. Paraformaldehyde induces vasodilatation and increased blood flow continuing for a longer time; stasis appears only after some hours. The intravascular collections of cells then consist of both leucocytes and erythrocytes in the form of mixed thrombi.

If the injury is great enough to produce early stasis edema rarely appears since blood flow ceases in the injured area before sufficient fluid can pass out of the blood vessels to distend the tissues grossly (Ricker and Regendanz, 1921). Milder grades of damage persisting over longer periods of time, however, permit fluid to filter in sufficient amount to produce edema. Tainter and Hanzlik (1924) attribute the edema produced by paraphenylenediamine to injury of the capillary wall with escape of plasma protein. Colloidal dyes such as Congo red and trypan blue pass readily into the tissue fluid of the edematous region. The tissue fluid itself contains fibrinogen and forms a gelatinous coagulum in the distended tissue spaces. At blood pressures below 75 mm. Hg edema does not appear though at pressures above 85 mm. Hg the same dose of paraphenylenediamine produces edema regularly. This form of edema has no relation to colloid imbibition, local acidosis or to the central or peripheral nervous system. Local anesthesia or atropine has no effect on the appearance of the edema. The absence of a deep fascia in the head and neck favors the collection of edema fluid in these regions but edema can also be produced in the limbs of cats and rabbits (Gibbs, 1931). Edema of the lung does not appear, either because there is little or no normal interchange of fluid in this area (Gibbs, 1931), or because of the lower blood pressure in the pulmonary circuit.

Uranium salts, frequently used to produce experimental nephritis, also produce edema of the tissues if sufficient water is given the animal (Aubel, Mauriac and Boutiron, 1926) or if the tissues are perfused (Sato, 1928d). On account of the high protein content of the extravascular fluid Govaerts (1928a) concludes that the edema of acute uranium poisoning is primarily extrarenal in origin. Whitney (1928) found that uranium poisoning diminishes the rate at which antibodies penetrate

into the tissues and lymph; the reason for this slower penetration is not clear.

The wheal, a form of local edema, forms one part of the triple response reviewed by Lewis (1927) and Krogh (1929). Such localized collections of extravascular fluid can be produced in the skins of all young subjects when suitable stimuli are applied, though the susceptibility of the skin in different individuals varies (Lewis, 1924). Wheal fluid contains large amounts of protein (Lewis, 1924), and dyes which pass through the normal capillary wall very slowly, appear quickly in the wheals produced by stroking the skin (Hoff, 1927) or by injecting various irritant substances (Adlersberg and Perutz, 1932). External pressures above 30 to 50 mm. Hg prevent the wheals from forming even though the tissues have been injured. Lewis (1924) concludes that the wheal is due primarily to increased capillary permeability which is independent of capillary dilatation. The filtration of fluid and protein is not inherently due to increased filtration pressure, though aided considerably by high filtration pressure and rapid blood flow. Török, Rajka and Wessely (1928) found that mild venous congestion makes the wheal larger owing to high capillary pressure while severe venous congestion reduces its size owing to restricted blood flow. Starr (1930) uses the size of the histamin wheal to detect clinically the degree to which the flow of blood is reduced in peripheral vascular disease.

When once a wheal has been produced, a second stimulus in the same area after the disappearance of the first wheal fails to produce the gross evidences of increased capillary permeability in that area. Lewis and Grant (1924) attribute this to refractoriness, caused by alteration of the capillary endothelium so that it becomes for a time impermeable, even when stimulated and dilated a second time by histamin or a histamin-like substance. Hoff (1927) studied areas previously the site of whealing and, by elastometry, identified a latent edema which persisted after the wheal had to all external appearances gone away completely. According to Hoff (1927) in such a refractory area plasma and Congo red leave the blood stream rapidly but the skin is not elevated since the fluid leaks away from the injured area into the subcutaneous tissues through numerous fissures opened up by the previous edema in that region. The observations of Hoff are of considerable interest in connection with the rapid disappearance of intradermally injected salt solution from the skin of patients with edema or pre-edema. Pilcher (1926) observed that edema, whatever its cause, lessens wheal formation though in nephritis and heart disease unaccompanied by edema, the wheals produced by codein are normal.

Edema fluid removed from wheals in a case of Quincke's edema contained 3.12 per cent of protein, of which two-thirds was albumin with a trace of fibrinogen. Govaerts (1928b) concludes, therefore, that injury of the capillary wall, local in distribution, and of unknown origin, is responsible for this type of edema.

The local application of irritants to epithelial surfaces produces edema in the underlying tissue. Hirschfelder (1924) applied mustard oil to the conjunctiva of the rabbit and showed that this form of inflammatory edema is associated with demonstrable injury of the capillary wall. The edema is not due to imbibition of water by colloids, nor in any direct way to the activity of nerves. A low systemic blood pressure, or local vasoconstriction inhibits the appearance of edema. Vasodilator drugs increase the edema unless systemic blood pressure is very low. Local anesthetics and calcium chloride affect the edema in general accordance with their effect on local capillary blood pressure. Hirschfelder concludes that though the edema of mustard oil conjunctivitis is due primarily to injury of the capillary wall, the appearance of edema is conditioned by the capillary blood pressure in the inflamed area.

