THE ORIGINAL idea of a blood-brain barrier arose at the turn of the century as an explanation of the properties of the living brain in relation to certain dyes and pharmacologically active compounds, injected either into the bloodstream or directly into the cerebrospinal fluid (CSF) of experimental animals (reviewed by Bradbury, 1979). This developed into the general concept of a cellular barrier between blood and the interstitial fluid of brain (Krogh, 1946), but the hypothesis had no firm structural basis and was abandoned by many when early electron micrographs showed no differences between capillaries in brain and those elsewhere, e.g., in skeletal muscle (Maynard et al., 1957).

In the late 1960's, the use of various hemeproteins and other markers which could be made visible under the electron microscope established unequivocally that the barrier within the brain to molecules of 1,800 daltons and above was the endothelium of cerebral capillaries (Reese and Karnovsky, 1967; Brightman and Reese, 1969). Since that time, there has been an explosive increase in experimental work on the properties of transport across the barrier. The final objective must be to elucidate the cellular and molecular mechanisms involved in this transport, and evidence about these is now beginning to appear. A number of reviews and monographs are available which deal both with general features of structure and function (Davson, 1976; Rapoport, 1976; Bradbury, 1979; Fenstermacher and Rapoport, 1984) and with specific aspects of barrier function. Particular topics for which there are recent and excellent reviews are substrate supply to the brain (Pardridge and Oldendorf, 1977; Crone, 1980; Pardridge, 1983), glucose transport (Lund-Andersen, 1979), modulation of transport (Gjedde, 1983; Gjedde and Crone, 1983), mechanism of ion distribution (Fenstermacher, 1975), volume regulation of the brain (Fenstermacher, 1984), comparative physiology (Cserr and Bundgaard, 1984), handling of monoamines (Hardebo and Owman, 1980), peptides, and the blood-brain barrier (Meisenberg and Simmons, 1983; Pardridge, 1984), and function particularly in relation to studies with isolated suspended microvessels (Goldstein and Betz, 1983; Joo, 1984). My objective here will be to consider how the ultrastructure of the cerebral endothelium and adjacent structures differs from that elsewhere and how this gives a basis for the transport properties of the barrier. Also of particular interest in relation to the physiology of the microcirculation in general are the properties of net fluid movement across the cerebral vessels and the recent demonstration of a relation between apparent permeability of the barrier and cerebral blood flow.

Ultrastructure and Function

The Cerebral Endothelium

As has been indicated, the site of the barrier to horse radish peroxidase of molecular weight 40,000 (Reese and Karnovsky, 1967; Brightman and Reese, 1969), cytochrome c of 17,000 (Milhorat et al., 1973), microperoxidase of 1,800 (Reese et al., 1971), and colloidal lanthanum hydroxide is the endothelium of all intracerebral vessels, except those in certain high-permeability regions. Movement across the endothelium in either direction is stopped by the presence of occluding tight junctions in the interendothelial clefts. Tight junctions have been observed in every interendothelial cleft examined, suggesting a continuous belt or zonula occludens around each endothelial cell. In 49 of 100 cross-sections of cortical and cerebellar capillaries (Oldendorf et al., 1977), no intercellular clefts were cut across, indicating that individual endothelial cells can form an uninterrupted cylinder around the lumen. In addition, there normally is no vesicular uptake of peroxidase (Reese and Karnovsky, 1967) or of colloidal iron (Clawson et al., 1966) into cerebral endothelial
cells, so that pinocytosis can play little role in transport across the normal blood-brain barrier.

When interendothelial junctions in mammalian (Connell and Mercer, 1974; Dermietzel, 1975; Tani et al., 1977) and reptilian brain (Shivers, 1979) have been subjected to freeze fracture, they can be seen to be highly complex, consisting of an Anastomosing network of intramembrane ridges of particles and complimentary grooves. The number and complexity of these strands is comparable to those of very tight epithelial junctions (Claude and Goodenough, 1973).

