THE PRESENT POSITION OF THE PROBLEM OF THE INTRA-OCULAR FLUID AND PRESSURE

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ALMOST half a century ago when Parsons was working on the problem of the intra-ocular pressure, a change in the conception of the nature of the aqueous humour was emerging. Previously—without firm experimental evidence—the aqueous was generally accepted as being a secretion: it was of “vital” origin and in an age of dogma it was accepted as such. With the growth of the mechanistic conception of biology which characterised the end of the last century, however, and stimulated particularly by Starling’s work on the body-fluids generally, Parsons, in conjunction with Henderson and Starling in England, concluded that the aqueous, like the tissue-fluids elsewhere, was a simple filtrate governed by hydrostatic and osmotic forces. A quarter of a century later advances in experimental technique, particularly in the physico-chemical approach to biological problems, made it clear that a conception so simple would not suffice. The chemistry of the aqueous was found to be incompatible with such an origin, and a new theory was introduced that this fluid was a dialysate in thermo-dynamical equilibrium with the blood and that upon it a through-and-through circulation was superimposed by pressure-differences at two points of its most intimate association with the blood—the ciliary capillaries and Schlemm’s canal.

Such a theory has very special requirements:—

(a) The intra-ocular pressure (I.O.P.) should be determined by the mean level of the capillary pressure (C.P.) less the colloid osmotic pressure of the plasma proteins (O.P.), *i.e.*, by the relationship:

$$C.P. - O.P. = I.O.P.$$

With an average value of 20 to 25 mm. Hg for the intra-ocular pressure and a figure of 28 mm. Hg for the colloid osmotic pressure of the plasma proteins, the theory therefore demands a mean level of capillary pressure of about 50 mm. Hg. As a corollary to this relationship a rise in the level of capillary pressure should be reflected in a rise in intra-ocular pressure, whilst a rise in the colloid osmotic pressure of the plasma should lower the intra-ocular pressure.

(b) A fluid formed by filtration from the blood plasma and retained for some length of time in the chambers of the eye is not only an ultra-filtrate but a dialysate, *i.e.*, it has had time to

come into thermodynamic equilibrium with its parent plasma supposing that this equilibrium had not been established at the moment of filtration. The Gibbs-Donnan equilibrium should therefore apply to the aqueous humour and plasma: this requires that the concentrations (or activities) of all non-electrolytes capable of penetrating from the plasma into the aqueous humour be equal in the two fluids. The following relationship should apply to the distribution of the univalent ions:—

$$\frac{[\text{Concent. of Na in Plasma}]}{[\text{Concent. of Na in Aqueous}]} = \frac{[\text{Concent. of Cl in Aqueous}]}{[\text{Concent. of Cl in Plasma}]}$$

From this it follows that the osmotic pressure of the plasma should be greater than that of the aqueous humour.

(c) A rise in the concentration of one of the constituents of the blood, (*e.g.*, sugar), or the introduction of a diffusible foreign substance into the blood should be followed by diffusion of the substance in question into the aqueous humour in accordance with Fick's Law, *i.e.*, at a rate proportional to the difference in the concentrations in the two fluids. The relative rates at which various substances enter the eye under these circumstances would be a characteristic of the "Blood-Aqueous Barrier." It should be noted that the complete impermeability of the barrier to certain substances is not inconsistent with the dialysis theory.

These are the main demands of the theory and we have indicated that fifteen years ago there was no serious discrepancy between theory and experimental fact. The same evolution, however, has repeated itself in scientific progress. Further factual experimental results obtained by more exact and elaborate techniques have appeared: these have again rendered a relatively simple and apparently satisfactory theory inadequate. And when any theory—no matter how simple and satisfying—fails to accommodate new facts determined by newer and better methods of experimentation, the theory—no matter how useful it may have appeared—must be sacrificed. Just as Newton's Theory of Gravitation gave place to Einstein's Theory of Relativity, so the theory of dialysation must give place to something else. Unfortunately the phase of transition from one conception to another is usually a period of some confusion, and for this reason it may be of value to assess the present position and to indicate the possible direction of progress.

EXPERIMENTAL FINDINGS

Some experimental facts will now be recapitulated.

