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THE INFLUENCE OF INTRA-OCULAR PRESSURE ON THE RATE OF DRAINAGE OF AQUEOUS HUMOUR. STABILIZATION OF INTRA-OCULAR PRESSURE OR OF AQUEOUS FLOW? * †

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I.—Introduction

THE problem of the stabilization of intra-ocular pressure has aroused much interest. There are theories postulating reflex regulation of some kind or other. These have been critically examined elsewhere (Bárány, 1946 *a*). On the other hand, there are two theories, namely those of Duke-Elder and of Friedenwald and Pierce, which put the burden of stabilization on the mechanism of aqueous outflow.

Based on his elegant determinations of intra-scleral venous pressure in the dog, Duke-Elder (1926) has proposed a "safety-valve action" theory of the aqueous drainage mechanism. According to this theory, the pressure relations between the anterior chamber and the drainage channels are such as to prevent any flow of aqueous at normal intra-ocular pressure. When the intra-ocular pressure is raised, however, the pressure relations are reversed and become favourable for drainage of the aqueous. It is obvious, that any drainage mechanism which permits an increase of aqueous outflow with increasing intra-ocular pressure will, in a certain sense, tend to stabilize the intra-ocular pressure. The efficiency of a mechanism in stabilizing intra-ocular pressure depends on the slope of the curve relating aqueous flow to pressure. If the mechanism is efficient, even a small change in pressure will cause a large change

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in aqueous outflow. The "safety-valve" mechanism of Duke-Elder is one way in which this could be realised without necessitating a large flow of aqueous under basal conditions.

The application of Duke-Elder's theory to other species has been criticised, however, from an anatomical point of view by Troncoso (1942) after a thorough study of the vascular apparatus of the drainage angle. In view of the conclusive demonstration by Ascher (1942) and independently by Goldman (1946) of a continuous aqueous outflow in man and the proof of a considerable outflow under completely physiological conditions in the rabbit's eye by Kinsey and Grant (1942) the theory must probably be modified at least for these species.

It might conceivably be possible to retain the gist of the "safety-valve" theory by restating it as saying that the intra-ocular pressure is stabilized by means of an overflow mechanism.

If the drainage mechanism is to function as an overflow arrangement, which seems to agree with the ideas of Friedenwald and Pierce (1932), two conditions have to be fulfilled. First, the pressure in the drainage channels, as determined by the intra-scleral circulation, must be—if not actually higher than the intra-ocular pressure—at least only a little lower. Second, the resistance to aqueous flow from the anterior chamber to the drainage channels must be very low. If the drainage mechanism acts as an overflow arrangement, then the normal, not inconsiderable flow of aqueous is the result of a small driving force and a small resistance and even a small change in intra-ocular pressure will cause a large relative change in driving force and a large relative change in aqueous flow.

Since at present no means are known for measuring the pressure in the actual drainage channels nor for determining the resistance to flow from the anterior chamber under physiological conditions, the efficacy of the drainage mechanism as a pressure stabilizer can only be tested by direct measurement of the influence of intra-ocular pressure on the rate of aqueous flow.

This has been tried before by Niesnamoff (1896) and by Friedenwald and Pierce (1932). These authors introduced cannulas into living eyes and measured the rate at which normal saline entered the eye at different pressures. For a rabbit's eye Niesnamoff found an inflow of 1 mm.³ per minute at 25 mm. Hg and of 5 mm.³ per minute at 33 mm. Hg. For dogs, Friedenwald and Pierce found an inflow of 5-10 mm.³ per minute at a pressure not more than 5 mm. Hg over the normal level of the anaesthetised dog. In Niesnamoff's rabbit, the intra-ocular pressure was obviously a little lower than 25 mm. Hg, probably about 23 mm. Hg. Thus, a pressure increase of about 10 mm. Hg above normal brought an increase of aqueous flow by about 5 mm.³ per minute. Under completely physiological conditions, the rate of flow in rabbits is

about 4 mm.³ per minute (Kinsey and Grant, 1942). On a relative scale, therefore, Niesnamoff found an increase of 125 per cent. in aqueous flow caused by an increase of 43 per cent. in intra-ocular pressure. A similar calculation cannot be made for the data of Friedenwald and Pierce because we have no corresponding information about the rate of flow of aqueous in the dog under completely physiological conditions.