Local injury, chemical or thermal, if very severe often produces constriction of the arteries with simultaneous stasis in the capillary network (Ricker and Regendanz, 1921; Krogh, 1922; Landis, 1927a, 1931). If injury is mild, however, arteriolar dilatation and increased rate of blood flow are the rule, though prolonged action of mild noxae produces eventually the same result as a brief exposure to severe noxae. Ricker and Regendanz (1921) believe that the effects of injury, including even stasis, are due to stimulation of vasoconstrictor and vasodilator nerves, capillary permeability being affected secondarily. In some instances certainly (Landis, 1927a; 1928) injury affects the endothelium directly. Takenaga (1925) observed that the local redness produced by mustard oil appears though the sensory nerves to the inflamed area have degenerated. He concludes that the contractile elements of the capillaries are damaged by direct action, the axone reflex if involved being of secondary importance.

Heat and cold if sufficiently severe lead to blister formation (Lewis and Grant, 1924; Lewis, 1927); the fluid of the blister contains considerable protein indicating conspicuous damage of the capillary wall. Milder forms of heat and cold produce swelling of the skin without blisters, the swelling being due to an increase in the amount of subcutaneous fluid. Light, if sufficiently intense, injures the capillary wall and increases its permeability (Campbell and Hill, 1924; Levy, 1929; Hudack and McMaster, 1932).

Few measurements of capillary blood pressure have been made in inflamed tissues. Landis (1930) observed that freezing and the application of cantharides elevate cutaneous capillary blood pressure conspicuously. This must favor exudation after injury particularly since the effective colloid osmotic pressure of the blood is simultaneously reduced.

The systemic effects of endothelial injury and increased capillary permeability on blood volume have been studied exhaustively in relation to shock and need not be considered here. Recently Blalock, Beard and Thuss (1932) found that in animals whose blood pressure remained normal, salt, glucose or acacia solutions can be injected intravenously without diminishing the total circulating plasma protein. The fluid filtering through the capillary wall after salt and glucose injections is practically protein-free. In the presence of a declining blood pressure (Blalock, Beard and Thuss, 1932), local trauma (Beard and Blalock, 1932), and histamin (Beard, Wilson, Weinstein and Blalock, 1932), the circulating plasma protein diminishes considerably after similar intravenous injections indicating that plasma protein is lost through the capillary wall. Freeman (1933) injected adrenalin constantly over a period of hours in physiological amounts, finding that blood pressure and blood volume gradually diminish. He suggests that prolonged vasoconstriction of itself produces loss of fluid from the circulation. This is due presumably to increased capillary permeability from asphyxia after prolonged periods of diminished blood flow.

The inflammations seen in pathological conditions include in their early stages all of the reactions characteristic of local injury, but in later stages are far more complicated. There can be little doubt that the permeability of the capillary endothelium is increased in inflammation; colloidal dyes pass more easily (Hoff and Leuwer, 1926) and exudates, subcutaneous and serous, contain protein in concentrations approaching that in blood plasma. Even particulate matter passes through the capillary wall during true inflammation (Menkin, 1931b). Vasodilatation, increased blood flow, later sluggish blood flow and even stasis in isolated areas, with accompanying changes in capillary blood pressure are all found in various stages of inflammation.

The absorption of dyes or toxic substances injected into an injured tissue is often much delayed (Menkin, 1929; Underhill, Kapsinow and Fisk, 1930; Okuneff, 1930), and considerable evidence indicates that foreign substances in general are fixed in injured tissues (Menkin, 1931a, 1933) though lymph flows copiously from the same region (White, Field

and Drinker, 1933). This mechanism of nonspecific fixation protects the organism at the expense of local injury (Menkin, 1931a, c). Superimposed on the immediate effects of injury are leucocytic infiltration and the other reactions to long-continued, low-grade irritation. Schade (1927) reviews the changes in the tissues which play a rôle during inflammation by favoring the movement of fluid from the blood to the tissue spaces. The modified elasticity of connective tissue (Landerer, 1884; Schade, 1926), the greater depression of freezing point in purulent exudates (Schade, et al., 1926), modified reactions of blood vessels (Ricker and Regendanz, 1921; Krawkow, 1924), and possible increased metabolism of the injured tissues (Gessler, 1931a, b) all imply that inflammation, in both its development and its resolution, involves much more than the relatively simple changes in permeability and pressure which are characteristic of acute chemical or physical injury.

Summary. Local injury initiates a complex response including vasodilatation, rise in capillary blood pressure, first increased, then decreased blood flow, increased endothelial permeability and finally stasis. All forms of local or general edema produced by injury are due fundamentally to increased capillary permeability with easy passage of proteins and water through the endothelium. Agents which reduce systemic blood pressure or local capillary pressure prevent edema fluid from collecting even though the capillary wall is severely damaged.

CONCLUSION

The movement of fluid through the capillary wall depends primarily upon the balance between capillary blood pressure and the colloid osmotic pressure of the blood. The effectiveness of this balance is modified, however, by endothelial damage, by tissue pressure, by temperature, by the accumulation of metabolic products and by other unidentified factors. Conclusions concerning capillary permeability are often made without considering in detail the many simple physical forces concerned in the movement of water and of dissolved substances through the capillary wall. Of these forces, capillary blood pressure is neglected more frequently than any other. This has resulted in the postulation of theories involving either active intervention of the endothelium or various modifications of its permeability under conditions inadequately controlled from the physical standpoint. Many facts concerning fluid balance, particularly in the intact animal or in patients with clinical edema, cannot be explained in terms of the simple physical forces which have been considered in this review. It seems probable, however, that adequate control of

these elementary forces will make the search for other factors both simpler and more productive.

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