I. *The Distribution of Sodium and Chloride.*—Van Slyke calculated that the ratio (R_{Na})—concentration of Na in plasma/concentration in a dialysate—should be 1.04, the corresponding ratio

for chloride (R_{Cl}) being 0.96. Recent studies from this laboratory (Davson, Duke-Elder and Benham, 1936; Davson, 1939; Davson and Weld, 1941; Hodgson, 1938) have partly confirmed and partly disproved the existence of a Donnan equilibrium in this regard. Thus in cats the value of R_{Na} is 1.03 ± 0.004 ; R_{Cl} is 0.945. In the dog R_{Na} 1.04 ± 0.004 , *i.e.*, it agrees exactly with Van Slyke's theoretical requirement. R_{Cl} , however, is grossly aberrant, being on the average 0.92, extreme values as low as 0.89 having been observed. Chloride is thus not in equilibrium with the blood plasma, its concentration in the aqueous humour being too high. The position, however, is complicated by the fact that recent studies on dialysis with collodion membranes indicates that Van Slyke's theoretical ratios may be wrong. Greene and Power (1931) and Ingraham, Lombard and Visscher (1933), for example, obtained results which indicate that R_{Na} should be nearer 1.08 than 1.04 and that R_{Cl} should be in the region of 0.99 rather than 0.96. If this is true the observed values of R_{Na} , namely 1.03 in the cat and 1.04 in the dog, are no evidence for equilibrium but rather of the existence of an excess of sodium in the aqueous; similarly the observed value of R_{Cl} of 0.945 and 0.92 indicate an excess of chloride in the intra-ocular fluid. By dialysing aqueous humour against plasma from the same animal it has been shown in our laboratory (Davson, Duke-Elder and Maurice, 1948) that sodium and chloride do actually migrate from aqueous humour to plasma to give final equilibrium ratios of 1.06 to 1.07 for sodium and 0.98—0.99 for chloride. There is thus no doubt that the sodium and chloride of the aqueous are not in thermodynamic equilibrium with these substances in the plasma.

Here, however, we are not certain that all the circumstances have been taken into consideration. Thus it is known that the aqueous contains a higher concentration of lactic acid than the blood of the jugular vein (an excess of 1.7 millimoles per litre, Fischer, 1931), due, presumably, to the formation of this substance as a metabolite by the lens and retina. Some part of the excess of sodium in the aqueous might be fairly accounted for by its combination with lactic acid (1.7 out of a total excess of about 3.0 millimoles per litre): the remaining moiety is not accounted for—nor can the excess of chloride be explained on a similar basis, and since it persists in the aphakic eye any metabolic influence of the lens must be ruled out. Some activity in respect of sodium and chloride other than dialysis must therefore exist.

A further complicating factor is the entrance of sodium and chloride into the posterior segment of the eye. It has been shown from this laboratory (Davson, Duke-Elder, Maurice, Ross and Wooden: *in press*), by the use of tracer elements, that sodium

(and potassium) do not penetrate into the vitreous chamber from all the vascularised tissues as do substances like glucose and thiocyanate, but enter essentially through the ciliary region. In this, as we shall see in a moment, there is an analogy with the cerebral circulation; but from the point of view of the immediate argument, this fact reinforces the argument for a special mechanism for the transference of these substances through the blood-aqueous barrier and localises it (largely, at any rate) to the ciliary region. Not only must we therefore postulate some mechanism of transfer for electrolytes differing quantitatively from simple ultra-filtration or dialysis, but we must also admit the existence of qualitative regional differences in the operation of this mechanism.