However, the results quoted above are open to criticism because they were obtained with a cannula in the anterior chamber of anaesthetized animals, that is on eyes under definitely unphysiological conditions. Moreover, the rabbit data derive from one experiment on one eye only and there might be species and individual differences. It therefore seems justified to take up the question anew. I have therefore used a new method to obtain an idea of how rapidly the aqueous outflow changes with a change in pressure in eyes which have not been subjected to any trauma whatever. Unfortunately, the method does not permit a study of the functional relation over a large range of pressure but only gives the slope of the curve in the vicinity of the normal equilibrium. However, this is the most interesting region from the point of view of physiological regulation.

II.—Experimental part

The principle of the method used is the following:

Under equilibrium conditions the composition of the aqueous is constant. This means that per unit of time, the same net amount of any substance as enters the anterior chamber will have to leave it by means of aqueous outflow or by diffusion. If diffusion plays no part the equilibrium condition is

Net rate of entrance E_0 of substance =
(concentration C_0 of substance) $\times$ (rate of flow of aqueous F_0)

If we now change the equilibrium level of the intra-ocular pressure of an eye by some non-traumatic intervention, the corresponding rate of aqueous drainage F_1 can be obtained from the relative change in rate of entrance of a substance and the relative change in its equilibrium concentration.

$$\frac{F_1}{F_0} = \frac{E_1/E_0}{C_1/C_0} \quad (1)$$

Thus, the experimental problem consists in finding a suitable non-traumatic way of changing the intra-ocular pressure and a suitable substance. Then the related changes in intra-ocular pressure, equilibrium concentration and net rate of entrance of the substance are determined.

In the experiments to be described, the change in equilibrium levels was brought about without touching the eye proper by unilateral closing of the common carotid artery in rabbits. A very large

number of experiments on unanaesthetized animals have shown that, on an average, this reduces the mean blood pressure in the ophthalmic arteries by about 30-40 mm Hg from the normal level of about 100 and the intra-ocular pressure by about 4 mm Hg from the normal level of about 30. The pressures assume new levels which do not change appreciably from 10-20 minutes after closing of the vessel to 24 hours after the operation (Bárány 1946*a*, *d*, 1947*b*).

Carotid closure may appear to be a rather indirect way of changing the intra-ocular pressure. It has the quite invaluable advantage, however, of leaving the other eye unchanged and usable as a control.

The test substance used for the studies was the radio-active sodium isotope Na (24). As Kinsey and Grant (1942) have shown, there is no significant diffusion exchange of sodium between aqueous and blood, sodium enters by secretion and leaves by a process of flow. Consequently, this substance is especially suited for our purposes.¹

Aqueous samples can be obtained under topical anaesthesia but it is much easier and safer to use general anaesthesia. The question then arises, whether the drug used, allyl-isopropyl barbituric acid, Numal Roche, might influence the relevant relations between levels of concentrations and pressures. In order to avoid possible pitfalls here, some of the experiments to be described were made with intra-peritoneal administration of Numal. In these cases the animals had been under the influence of the drug for up to two hours when the aqueous was withdrawn. In other experiments, the drug was given intravenously only 5 minutes before the corneal puncture. There was no noticeable difference between the results. The pressure effect

¹ The fact that radio-active test substances in the body fluids can be detected by means of counter arrangements outside the body suggests the following possibility for studying the rate of aqueous exchange in the intact eye: By means of a suitable time schedule of injection (if necessary controlled by continuous observation of the plasma concentration with a counting rate meter) a practically constant plasma level of a test substance could be maintained from the very start. The test substance preferably should be a radiator of not too penetrating corpuscles. A counter arrangement subtaining a small "visual angle" and equipped with suitable filters could then be arranged to measure radiation practically exclusively from the cornea and the superficial layers of the aqueous. The accumulation of the test substance in these two compartments could thus be followed. The fluid exchange of the cornea is slow and the total electrolyte content relatively low. Therefore, the initial slope e of the accumulation curve would certainly depend almost exclusively on the rate of accumulation of radio-active substance in the aqueous and thus be a measure of the rate of entrance of the test substance in arbitrary units. After a certain interval, the aqueous concentration would have reached an equilibrium level. If the corneal concentration were still sufficiently low, the radiation from the eye at this juncture would express the equilibrium concentration c of the substance in the same arbitrary units as the initial slope e . The quotient e/c would then be a measure of the rate of aqueous exchange, showing directly how large a fraction of the test substance is exchanged per unit of time. It is possible that the amount of radiation coming from the substance of the cornea will no longer be negligible when the aqueous equilibrium is reached. This would hamper the application of the method to human eyes, if no method is found for isolating the corneal radiation. In animal experiments, the activity of the cornea could be determined separately after removal.