The permeability properties of almost all capillaries outside the central nervous system (CNS) depend largely on the presence of water-filled channels which traverse the vessel wall and which are probably interendothelial in position. These allow free passage of all molecules up to the size of inulin (5,000 daltons) and beyond. Since the interendothelial clefts in brain are completely sealed with zonulae occludentes, the transport properties of the blood-brain barrier must be largely those of the plasma membranes of the endothelium. There has been some argument as to whether small polar molecules may diffuse across the barrier relatively faster than predicted for solution in a pure lipid layer, because of a limited water-filled route across the endothelium. The presence of such a route was indicated by Fenstermacher and Johnson's (1966) estimations of reflection coefficients at the blood-brain barrier and by calculations of permeability-surface area (PS) product/diffusion coefficient in water for various polar molecules by Bradbury (1979). The idea has received recent support from measurements of dilution potentials for NaCl and KCl across cerebral capillaries in the frog (Crone, 1984). The results suggested a small number of neutral or weakly charged pores which did not discriminate between Na, K, and Cl. The presence of water-filled channels is also suggested, if the osmotic permeability of a membrane is greater than its diffusional permeability to tracer water. Although indicator diffusion studies of the blood-brain barrier first indicated that this might be so (Paulson et al., 1977), a later mathematical analysis showed that the results could be explained by a nonporous blood-brain barrier, together with an unstirred layer between moving blood and the barrier (Patlak and Paulson, 1981). Overall it can be concluded that if there are water-filled channels, their total effective area is too small to cause an unambiguous physiological effect.

Electrical and Diffusional Resistance

This picture of a very tight cellular barrier has been given striking quantitative substance by measurements of the electrical resistance across the walls of capillaries near the surface of living frog brain (Crone and Olesen, 1982). Current was injected into the lumen via a microelectrode, and the intravascular profile of potential was measured with a second electrode placed at various distances from the source. Membrane resistance was calculated from cable theory and was found to average 1900 ohm-cm². This specific resistance of brain endothelium is of a size similar to that measured across amphibian tight epithelia, such as skin and urinary bladder, and across amphibian erythrocyte membranes. In line with this high resistance, cerebral interendothelial junctions in both the frog (Bundgaard, 1982) and in a mammal are impermeable to ionic lanthanum (Bouldin and Krigman, 1975).

This potent restraint at the level of the blood vessels leads to the situation whereby solutes, e.g., sucrose and inulin, which freely enter the extracellular space of most tissue and are restricted to it, barely enter the brain at all. Similarly, solutes—which, in other tissues, penetrate into parenchymal cells and which suffer their major hindrance at this entry—in brain are delayed primarily at the capillary endothelium. Since the surface area of endothelium is insignificant compared with that of all the cells and processes within the brain, uptake from interstitial fluid into cells is not rate limiting. Hence, many solutes of differing properties and solubility enter brain from blood according to a single rate constant (Bradbury, 1979). This 'ready mixing beyond the barrier has greatly simplified the kinetic analysis of blood-brain barrier permeability.

In addition to lipophilic solutes, a number of polar metabolic substrates cross the plasma membranes of the cerebral endothelium via specific transport sys-
Cytochemistry of the Cerebral Endothelium

No other transporting protein has been tentatively isolated from the cerebral endothelium, but increasingly sophisticated ultrastructural techniques, together with biochemical studies of isolated capillaries, are leading to insights concerning those enzymes which are localized in cerebral capillaries. Some of these may be involved in transport mechanisms. Enzymes which are present at high concentration in tight cerebral endothelium include γ-glutamyl transpeptidase, alkaline phosphatase, the Na⁺,K⁺-ATPase, butyrylcholinesterase, and aromatic-L-amino acid decarboxylase. γ-Glutamyl transpeptidase has become a standard marker enzyme for transporting epithelia rather than in connective tissue. The glial end-feet must be a natural candidate for mediating such an influence.