II. *Reducing Substances: Carbohydrates.*—The distribution of sugars is somewhat simpler. If the concentration of reducing substances (glucose) in the aqueous is estimated it is found to be lower than that in the plasma, while that in the vitreous is lower still. In the cat, for example, the relative values have been found in this laboratory to be: arterial plasma 108, aqueous 82.5, vitreous 57 (Davson and Duke-Elder, 1948; see also Adler, 1930). Regarded superficially it might be said that a theory of simple dialysis requires these values to be equal; but the deficiency in the aqueous is approximately equal to the glucose uptake of the lens, and that in the vitreous to the metabolic requirements of this tissue and the retina. That this explanation actually accounts for the deficiency is suggested by the fact that it largely disappears, so far as the aqueous is concerned, in the aphakic eye (when the concentration of sugar in the aqueous approximates that in the plasma), and becomes very much greater in the posterior segment if an excised eye is incubated so that the retinal metabolism is maintained and the alternative sugar supply by the blood cut off (when the retina will consume more sugar) (Davson and Duke-Elder, 1948). It is interesting that the concentration of glucose in the cerebrospinal fluid is very low, about the same as that in the vitreous body: in the brain conditions are very similar to those in the posterior segment of the eye.

Moreover, a study of the kinetics of the entry of carbohydrates into the eye has shown that this class of substance passes the blood-aqueous barrier at relative speeds which suggest a simple physical diffusion depending on the size of the molecules concerned (Davson and Duke-Elder, 1948). Thus pentoses (xylose) and hexoses enter the aqueous at about the same rate, disaccharides (sucrose) at a rate about one-seventh of this and polysaccharides (raffinose, inulin) at a barely measurable rate. This would suggest a simple diffusion through pores of a limiting size slightly larger than the molecules of sucrose; and the fact that natural sugars (glucose) enter at the same rate as synthetic sugars of comparable

molecular size (3-methyl-glucose, which is not phosphorylated *in vivo*) would seem to preclude any secretory mechanism so far as this type of substance is concerned. Into the vitreous body the rate of entrance is much slower, suggesting a quantitative difference in the posterior segment of the eye; and the fact that pentoses and hexoses enter at somewhat different rates into the vitreous body may indicate the presence in this region of a qualitatively different mechanism which can exert a chemical as well as a physical differentiation.

III. *Nitrogenous Substances*.—The case of nitrogenous substances is peculiar. As long ago as 1933 Adler drew attention to the fact that the concentration of urea in the aqueous humour was definitely below that in the plasma: according to his figures the concentrations in aqueous and plasma in the cat are 46.3: 54.9, that is, there is a difference of 0.0014 M. The subject has been investigated in greater detail subsequently in Adler's laboratory as well as in ours and at Boston (Adler, 1933; Kinsey and Grant, 1942; Benham, 1937; Scheie, Moore and Adler, 1943-7; Kinsey and Robinson, 1946; Ross, unpublished). The observed ratio depends in a considerable measure on the chemical methods of estimation; thus Kinsey and his co-workers claimed one ratio only to alter it as a result of applying another chemical method: with a conductivity method Benham from this laboratory obtained a ratio of 0.8 to 0.95 in the rabbit and 0.9 to 0.95 in the cat: whilst with the Conway method, Ross, working in our laboratory, has recently obtained a ratio in the cat of 0.81. There is no doubt, however, that urea is present in lower concentration in the aqueous humour than in the blood plasma. Accurate studies of other organic compounds such as amino-acids and creatinine have not been reported and would probably mean little owing to the unspecificity of the chemical methods employed: what evidence we have obtained in recent permeability studies suggests that there is a deficiency of these compounds in the aqueous humour. Again, this deficiency cannot be explained by a theory of dialysis; nor can metabolic consumption provide a reason for the discrepancy. It has been found in this laboratory, however, that not only urea, but all nitrogenous substances such as creatinine, and amino acids as glycine and alanine with their relatively small molecules, penetrate the blood-aqueous barrier very slowly and with difficulty (at about 1/3 the rate of the large-moleculed sugars) (Davson, Duke-Elder, Maurice, Ross and Woodin, *in press*). It is obvious that if there is a relatively easy exit from the eye by fluid in bulk and a preferentially difficult entrance of these substances, they may for purely physical reasons be in constant deficit in the "steady-state" of normal conditions (Kinsey and Grant, 1942-4; Duke-Elder and Davson, 1943; Bárány and Davson, 1948).