The author is engaged in the construction of equipment necessary for experiments along these lines.

of the carotid closure has not been studied as extensively under Numal as in the unanaesthetized state, because it is much more difficult to tonometrize under Numal. The rabbits often develop considerable nystagmus and with our standardized technique, the flaccid animals are more difficult to handle. Enough measurements have been made, however, to allow the statement that on an average carotid occlusion gives about the same pressure drop under Numal as in the unanaesthetized state. The normal intra-ocular pressure is about 5 mm Hg lower under Numal.

The equilibrium concentration of $\text{Na}^{(24)}$ in the aqueous after carotid occlusion was determined in 12 rabbits. One common carotid was ligated and an intra-peritoneal injection of $\text{Na}^{(24)}$ given within 2 hours afterwards. After about 15 hours, an ample time for equilibration, samples of aqueous were drawn from both eyes and the activity of the samples determined with a conventional counter arrangement, with a capacity well above the activity of the samples. At least 2-3000 impulses were counted, the counting error thus is about 2 per cent. Tonometry of the eyes was not performed in order to avoid every trauma.

Some of the animals which had received Numal intra-peritoneally needed a few supplementary drops of ether and were moreover given one drop of 0.4 Diocain Ciba topically immediately before the paracentesis. Details of technique have been described elsewhere (Bárány 1947c). The last animal in the intra-peritoneal group died a few minutes before the aqueous was aspirated. It is included in the table all the same, since there is little reason to expect the equilibrium to change during the first minutes after cessation of breathing.

The result is summarized in table I.

The table shows that there was almost no difference between the sodium content of the aqueous on the side of the closed carotid and that of the control eye. The mean ratio is 0.99. The kind of anaesthesia obviously played no rôle.

There seems to be only one systematic source of error which could play a part in this result, namely contamination of the aqueous with plasma. It is well known that the reduction in intra-ocular pressure caused by a corneal puncture leads to a capillary dilatation and the formation of plasmoid aqueous. When drawing aqueous samples one tries to avoid contamination with newly formed plasmoid aqueous by avoiding contact with the iris, by not emptying the anterior chamber completely, by using only very gentle aspiration and by working quickly. All the same, some slight admixture of plasma might easily occur. We know that at equilibrium in the normal eye, the sodium concentration in the aqueous is about 90 per cent. of that in the plasma. Assume that the aqueous withdrawn from a normal eye is contaminated with 10 per cent. of plasma. A simple calculation shows that this will increase the sodium content of the aqueous by 1 per cent.

TABLE I

The influence of unilateral carotid occlusion on the equilibrium concentration of radiosodium in the aqueous humour.

All activities are corrected for radio-active decay. They have been made comparable by multiplication by the body weight of the animal, because all animals received the same dose of radiosodium. The blood pressures were obtained by means of an ear capsule about 24 hours after the withdrawal of aqueous and about 40 hours after ligation of the carotid.