An intriguing feature of the astrocytic plasma membrane is the presence of "assemblies" of intra-
membrane particles (Landis and Reese, 1974; Brightman et al., 1983). These particles are 5–7 nm wide and are grouped in orthogonal aggregates. They are revealed on the inner face of the cleaved membrane at freeze-fracture and may connect with the underlying cytoskeleton of filaments. They are particularly numerous in the end-feet of astrocytes, making contact with pia or with blood vessels. Their function is unknown, but their numbers increase greatly during the gliosis, induced by, e.g., cold injury. Cell culture experiments indicate that they may be responding in such injury to a fall in extracellular pH, associated with accumulation of lactic acid and CO₂.

Bradbury (1975) has discussed the concept that astrocytes, being epithelial in nature, have a polarity, their basal (vascular) and apical (neuronal) processes being distinct and asymmetrical. This idea has now received experimental support, at least as far as the Muller cells of the retina are concerned. The apical processes of these cells contact the photoreceptors, whereas the basal processes lie in the vitreous humor. Newman (1984) has investigated such cells, dissociated from the salamander retina, with microelectrodes. Almost all the membrane conductance is due to potassium movement, and 94% of the total conductance is attributable to the end-foot membrane. It is known that neuronal activity in the brain releases potassium into the local extracellular fluid. This will tend to depolarize adjacent astrocytic processes. If the basal vascular end-feet of cerebral astrocytes have as high a potassium conductance as the vitreous processes of Muller’s cells, electronic spread of depolarization will cause preferential movement of potassium ions into the perivascular extracellular space (Newman, 1984). This released potassium could well influence the permeability of the endothelium or the state of contraction of the endothelium or of the vascular smooth muscle. Alternatively, depolarization of the end-foot membrane might lead to calcium influx, mediator release, and/or other events with a potential effect on the vessel wall. It has already been mentioned that the enzyme, 5’-nucleotidase, which hydrolyzes adenosine 5’-monophosphate (AMP), is present in the membranes of glial end-feet.

Thus, circumstantial evidence available suggests that the role of glial end-feet at the blood-brain barrier is regulatory. First, they may induce and maintain the particular characteristics of the cerebral endothelium. Second, they may form a means of communication between neurones and capillaries whereby local perfusion or capillary permeability, or both, may be regulated in relation to the needs of neuronal activity.

**Net Fluid Movement across the Cerebral Endothelium**

**Filtration Coefficient**

The picture already presented of a very tight endothelium would suggest that the blood-brain barrier must have a very low filtration coefficient or hydraulic conductivity, Lp. This is confirmed by two experimental estimations. Fenstermacher and Johnson (1966) measured the changing volume of rabbit brain in response to raising the osmolality of blood. Sucrose and raffinose were considered to be nonpenetrating. When the concentration of either was raised in blood, the initial rate of water movement out of brain yielded a Lp of 0.8 × 10⁻⁹ cm/sec per cm H₂O. An almost identical value for Lp of the blood-brain barrier has been found by Paulson et al. (1977) in man by the intracarotid injection of a hyperosmotic bolus. Dallas and Fraser (1984) have measured the filtration coefficient of single pial capillaries in the frog. Fluid movements were estimated by introducing carboxyfluorescein into a capillary and measuring its fluorescence with a television microdensitometer. Capillaries were occluded, and the change in fluorescence during superperfusion with saline, made hypertonic with sucrose, was compared with that during superperfusion with isotonic saline. A minority of capillaries which remained tight had a mean Lp of 3.2 ± 0.5 × 10⁻⁹ cm/sec per cm H₂O. The variability indicated that water- and solute-conducting channels may have been opening up through the tight junctions, and further calculation suggested that the Lp for the water-only pathway (plasma membrane) would be 1.15 × 10⁻⁹ cm/sec per cm H₂O, very close to the average value of total Lp obtained by Fenstermacher and Johnson for capillaries in rabbit brain. This contrasts with a value of 74 × 10⁻⁹ cm/sec per mm Hg in the same units for capillaries in frog skeletal muscle (Curry and Froekjaer-Jensen, 1984) and a mean of 779 × 10⁻⁹ cm/sec per mm Hg for frog mesenteric capillaries [values collected from the literature by Gore (1982)].