It is interesting that sucrose injected into the blood stream tends to distribute itself between aqueous humour and plasma so that at equilibrium its concentration in the aqueous humour is only about half that in the plasma (unpublished). Sucrose penetrates from blood to aqueous humour very slowly indeed, much more slowly than even urea, and should, by the same explanation, have a distribution at equilibrium at the "steady-state" such that the ratio of the concentrations in aqueous humour and plasma is smaller than that for urea; this has, in fact, been found (unpublished). The finding of a deficiency of a substance in the aqueous humour is no evidence of itself in favour of a secretory origin of this fluid, as has been argued (Adler, 1933).

It has been known for some time that the concentration of ascorbic acid (vitamin C) in the intra-ocular fluid is considerably greater than that in the blood plasma: this difference is much more marked in some animals (*e.g.*, rabbit and ox) than in others (*e.g.*, the cat and dog). There are at present two schools of thought as to the cause of this excess of ascorbic acid: Müller and Buschke (1934) showed that in the aphakic eye the difference in concentration was very considerably less and brought forward evidence purporting to prove that the lens actually synthesised the vitamin (Müller, 1935). Friedenwald, Buschke and Michel (1943), on the other hand, regard the high concentration as evidence of secretion by the ciliary body and in a recent study Kinsey (1947) certainly supported this hypothesis by showing that ascorbic acid, injected into the blood, passed into the aqueous humour in spite of the fact that the concentration was higher than in the plasma. If, however, the lens synthesised ascorbic acid, it would continuously pass into the aqueous humour and thence into the blood stream by simple diffusion: increasing the blood concentration would lower the rate of loss from the aqueous humour and thus allow the ascorbic acid concentration to pile up to a greater extent. The matter clearly merits further investigation.

IV. *Osmotic Pressure*.—Our early studies on the osmotic pressures of the aqueous humour and plasma (Benham, Davson and Duke-Elder, 1937) indicated that there was an excess of osmotic pressure in the plasma as compared with the aqueous so that the requirements of the dialysis theory appeared to be met. More recent work from the same laboratory (Benham, Duke-Elder and Hodgson, 1938), however, has shown that when ether anaesthesia, which raises the osmotic pressure of the plasma, was avoided, the osmotic pressure of the aqueous humour was always greater than that of the plasma, a difference in osmotic pressure in the opposite sense from that required by the Donnan equilibrium. This finding has been confirmed by Roepke and Hetherington (1940) who have shown also that the excess of osmotic pressure in the aqueous humour could be abolished by poisoning the eye with an intra-ocular injection of mercuric chloride. The finding that when aqueous humour is dialysed against plasma there is a decrease in conductivity of the former fluid (Davson, Duke-Elder and Maurice, 1948) corroborates these later findings and indicates that the excess of osmotic pressure is at least in part due to an excess of electrolyte in the aqueous humour. Analyses of the concentrations of non-electrolytes certainly indicate that they are unable to contribute to an excess of osmotic pressure in the aqueous humour; in fact, they must cause a material deficiency. A rough estimate indicates that the deficiency of sugar, urea, creatinine, amino-acids and protein

would amount to about 4.5 millimoles per litre; consequently, if the osmotic pressure of the aqueous humour is to be actually greater than that of plasma, an excess of at least some 4.5 millimoles of some other material, presumably salt, would be necessary. The dialysis experiments described above indicate that the concentration of sodium in the aqueous humour is about two per cent. higher than the equilibrium concentration, *i.e.*, there is an "excess" of about 3.0 millimoles per litre. The excess sodium ions must, of course, be accompanied by negative ions and if these are monovalent (*e.g.*, chloride) this would demand a further 3 millimoles per litre. The excess sodium in the aqueous humour can thus fully account for the deficiencies of organic substances such as sugar and urea, in fact, it is sufficient to reverse the osmotic relationships between a dialysate and plasma causing the osmotic pressure of the aqueous humour to be the greater. It may be that the maintenance of this osmotic gradient is of considerable importance in the mechanism of the intra-ocular pressure.