Animal No.	Body weight kgm.	Aqueous, counts per minute per 0.1 ml, multiplied with body weight			Mean blood pressure, Occluded Control	Anaesthesia, Numal ml/kgm
		Occluded	Control	Occluded Control		
10	2.0	766	790	0.97	0.49	0.6 i.v.
12	1.9	1010	1065	0.95	0.53	0.6 i.v.
13	2.0	915	928	0.99	0.48	0.6 i.v.
14	2.1	767	734	1.04	0.57	0.6 i.v.
15	2.1	820	835	0.97	0.60	0.6 i.v.
16	1.7	795	843	0.94	0.43	0.6 i.v.
18	2.3	798	829	0.96	0.71	0.65 i.p.
19	1.9	880	911	0.97	0.48	0.65 i.p. + 0.15 i.v.
20	2.2	959	943	1.02	0.69	0.65 i.p.
21	2.1	890	870	1.01	0.48	0.65 i.p.
23	2.5	790	809	0.98	0.56	0.65 i.p.
24	2.5	848	815	1.04	dead	0.65 i.p.
				0.987	0.547	

Now, as is well known (Wessely 1908), plasmoid aqueous is less easily formed on the side of the closed carotid, where the blood pressure is much lower. Therefore, on an average this source of error will tend to increase the sodium concentration predominantly in the control eye. Some part of the slight difference between

experimental eye and control eye found might depend on this source of error.

This result, that carotid occlusion hardly or not at all changes the equilibrium concentration of sodium in the aqueous is in excellent agreement with similar experiments previously made concerning the total osmotic pressure of the aqueous (Bárány 1946*b*, 1947*d*). In 29 experiments on 22 animals, using the Hill-Baldes' thermo-electric vapour tension method, it was found that carotid occlusion changes the osmotic pressure of the aqueous by less than a fraction of one per cent. As sodium chloride is responsible for the absolutely dominant part of the osmotic pressure of the aqueous, the result can hardly imply anything other than that carotid occlusion does not change the sodium chloride concentration.

Thus we have found that in equ. (1) $C_1 \cong C_0$. But then the expression degenerates into

$$\frac{F_1}{F_0} \cong \frac{E_1}{E_0}$$

It is interesting to note that, because $C_1 = C_0$, the same relation would hold even if sodium had entered by diffusion instead of secretion.

Thus, the constancy of the sodium concentration shows that the relative change in aqueous outflow caused by carotid closure must be very nearly equal to the relative change in rate of entrance of sodium.

How large, then, is the change in rate of entrance of sodium caused by carotid occlusion? With the aid of the result just arrived at, this can be deduced from previous measurements by the author, made for a different purpose (Bárány 1946*c*, 1947*c*).

In these experiments, Na (24) in the form of 5 ml. of normal saline was injected into rabbits intra-peritoneally. One carotid of the animals had been closed a few hours earlier. After 40-60 minutes, aqueous samples were withdrawn and the activities measured. At this stage, the Na (24) content of the aqueous is still far below that of the plasma. The figures obtained would therefore be almost direct measures of the rates of entrance of Na if the rate of aqueous outflow had been constant. But, as carotid occlusion reduces the intra-ocular pressure and the rate of aqueous drainage, any reduction in rate of entrance caused by carotid occlusion will be partly compensated for by the concomitant reduction in aqueous drainage. Consequently, a correction factor has to be applied. This can be derived as follows:

The experiments were made under the same conditions as those of Kinsey, Grant, Cogan, Livingood and Curtis (1942) on which the theoretical treatment of Kinsey and Grant (1942) is based. Therefore, equ. (10) of these latter authors which fits their sodium data should be applicable to ours too. The equation is

$$c_2 = k_2 \cdot c \left\{ \frac{1}{k'} \left(1 - e^{-\frac{k't_1}{V}} \right) - \frac{1}{k_1 V - k'} \left(e^{-\frac{k't_1}{V}} - e^{-k_1 t_1} \right) \right\}$$

Here, c_2 is the radio-sodium concentration in the aqueous,
 c the equilibrium concentration in the plasma,
 k_2 the co-efficient of rate of entrance,
 k' the co-efficient of rate of exit by aqueous flow,
 $1/k_1$ the time constant of the equilibration process between the intra-peritoneal depot and the blood,
 t_1 the time after intra-peritoneal injection of the sodium salt,
 V the volume of the anterior chamber.

The numerical values of the constants are as follows: k' was found by Kinsey and Grant to be about 4 mm.³ per minute in the normal rabbit's eye, V is about 250 mm.³ and t_1 in our experiments was about 50 minutes. For k_1 we can get a value from the plasma concentration curves of Kinsey *et al.*, which show full concentration after 20-30 minutes. This time thus is about 3 time constants long and k_1 consequently is about 0.1-0.2.