Net volume flow across a membrane is determined by the equation

\[ J_v = L_p(\Delta P - \sigma\Delta \pi) \]

where \( \Delta P \) is the difference in hydrostatic pressure and \( \Delta \pi \) is the difference in osmotic pressure due to solutes, if impermeant. If \( \sigma \) for NaCl is 0.5 (it is probably much higher), a 10 mm difference in NaCl concentration across a brain capillary would produce an osmotic pressure difference of 170 mm Hg. Thus, the potential osmotic pressure due to solutes of small molecular weight is overwhelming, compared with that due to protein. Whereas filtration cannot reasonably account for the production and for the composition of cerebral intestinal fluid, the presence of a tight endothelium, with a high density of Na⁺,K⁺-ATPase in its abluminal membrane and with numerous mitochondria, indicates that secretory mechanisms can generate and maintain ion gradients and may cause bulk flow of fluid.

**Production and Bulk Flow of Interstitial Fluid**

It is now pertinent to ask, first, whether there is experimental evidence for the bulk production of
interstitial fluid within the brain, and, second, if this occurs, what the mechanism for net movement of sodium and chloride ions from blood to cerebral interstitial fluid may be, and how may it be influenced. With regard to the first question, Cserr and colleagues have provided much evidence that there is convection within cerebral interstitial fluid. After microinjection into brain, it was found that anatomical tracers moved through the tissue away from the injection site along preferential channels, yielding a pattern of distribution consistent with bulk flow rather than with diffusion (Cserr and Ostrach, 1974; Cserr et al., 1977). Channels of flow outlined by the tracers included the perivascular spaces, spaces between fiber tracts in the white matter and within the subependymal layer of the ventricular ependyma. Most striking was the observation that radiotracers of molecular weights from 900 to 69,000 (differing in their diffusion coefficients by up to 5 times) were cleared from brain according to a single exponential rate constant (Cserr et al., 1981) (Fig. 3). This can only be due to convection, not to diffusion. It suggests a largely centrifugal bulk flow of interstitial fluid, the driving force being the hydrostatic pressure gradient generated by its secretion across the endothelium, but other factors such as to-and-fro movement of cerebrospinal fluid (CSF) in the perivascular spaces due to arterial pulsation need to be excluded. Although metabolic production of water could almost quantitatively account for the apparent flows observed, such water is likely to be immediately reabsorbed into blood by osmotic forces, since it contains no solute. If it is assumed that clearance of large molecules is due entirely to a unidirectional bulk flow due to production by the endothelium, the following production, and, hence, drainage rates, may be estimated: for the rat, caudate nucleus 0.18 μl/g per min, internal capsule 0.19 μl/g per min, and mid-brain 0.29 μl/g per min (Szentivanyi et al., 1984), and in the rabbit caudate nucleus 0.11 μl/g per min (Bradbury et al., 1981).