V. *The Intra-ocular Pressure.*—It has frequently been said that the absence of an invariable and proportional variation in the intra-ocular pressure in response to changes either in the blood pressure or the colloid osmotic difference between plasma and aqueous is incompatible with a dialysation theory. The classical researches of Parsons (1904—8) and Henderson and Starling (1904) have shown that the intra-ocular pressure does indeed follow the arterial in sudden changes in experimental animals; the more recent work of Duke-Elder (1926—30) has confirmed this. This, however, applies only to dramatic experimental changes. It must be remembered that the intra-ocular pressure will vary with the capillary pressure. It has not been possible to measure the capillary pressure directly in experimental investigations of this problem and one has had to assume that a rise in arterial pressure would be reflected in a rise in capillary pressure, but it would be rash to say what fraction of the rise would correspond to a rise in capillary pressure, or that the rise is in all circumstances proportionately the same. Duke-Elder found in general that the rise in intra-ocular pressure in experimental animals was about one-tenth of the rise in arterial pressure, but outside the experimental environment this relationship probably does not hold. It would seem that, teleologically speaking, the vascular system is designed to provide a reasonable constancy of capillary pressure; changes in the calibre of the arterioles may produce changes in the peripheral resistance so that a rise in arterial pressure could be largely compensated and the capillary pressure remain comparatively unchanged.

Recently Bárány (1946—7) has shown that unilateral closure of

the carotid artery in the rabbit causes a fall in intra-ocular pressure associated with a fall in arterial pressure; after a time, however, the intra-ocular pressure returns to normal although the arterial pressure remains permanently depressed in the ear of the operated side. Bárány's results seem to show that the intra-ocular pressure does, indeed, respond to a sudden change in arterial pressure, but that there is some compensatory mechanism at work which eventually keeps the intra-ocular pressure independent of the arterial. Bárány has argued that the response of the eye to a change in arterial pressure is not by any means as large as might be expected on the basis of the dialysis theory if it is assumed that the capillary pressure remains a constant fraction of the arterio-venous difference. This assumption, however, requires justification.

The influence of the colloid osmotic pressure of the plasma on the intra-ocular pressure may, as we have seen, be deduced from the simple equation already stated: a decrease in the former should raise the latter and *vice versa*. In experimental animals these deductions have been borne out qualitatively. Dilution of the plasma with isotonic saline undoubtedly causes in experimental animals a considerable rise in intra-ocular pressure (Duke-Elder, 1931); it is difficult to increase the colloid osmotic pressure of the plasma by injections of gum acacia; Bárány (1947) has recently suggested that the earlier results of Duke-Elder (1931) may have been a factitious result of the toxicity of the gum acacia rather than a true osmotic effect. The decrease in intra-ocular pressure following a massive injection of hypertonic NaCl or sucrose belongs to the same category of osmotic effects; temporarily the osmotic pressure of the blood is raised in comparison with that of the aqueous humour and water is withdrawn from the eye by osmosis. If the high osmotic pressure of the plasma were maintained for some time, as in experimental animals, the extra NaCl or sucrose would diffuse into the eye and so tend to lower the osmotic pressure difference, and eventually the intra-ocular pressure would tend to return to normal. The effects of long-continued maintenance of an abnormal colloid osmotic pressure of the plasma may be observed in man in nephritis: Robertson (1939) has emphasised that there is no coincidental rise in the intra-ocular pressure in this condition and has made this the basis for the claim that the aqueous humour is formed as a pure secretion. His conclusions indicate the existence of some compensatory mechanism whereby slowly developing and long maintained changes in the osmotic pressure of the plasma may be neutralised in so far as the intra-ocular pressure is concerned.

This compensatory mechanism is at present unknown; but we may suppose it may involve two components, one vascular and

the other concerned with drainage of fluid from the eye. The presence of local axon reflexes exerting a powerful influence on the ocular circulation has been demonstrated (Duke-Elder, 1931); the eye is the only organ in the body wherein these have been found and in their presence is surely of significance. Moreover, the presence of a central mechanism (? hypothalamic) maintaining the control of the tonus of the eye at a relatively constant value would merely bring this into line with practically all physiological functions. About this at present we know nothing; but many facts regarding the tension of the eye and the interdependence of the tensions of the two eyes suggest its presence.