Now, what we want to know is how a proportionally equal reduction in the rates of entrance k_2 and of exit k' influences the concentration c_2 as compared with the other eye of the same animal where k_2 and k' are unchanged.

If the above numerical values are inserted and the expression is evaluated by series expansion including the fourth order terms the following figures are obtained:

Reduction of rates k_2 and k' in per cent. of the normal 10 20

Reduction of concentration c_2 in per cent. of the normal 7.3 15

This result is obtained with $k_1 = 0.1$. If the upper limit $k_1 = 0.2$ is used instead, the figures become 7.0 and 14.5. On the other hand, if the fifth-order terms are included, the figures increase by a few tenths of one per cent.

The result of the calculations shows, that under our conditions of experiment, the relative reduction in the rate of entrance of sodium is reflected in the scale of 3:4 in the reduction in concentration 50 minutes after the injection. This knowledge allows us to make use of the concentration ratios between experimental eye and control eye obtained in the previous study. These ratios were

0.71, 0.92, 0.93, 0.93, 0.96, 0.98, 1.03, 1.22

The extreme values are without doubt the result of contamination with plasma, which in these experiments had an activity at least twice as high as the aqueous. The mean ratio is 0.96 and the median 0.95. The reduction in concentration caused by carotid clamping is thus about 5 per cent. or probably less because of the systematic error discussed before. Applying the correction factor to this value, we find the reduction in rate of entrance of sodium to be about 7 per cent. And now we have the answer to our problem, because in view of the constancy of the equilibrium concentration, this figure must also very nearly represent the reduction in aqueous outflow caused by carotid occlusion.

The remarkable thing about this figure (7 per cent.) is that it is so small. Even if various errors of estimation have co-operated to give too small a value, this result certainly does not support the idea of an overflow mechanism in the intact rabbit's eye. An intra-ocular pressure drop of 10-15 per cent. should have given a much more

pronounced reduction in aqueous outflow if an overflow mechanism had really existed. The discrepancy is even more striking if one considers the reduction in driving hydrostatic pressure head instead of intra-ocular pressure. According to Seidel (1923), the pressure in the episcleral veins is about 9 mm. Hg in the rabbit. Thus, the hydrostatic pressure in the aqueous drainage channels cannot be less than, say, 10 mm. Hg. The pressure head for aqueous outflow is thus certainly less than 20 mm. Hg in the normal eye and carotid closure causes a reduction amounting to certainly more than 20 per cent. Still there is only a small reduction in aqueous outflow.

III.—Theoretical part

A discrepancy of the magnitude found between the change in aqueous flow and in the pressure head must have an explanation. There seem to be two possibilities.

The first is that in our experiments, the rate of aqueous outflow was influenced, not only by the change in intra-ocular pressure but also by the change in arterial blood pressure as such. If the pressure in the drainage channels were directly dependent on the arterial blood pressure to any appreciable degree, a reduction in arterial pressure could conceivably increase the pressure head between the anterior chamber and the drainage channels and thus partly compensate for the reduction in intra-ocular pressure. It seems improbable, however, that this mechanism is very important. The drainage channels are venous vessels, the pressure of which is only dependent to a very slight extent on the arterial blood pressure. In so far as there is a small dependence, however, this mechanism could explain part of the discrepancy.

The other and more probable explanation is that the force which causes the outflow of aqueous consists of two parts, one of them a hydrostatic part which changes directly with the intra-ocular pressure and the other one an osmotic part, which is more or less constant.

The idea that osmotic forces play a part in the mechanism of Schlemm's canal originates from Friedenwald and Pierce (1932). Troncoso (1942) assumes that the drainage vessels of the sub-primate eyes, the trabecular veins, contain flowing blood which osmotically attracts aqueous humour. In animals, Friedenwald and Scholz (quoted Friedenwald 1940, 1942) have demonstrated "plasma and some red blood cells in the vessels which formed the base of the sclero-corneal trabeculum" after freezing the anterior segment of the eye with liquid air. The present findings indicate the existence of a constant absorptive force besides the changing hydrostatic one. There is thus every reason to consider how the mechanism of aqueous drainage will behave if the movement of the aqueous is the result of a combination of the two forces working in the same direction. The

histological findings of Friedenwald and Scholz indicate that attention should be given to the possibility of a considerable dilution of the plasma in the relevant vessels.