**Ion Transport and Secretion by the Endothelium**

Little is known of the membrane mechanism which might be involved in such a net secretion of interstitial fluid. The Na\(^{+}\),K\(^{-}\)-ATPase in the abluminal membrane of the endothelium probably contributes to the homeostasis of potassium in interstitial fluid by leading to increased efflux when its concentration is raised (Bradbury and Šulcová, 1970). The enzyme is also well placed for pumping sodium into interstitial fluid, thus providing the driving force for the movement of other ions and of water. Chloride transport across the endothelium into brain has been shown to be a saturable concentration-dependent process with similarities to the chloride exchange process in erythrocyte membranes (Smith and Rapoport, 1984). Betz (1983b) has sketched a model of ion transport across the cerebral endothelium which includes furosemide-sensitive coupled influx of sodium and chloride at the luminal membrane and amiloride-sensitive Na\(^{+}\)-H\(^{+}\)-exchange at the abluminal membrane, in addition to the ouabain-sensitive Na\(^{+}\)-K\(^{-}\)-pump. This model was based on the intracarotid bolus technique for the luminal membrane (Betz, 1983b) and on the isolated capillary preparation for the abluminal membrane (Betz, 1983a). Whereas coupled NaCl influx, together with sodium pumping, might form a good basis for secretion, c.f. various epithelia (Frizzell et al., 1979), the presence of Na\(^{+}\)-Cl\(^{-}\)-cotransport is not supported by the experimental evidence. A 50% reduction in chloride influx did not alter sodium influx into parietal cortex (Smith and Rapoport, 1984), and the furosemide inhibition observed by Betz (1983b) apparently required 1 mm of the drug and occurred only at the low sodium concentration of 1.4 mm.

The volume of the vertebrate brain is regulated in the face of maintained osmotic disturbances in the blood, either hypo- or hyperosmolality. This control appears to include regulation of both the extracellular and intracellular volumes, the former being based on net movement of sodium chloride either out of (hypoosmolality) or into (hyperosmolality) the brain [reviewed by Bradbury (1979)]. This regulation occurs in brains with a glial blood-brain barrier—e.g., that of the skate (Cserr et al., 1983)—as well as in the mammal. In the skate, the increased influx of \(^{22}\)Na which occurs into brain when the fish is rendered hyperosmotic takes place across the blood-brain barrier and is probably inhibitable by furosemide and bumetanide, neither drug influencing the isosmotic influx (Mackie et al., 1984). This suggests that coupled NaCl transport across the glial barrier is activated in hyperosmolality. Mammalian brain also takes up sodium chloride in hypernatremia, but this probably occurs from subarachnoid fluid (Pullen and Cserr, 1984), the rate constant for

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**Figure 3.** Disappearance of radiolabeled polyethylene glycols and albumin from brain, following microinjection into rat caudate nucleus. k's are first order rate constants for total efflux from brain, and points are the means from five to seven animals. Rates of efflux are similar, despite a 5-fold range in diffusion coefficients (from Cserr et al., 1981).
23Na influx from blood being unaltered in hyper-natremia (Patel et al., 1982; Csern and DePasquale, 1983).

Although the cerebral interstitial fluid clearly is maintained by active mechanisms under physiological conditions, the situation will be reversed when there is marked opening of the blood-brain barrier. When the permeability to small solutes is high, e.g., in the posts ischemic period (Sage et al., 1984), there is likely to be pressure-dependent filtration across capillary walls into brain (vasogenic cerebral edema), and this will become severe if albumin can also escape into the interstitial fluid.

Apparent Capillary Permeability and Blood Flow

Renkin-Crone Analysis

Since there often is doubt as to the precise area of capillary endothelium across which transport is occurring, the facility of exchange of a solute across the blood-brain barrier, as across other capillaries, is often expressed as a permeability-surface area product, rather than as a permeability coefficient (Bradbury, 1979). This is defined as the unidirectional influx of the solute, mass entering brain per unit time, divided by average capillary concentration. It is often related to unit wet weight of brain and, thus, may be given units of ml/g per min. Since the blood-brain barrier is the main limitation to movement of most solutes from blood into brain, this PS product can be estimated by measuring either the uptake of a radiotracer into brain or its extraction from blood. It is necessary to choose times at which backtransport from brain to blood is not significant.