VI. *The circulation of the intra-ocular fluid.*—The evidence in favour of a continuous drainage from the eye is largely clinical, depending on the occurrence of iris bombé and the effects of denying access of the fluid to the angle of the anterior chamber. There have been several attempts to measure the rate of drainage or flow in experimental animals. Thus Troncoso (1921) measured the dilution of the blood in the anterior ciliary veins, and, on the assumption that this dilution was due to a bulk reabsorption of aqueous humour, computed that the rate of drainage was about 2 to 3 cu. mm. per min. Friedenwald and Pierce (1932) replaced the aqueous humour with plasma in an attempt to block the drainage route completely; they then measured the rate of inflow into the eye and argued that this was the normal flow. This method is open to some very serious objections, principally owing to the radical disturbance of the difference in colloid osmotic pressure between the two fluids. He obtained a flow-rate of 1 cu. mm. per min. in the dog. Kinsey and Grant (1942) computed a value of 4 cu. mm. per min. in the rabbit from the observed rate of penetration of radioactive sodium but the computation rests on assumptions that have not been proved and are difficult to justify in the light of our present knowledge. There has thus been no definite proof of a bulk *non-selective* drainage from the anterior chamber of experimental animals; but this has been provided recently in our laboratory (Davson, Duke-Elder and Maurice, unpublished). The principle adopted was to replace (under suitably controlled conditions) the aqueous of the cat by an artificial aqueous humour containing about 100 mg. per 100 c.c. of inulin (a large molecular weight substance that could only leave the eye by a non-selective drainage route: diffusion through the blood-aqueous barrier would be out of the question). Throughout the experiment the concentration of inulin was maintained at a higher level in the blood than it was in the artificial aqueous humour; any loss of inulin from the eye must therefore have been due to a bulk-flow mechanism since diffusion through the blood-aqueous barrier (assuming this to have been made sufficiently abnormal by the

experimental technique to permit the passage of inulin) could only occur from blood into the eye. After an interval of fifteen minutes or half an hour the "aqueous humour" was withdrawn and submitted to analysis. The results proved that inulin may be drained away from the eye and represent the first unequivocal proof of drainage in bulk.

It is obvious that the composition of the aqueous humour will be materially altered by this drainage; and it is equally obvious that it will upset any assumptions regarding the height of the intra-ocular pressure based on the formation of the intra-ocular fluid alone. The position is rendered still more complicated by the demonstration of aqueous veins by Ascher (1942—4) supplementing the original conception of drainage through the canal of Schlemm alone. It is interesting that Friedenwald and Pierce (1932) brought forward evidence to show that the capacity of drainage increased five to ten times if the intra-ocular pressure were raised a few mm. Hg above its normal level. Further consideration, both theoretical and experimental, on the influence of capillary and osmotic pressure on this mechanism will certainly produce results of more than usual interest.

DISCUSSION

From the above short recapitulation of experimental facts it is obvious that the intra-ocular fluid cannot be a simple dialysate in equilibrium with the capillary plasma. It is true that the metabolism of the sugars is largely compatible with such a theory—simple dialysation through the jellyish cement substance occupying the intercellular spaces in the capillary endothelium and epithelial membranes, the watery spaces of which act as pores. A study of nitrogenous substances, however, completely upsets this view-point; urea penetrates more slowly than glucose although it has much the smaller molecule; the same is true for creatinine and more so for amino-acids. Penicillin is smaller than sucrose yet its rate of penetration is very slow indeed, about one fifth of that of sucrose. Evidently the presence of the nitrogen atom in the molecule slows down the rate of penetration, in comparison with a molecule of the same size without nitrogen; this is tantamount to saying that the chemical composition of a substance is more important as a determinant of rate of penetration of the barrier than its molecular size. From this it may be concluded that some substances at least must penetrate by way of the cells; the interstitial spaces could not select molecules on the basis of their structure, such selection being a characteristic of the envelopes of individual cells. A striking instance of the importance of chemical structure in penetration is shown by the observation of

Palm (1947) that ethyl alcohol penetrates very rapidly into the aqueous humour, some five to six times as fast as glucose; undoubtedly this is because of the high fat solubility of ethyl alcohol which permits it to diffuse rapidly through cellular membranes. Moreover, the excess of electrolytes with the consequent excess of osmotic pressure of the intra-ocular fluid suggests that some cellular activity is in question. Studies of the most varied nature in other organs of the body have consistently failed to produce any evidence that the capillary wall acts otherwise than as a simple filter; it may block substances, but it has not, so far, been detected in the act of secreting any substance (Landis, 1946). The presumption is, therefore, that any cellular activity is localised in the lining epithelium of the eye (presumably mainly in the ciliary region).