The veins of the filtering angle, which are supported by scleral strands, are, as far as the author is aware, the only minute vessels of the body which need not collapse as soon as the external pressure exceeds the internal. Consequently, in these vessels, the osmotic pull of the plasma colloids and the hydrostatic push can co-operate. This fact allows higher driving forces for fluid absorption than elsewhere and dilution of the streaming plasma by absorbed fluid should consequently more easily become evident.

Consider such a vessel. If it were completely filled with blood, the situation would be simple. The driving force behind the passage of aqueous humour would then be the sum of the hydrostatic pressure difference and the colloid-osmotic attraction of the blood plasma. However, the blood in the vessel is not pure: it becomes more or less diluted by aqueous humour when it absorbs the efflux from the anterior chamber. This reduces the osmotic attraction along the path of the blood through the vessel. When the intra-ocular pressure rises and more aqueous humour is forced out hydrostatically, this dilution will become greater and the colloid-osmotic attraction consequently smaller. When the intra-ocular pressure falls, the blood in the vessel becomes less diluted, and the colloid-osmotic attraction for aqueous humour rises. Plainly, we have here a mechanism that tends to keep the flow of aqueous humour constant, the direct opposite of an overflow mechanism. The degree of constancy achieved is clearly dependent on the rate of the blood stream through the vessel. When there is no blood supply at all, the colloid-osmotic factor disappears. The rate of efflux of the aqueous humour will then be in direct and simple proportion to the hydrostatic factor; there will be no stabilization of aqueous flow. When there is a very rapid flow of blood, the converse will be found—*i.e.*, a constant and fairly high osmotic attraction, which admittedly reduces the relative importance of the variable hydrostatic factor, but on the other hand does not stabilize the flow of aqueous absolutely. The stabilization tendency only appears in intermediate cases, but here the quantitative relations become so complicated that they cannot be treated in words. I have therefore made a mathematical calculation of how the fluid exchange over a vessel wall behaves, taking into account the change of the colloid-osmotic pressure which the plasma undergoes when it flows through the vessel.

I have not been able to find any previous treatment of this problem, which is one of general physiological interest. This may possibly be because the general case of the problem leads to a differential equation which cannot be solved exactly. The difficulty arises if one tries to pay regard both to the osmotic conditions varying along the

vessel, and to the variations in the hydrostatic lateral pressure along its course. As we are dealing with a venous vessel with relatively large surface and cross section a first approximation can ignore the differences in lateral pressure which may exist between different parts of the vessel: these can only be very small in relation to the other active forces. We therefore assume that there is the same hydrostatic pressure in the whole vessel as far as this comes into contact with the aqueous humour.

Thus, we consider a linear vessel, through which blood flows. The lateral pressure in the vessel is everywhere equal to p_v . The colloid-osmotic pressure p_o is a function $p_o(l)$ of the position l . On entering the vessel $p_o = \bar{p}_o$. Outside the vessel there is aqueous humour under the intra-ocular pressure of p_i . (It is in relation to the aqueous humour that the colloids have the osmotic pressure of p_o — by this definition, we avoid most of the complications that might arise from considerations of Donnan effects). The blood streams into the vessel with the volume rate of V_i for plasma. During its passage through the vessel it takes up a certain volume of aqueous humour, partly by osmotic attraction and partly by hydrostatic filtration. The volume absorbed per unit of length and time, the specific absorption rate, will be called a . It is a function of l . The quantity absorbed in the vessel up to a point l is called A . We then have

$$A = \int_0^l a dl \text{ and } a = \frac{dA}{dl}$$

At the point l , the plasma has already been diluted to a certain degree. If there has been complete mixture, the degree of dilution is $V_i/(V_i + A)$. The diluted plasma has a lower colloid-osmotic pressure. We will assume for the sake of simplicity that the pressure is proportional to the concentration. This is not strictly so, and we shall be discussing what the simplification implies. On this assumption, however, the colloid-osmotic pressure at the point l will be

$$p_o = \bar{p}_o \cdot \frac{V_i}{V_i + A}$$

The hydrostatic pressure head is everywhere $p_i - p_v$.