A complication arises in this, if the extraction of a solute from capillary blood is moderate, its concentration in the venous blood will be less than that in the blood entering the capillary. This progressive reduction in the driving force to solute movement may be allowed for. If it is assumed that all capillaries are cylindrical tubes having uniform dimensions and permeability and receiving uniform perfusion, and that there is no back diffusion, then extraction, E, may be related to PS product and to perfusion flow, Q, by the equation derived by Renkin (1959) and Crone (1963).

\[ E = 1 - e^{-PS/Q} \]

It might be anticipated that PS product would be independent of flow, but in several tissues, including skeletal and myocardial muscle, several solutes of differing molecular and ionic weight show markedly varying apparent permeability with flow (Renkin, 1959; Alvarez and Yudilevich, 1969; Yipintsoi et al., 1970). The phenomenon of an increase in PS product with augmented flow has been ascribed to capillary recruitment, a theory which fits with the presence of unperfused capillaries at low flows and with the PS product reaching a saturation value at high flows, when all capillaries are perfused.

It is generally believed that capillary recruitment does not occur in brain, in the sense that a proportion of capillaries are intermittently or continuously unperfused under physiological conditions. Indeed, a study in the monkey with water and alcohols, labeled with positron-emitting isotopes (Raichle et al., 1976) showed no variation of PS product with random changes in flow, or for the alcohols when flow was altered by hyperventilation and by administration of 10% CO₂ with 90% O₂. The living frog brain may be transilluminated, enabling movement of red cells to be seen in microvessels to a depth 25 μm or more. No intermittent opening or closing of microvessels can be seen when the state of the brain is healthy (P.A. Fraser, personal communication). Recently, doubt has been cast on the assumption that clear-cut recruitment does not occur in brain. Weiss et al. (1982) injected fluorescein-labeled dextran of high molecular weight intravascularly into pentobarbital-anesthetized rats. At 20 seconds, the head was decapitated into liquid nitrogen, and thin frozen sections were obtained. Fluorescence was present in only about 50% of total capillaries, stained for alkaline phosphatase. Asphyxia caused a large increase in the number of capillaries perfused. Certainly, much evidence is accumulating that the PS product of the blood-brain barrier to a number of solutes increases with flow.

Experimental Evidence for Varying PS Product

In two studies of glucose uptake into the perfused brain, a marked relation between influx into brain and flow was demonstrated. In the first (Zivin and Snarr, 1972), net uptake into the rat brain was found to rise rapidly as flow was increased, reaching half-maximal levels at a total brain flow of about 1 ml/min. In the second (Betz et al., 1973), unidirectional uptake was determined in the dog brain by indicator dilution with [3H]glucose. Uptake (μmol/g per min) increased from 0.5–1.0 when the plasma flow was raised from 0.3–0.8 ml/g per min. Since the Renkin-Crone correction was not used, the increase in uptake might be attributed to flow limitation. This is very unlikely, since the approximate maximal PS product for glucose at the concentration used in the latter study was 0.2 ml/g per min. Flow limitation will not be important for flows above 0.4 ml/g per min (Fig. 4).