The second general point which emerges is that not only is the mechanism more complicated than dialysis since it differentiates between substances on a chemical basis, but the blood-aqueous barrier differs radically in different localities of the globe. In general, when a given substance penetrates into the aqueous humour it also penetrates the vitreous body more slowly. We have seen that in the most simple case—that of sugars—entrance into the anterior chamber (through the iris) is easy and undifferentiated except in respect to the physical size of the molecules: entrance into the vitreous, on the other hand, is slower and shows some chemical discrimination. By freezing the eye suddenly during the diffusion process it may be shown that certain substances enter the vitreous body predominantly by way of the ciliary body and diffuse backwards towards the posterior pole; other substances, however, can apparently enter the vitreous body rapidly from all parts of its periphery (Davson and Duke-Elder, 1948; Davson, Duke-Elder, Maurice, Ross and Woodin, *in press*). Sodium and potassium are two instances of substances the route of which to the vitreous body is largely confined to penetration from the ciliary region; glucose and thiocyanate, on the other hand, are examples of substances that can diffuse from the choroidal and retinal circulations. This is a remarkable finding and brings out the strong analogy, if not the identity, between the capillaries of the cerebral and retinal vascular systems. It has been recognised for some time that the capillaries of the cerebral system are radically different from those in other parts of the body. Palm (1947) has recently shown that, alone of the capillaries of the body, those of the central nervous system and the retina do not take up certain acid dyes (trypan blue). On the other hand, Friedenwald and Stiehler (1938) found that acid dyes penetrated the ciliary capillaries with ease. In the rest of the body the

capillaries show no power of differentiating between such substances as urea and sugar and it is generally accepted that diffusion through the walls of these capillaries is a matter of diffusion through quite large intercellular spaces, spaces that are large enough to allow the molecule of inulin, for example, to pass through. The capillaries of the cerebral system, on the other hand, seem to allow sugar and various monovalent ions to penetrate into their surrounding interstitial or perivascular spaces at much slower rates, and they also show some selectivity. If the retinal vessels were similar to those in the muscles, for example, we should expect glucose, sucrose, raffinose and even inulin to penetrate rapidly into the vitreous body, and the fact that penetration of these substances, when it does occur, is less rapid than that into the aqueous humour indicates the highly selective character of the retinal capillaries. The vitreous body, of course, comes into relation with the capillaries of the uveal system—the capillaries of the choroid and ciliary body; here, however, it is separated by membranes and cellular structures from these capillaries and their interstitial fluid (the epithelium of the ciliary body and the whole of the retina including the pigment epithelium). It might be presumed that these structures could impart some selectivity to this part of the barrier separating the vitreous body from the uveal blood plasma.

Although the simple dialysis theory appears to be wrong, as the most recent work from our laboratory (among others) has shown, nevertheless the fairly close similarities in chemical composition of aqueous humour and plasma, together with the partial conformity of the intra-ocular pressure to changes of osmotic pressure and capillary pressure indicate that the simple physical factors of diffusion and osmosis are operative. Can these apparently contradictory findings be reconciled? At the moment there seem to us to be two general possibilities. First we may consider in detail an idea adumbrated from this laboratory ten years ago (Duke-Elder, 1938); on this basis the aqueous humour is formed primarily as an ultra-filtrate of plasma and, superimposed on this simple process, there is some activity which modifies the concentrations of certain substances, notably sodium and chloride, in the aqueous humour, giving certain peculiarities including an excess of osmotic pressure to this fluid. It is well recognised that the permeability of membranes is influenced by differences in the surface electrical charges and in the hydrophilic swelling of the proteins on either side of the membrane so that some degree of uni-directional permeability and the capacity for maintaining concentration gradients exist. Such a complex membrane offers itself in the ciliary epithelium, and the work of Friedenwald and Stiehler (1938) suggests a possible mechanism. They suppose that the energy

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necessary for such modifications depends upon a difference of potential maintained between the ciliary stroma and epithelium by oxidative and reductive processes owing to the presence of Warburg's respiratory enzyme in the latter. It is true that these conclusions are based on the intra-vital action of dyes—a very confused and difficult problem susceptible to several explanations: but the possibility of some such activity cannot be ruled out of court. Further exploration along these lines would be of great interest.