Let us express the hydrostatic driving force in terms of the colloid-osmotic pressure of the undiluted plasma, $\bar{p}_o$, and define a relative hydrostatic pressure γ as

$$\gamma = \frac{p_i - p_v}{\bar{p}_o}$$

In the normal eye, γ cannot be much larger than about 1.0 or much less than 0.

The specific absorption rate $\alpha = \frac{dA}{dl}$ is the product of the driving force and the specific filtration capacity of the vascular wall, g , at the point l :

$$\alpha = \frac{dA}{dl} = g \left(\bar{p}_o \cdot \gamma + \bar{p}_o \cdot \frac{V_i}{V_i + A} \right)$$

The integration of this differential equation using the boundary conditions ($l=0$, $A=0$), gives

$$\bar{p}_o \int_0^l g dl = \frac{1}{\gamma^2} \left[\gamma A - V_i \ln \left(1 + \frac{A}{V_i} \cdot \frac{\gamma}{1 + \gamma} \right) \right]$$

On the left we have the absorption rate for aqueous humour which the vessel would have had for purely osmotic reasons if it had been filled with pure plasma. We will call it O . We express the true absorption A and the plasma flow V_i in O as unit.

$$A = \alpha \cdot O; V_i = v_i \cdot O$$

Insertion of this and rearrangement finally gives the relation sought, even if only implicitly, between relative absorption rate, α , and relative hydrostatic pressure, γ . As parameter we have v_i , the relative plasma flow:

$$\alpha = \gamma + \frac{v_i}{\gamma} \cdot \ln \left(1 + \frac{\alpha}{v_i} \cdot \frac{\gamma}{1 + \gamma} \right)$$

For $\gamma=0$ this expression is indefinite. The limiting value, however, is:

$$\alpha_o = \sqrt{v_i^2 + 2v_i} - v_i$$

The equation cannot be evaluated exactly for other values of γ . Fig. 1 shows a number of solutions for different parameter values, obtained by graphic and numerical approximation. This has been taken to a point where the errors of the single ordinates do not exceed some few per cent.

The result of taking plasma dilution into consideration is visible in two properties of the graphs of Fig. 1.

First, the whole level of the curves, inclusive of the intersection with the ordinate axis, is dependent on the rate of plasma flow, v_i . Without plasma dilution, they would all start at $\alpha=1.0$ for $\gamma=0$. Secondly, the slope of the curves is smaller than 1.0 and especially small in certain pressure regions, where an inflection occurs. If there were no plasma dilution, the slope would have been 1.0 everywhere. This now only is the case for $v_i=0$ and ∞ .

The smallest slope is found at the initial part of the curve for the smallest plasma flow, $v_i=0.01$. Here, consequently, the highest degree of absolute stabilisation of aqueous flow by the "dilution mechanism" occurs. The slope is only 0.7 and is even less for

negative γ and smaller v_i . With higher rates of plasma flow, the corresponding region, which is visible in the higher curves as a small inflection, is displaced towards higher γ values and become less and less important.

FIG. 1.

The rate of fluid absorption by a vessel under combined osmotic and hydrostatic influence.

Abcissae: γ = relative hydrostatic pressure head.

Ordinatae: a = relative rate of fluid absorption.

Parameter: v_i = relative rate of plasma flow through the vessel.

For $\gamma > 0$, the osmotic and hydrostatic forces co-operate, for $\gamma < 0$ they oppose each other. All the curves intersect at $a = 0$, $\gamma = -1.0$. Consequently the slope gradually decreases towards the left. The curve for $v_i = 0.001$ is steeper than that for $v_i = 0.01$ in the interval shown.

In Fig. 1 the reduction of slope caused by the "dilution effect" appears not to be very important except in restricted regions and at low rates of plasma flow. However, in the derivation of our formula we have neglected certain factors which certainly will increase the "dilution effect" considerably.