It is now well recognized that there is coupling between cerebral blood flow and glucose utilization. This is very tight when flow is related to utilization by different regions of brain at one metabolic state (Sokoloff, 1981) and also occurs, but less predictably, when metabolism is altered (Sokoloff, 1981; Cremer et al., 1983). Since unidirectional influx of glucose in most regions of brain is only about twice the respective glucose utilization in conscious control rats (Cremer et al., 1983), there would be little margin for adequate entry of glucose if metabolism appreciably increased without a change in PS product. Increased flow on its own would be of limited use (Fig. 4). In fact, unidirectional influx, hence PS
product, was decreased in pentobarbital anesthesia (Gjedde and Rasmussen, 1980) and was markedly increased when cerebral metabolism was stimulated by the tremor-inducing drugs cismethrin or decamethrin (Cremer et al., 1981, 1983). Such changes in PS product might be due to an alteration either in the true permeability of the endothelium to glucose or in its effective surface area. Although the transporter, facilitating the entry of ketone bodies into brain, may show adaptive changes in relation to the metabolic needs of the brain, probably mediated slowly via the concentration of ketone bodies in blood (reviewed by Gjedde, 1983; Gjedde and Crone, 1983; Bradbury, 1984), there is no indication as yet that the glucose transporter at the barrier can rapidly adapt in response to neuronal activity or metabolism. On the other hand, there is good evidence that altering cerebral blood flow, with or without a change in metabolism, can change the PS product for a number of nonmetabolized solutes. Bolwig et al. (1977) examined the permeability of the blood-brain barrier in man by indicator dilution. Permeability-surface area products of labeled sodium and chloride ions, urea, and thiourea increased markedly when cerebral blood flow was more than doubled by electrically induced seizures (ECT) or by hypercapnia. In a later study, it was found that hypcapnia decreased and hypercapnia augmented PS products for labeled sodium and thiourea, and phenylalanine (Hertz and Paulson, 1980). Paradoxically, hypcapnia somewhat enhanced the PS product for glucose. In an elegant study, Sage et al. (1981) estimated unidirectional leucine influx and cerebral blood flow in the brain of awake rats. Increasing cerebral blood flow from 1.5–4.5 ml/g by CO₂ administration nearly doubled leucine influx over a wide range of leucine concentrations in plasma (Fig. 5). Phelps et al. (1981) examined extraction of [¹⁵⁴]ammonia over a wide range of cerebral blood flows. The PS product for ammonia increased markedly with flow and saturated at a flow of about 2 ml/g per min in a manner reminiscent of glucose in the perfused brain. The results were interpreted as due to "saturation recruitment."

Is Capillary Recruitment the Mechanism?

Two questions arise. Is there a general mechanism whereby PS product is varied in relation to blood flow? If not, how do the mechanisms differ in the various experimental situations studied, i.e., altered arterial PCO₂, altered metabolism, including seizures, and spreading depression. As a general mechanism, capillary recruitment would provide a good explanation, but, as discussed, it may not occur in brain as an all-or-nothing phenomenon. However, it is necessary to suppose that capillaries are at any time completely closed. If flows were to be increased through paths with either a high permeability or a high endothelial area, or both, relative to flow through capillaries with low PS products, then the average PS product for the brain region or for whole brain would be increased. Indeed, Hertz and Paulson (1980) found evidence for heterogeneity of capillary flow. Short transit times corresponded to low extractions, and long transit times, to high extractions. To produce the observed effect, flow would have to be relatively increased in the high-extraction vessels.

Evidence concerning an answer to the second question is even more limited. Gjedde et al. (1981) demonstrated an uncoupling between PS product for glucose and cerebral blood flow during the onset of spreading depression. Although blood flow increased markedly, PS product was unaltered. Brain glucose fell, indicating that metabolism had indeed risen. Whether the coupling demonstrated in relation to CO₂-induced changes, on one hand, and to
most metabolically mediated changes in flow, on the other, depends on the same mechanism is uncertain. In a comprehensive study, Cremer et al. (1983) estimated not only blood flow with glucose influx and utilization, but also residual tissue blood volume in different brain regions. A particularly tight correlation was noted between maximum glucose transport capacity and blood volume in different brain regions from rats subjected to one experimental condition. This relation was still present when all experimental groups were placed together, but the spread was larger. Since residual blood volume was considered to represent the area of endothelium perfused, the results were taken to support capillary recruitment.

Overall, it would appear that altering cerebral blood flow by varying arterial Pco₂ or by altering metabolism must produce a change in PS product by leading to a redistribution of flow, apart from the straight alteration in the magnitude of flow. Whether this redistribution is equivalent in both conditions is uncertain at present. Certainly in one situation, spreading depression, the redistribution, if any, must be quite different.

Conclusions and Summary

The blood-brain barrier is now known to be the cerebral endothelium. Except in certain regions, this is a very tight cellular membrane with high electrical resistance, a low filtration coefficient, and low permeability to many polar solutes. It contains specific transport mechanisms for a number of metabolic substrates. The ionic composition of the interstitial fluid of brain is maintained by active transport by supporting capillary recruitment.

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