If we assume such an activity on the part of the ciliary epithelium, as a result of this excess of pressure the driving pressure of fluid into the eye consists of the whole of the capillary pressure (instead of the capillary pressure *minus* the colloid osmotic pressure of the plasma) *plus* an excess of osmotic pressure. Fluid is thus forced into the cavities of the eye with an available pressure-head of from 50 to 75 mm. Hg. Since there is no counter-pressure the intra-ocular pressure must equal this driving pressure unless there is a leakage of fluid out of the eye; the intra-ocular pressure is in effect 25 mm. Hg so that there must, in this view, be a rapid drainage of fluid out of the eye. This outflow would therefore be of maximal importance in the mechanics of the ocular tension, and blockage of the drainage routes must, on this basis, result in a serious rise in intra-ocular pressure since the normal intra-ocular pressure is maintained at its low level only as a result of leakage.

An alternative theory that must also be borne in mind when considering the experimental data is the following:— The aqueous humour may be elaborated entirely within the cells of the ciliary epithelium and possibly to a less degree in other cellular linings of the eye. The fluid so formed is extruded into the posterior chamber of the eye as a "primary aqueous humour"; as a pure secretion it may have characteristics entirely different from those of the blood. The fluid so formed would be forced into the posterior chamber with a certain secretion pressure; if drainage occurred at the angle of the anterior chamber this forcing of fluid into the eye would result in a flow through the pupil. The primary aqueous humour on its passage out of the eye would not, however, be insulated from the blood plasma, but would be in communication with it through the iris and, through the medium of tissue-fluid, through the intercellular spaces of all the lining membranes; it would thus tend to attain diffusion equilibrium with the blood. If diffusion equilibrium were completely attained the result would be that the aqueous humour would appear to be a simple dialysate in spite of its secretory origin. It can be postulated, however, that the aqueous humour does not remain in the eye long enough for

this diffusion equilibrium to be established, so that an intermediate state is achieved in which it has strong characteristics of a dialysate but betrays its secretory origin in important details, such as an osmotic pressure greater than that of the plasma, a higher concentration of sodium and chloride than required of a dialysate, a low concentration of urea, a high concentration of ascorbic acid, and so on. On the basis of this theory most substances must enter the eye by a cellular route whereas on the modified dialysis theory discussed above, much of the fluid formation could have been by way of the intercellular spaces only, the osmotic excess of material being added by the cellular activity of the lining membrane. On the experimental evidence, however, this hypothesis would seem unlikely.

Such are two tentative suggestions. Others may offer themselves, but it is obvious that in the present state of factual knowledge no pragmatic conclusion can be reached. The problems presented are full of interest and are not without their difficulties; their solution must await the results of more extensive and detailed experimental work.

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IN SYMPATHETIC OPHTHALMIA AND ITS
BEARING ON ENUCLEATION

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THE special incentive for this paper is my conviction that not infrequently following the enucleation of the exciting eye in sympathetic ophthalmia a considerable amount of inflamed tissue is left in the orbit. Sufficient emphasis does not seem to be placed on the fact that although sympathetic ophthalmia is primarily a disease of the inner eye yet the appendages may also be involved simultaneously.

NATURE OF SYMPATHETIC OPHTHALMIA

Histologically sympathetic ophthalmia declares itself in the guise of an infiltration of lymphocytes, epithelioid cells and giant cells in the uveal tract of each eye. The peculiarity lies not so much in the elements of the infiltration, which are similar to those of tuberculosis, but rather in the selective affinity that the disease exhibits for uveal tissue. A characteristic feature of the disease is the tendency of the infiltration to expand outward beyond the globe. Inwardly, any involvement of the pigment epithelium and retina is invariably so slight as to be of no real consequence. Nor is the choriocapillaris attacked, apparently because the interspace between the capillaries is composed of tissue that is not typically uveal and therefore is not suitable soil.