First of all, we have assumed that the colloid-osmotic pressure sinks in proportion to the degree of dilution of plasma. As a matter of fact, it sinks considerably more (see Meyer 1932 for references and discussion). This naturally increases the dilution effect.

Furthermore, we have assumed that complete mixing between plasma and aqueous takes place in the vessel. This is not quite impossible, but on the other hand it is very probable that a certain

degree of stratification occurs at higher rates of aqueous flow, so that the fluid actually in contact with the vessel's wall is more dilute than the bulk of the fluid. This would be in agreement with the observations of Ascher and Goldman on man, where stratification of the blood and aqueous in episcleral vessels has been directly observed. A mechanism of this kind would materially increase the "dilution effect."

Finally and this is probably the most important point, we have treated only one vessel. Let us consider the situation if there are several vessels connected "in parallel" in the electrical sense, at varying depth in the sclera. A considerable influx of aqueous into those who are most accessible will deflect the blood stream into other vessels which have less contact with the aqueous. The plasma in the most accessible vessels will then be even more diluted than in our calculations, with a corresponding reduction in osmotic pull and a tendency towards absolute stabilisation of the rate of aqueous flow.

Until now, we have discussed the matter with regard to the absolute amount of aqueous flow and the stabilisation of this absolute amount. With respect to the regulation of the intra-ocular pressure, however, the relative variations of aqueous flow with changing intra-ocular pressure are more important. Summarizing the situation from this point of view we find the following:

(a) If the plasma flow through the trabecular veins is considerable, there is possibly not much absolute stabilisation of aqueous flow but instead a considerable "basal" flow even at zero hydrostatic pressure head. This results in a considerable relative stability of aqueous flow in spite of changing intra-ocular pressure.

(b) If the plasma flow through the trabecular veins is small, there probably is only a small "basal" flow at zero pressure head but instead a considerable absolute stabilization of aqueous flow. This also results in a considerable relative stability of aqueous flow in spite of changing intra-ocular pressure.

Thus we find that the existence of an osmotic factor in the aqueous outflow mechanism reduces the efficiency of the drainage mechanism in its rôle as a stabilizer of intra-ocular pressure in several ways. The osmotic factor both absolutely and relatively reduces the rate of change of aqueous flow with pressure, it tends to keep up a constant flow of aqueous.

The theory given thus explains the experimental findings presented in the previous section at least qualitatively. Moreover, it is in excellent agreement with some findings by Friedenwald and Pierce (1932). These authors observed, that if the rate of inflow of saline into a dog's eye is plotted as a function of pressure, the curve shows a definite inflection where the increase in flow per unit pressure increase is much smaller than at higher and lower pressures. Some of their results are reproduced in fig. 2. There can hardly be any

doubt that this behaviour of the curve is due to the plasma dilution mechanism discussed above.

In the experiments of Friedenwald and Pierce, the normal intra-ocular pressure is stated to have been 3-10 mm. Hg below the beginning of the inflected region. A pressure drop of this magnitude could easily be caused by the general anaesthesia. Moreover, the intra-scleral venous pressure could have been higher during anaesthesia. It seems not impossible, therefore, that in the unanaesthetized

FIG. 2.

The rate of inflow of saline into the eyes of anaesthetized dogs. From Friedenwald and Pierce (1932).

dogs, the intra-ocular pressure was high enough to allow the drainage mechanism to operate in the inflected region, where aqueous flow is stabilized. The results obtained above for the normal rabbit's eye may perhaps indicate that this holds for the rabbit too.

How the situation in man remains to be seen. The results of this study are not directly applicable to man, who has no trabecular veins. Friedenwald (1936) has made it seem very probable that the aqueous in the canal of Schlemm is mixed with a certain amount of plasma derived from special arterial connections. On principle, therefore, a similar kind of dilution mechanism could very well operate in the canal of Schlemm too, keeping the flow of aqueous more or less constant and decreasing the pressure-stabilizing properties of the drainage mechanism.

IV.—Concluding remarks

We have now arrived at the end of this investigation. Starting with the expectation of finding properties of the aqueous drainage mechanism which might be useful in stabilizing the intra-ocular

pressure, we have arrived at quite the contrary result. Experimental as well as theoretical findings point to the existence of a mechanism which, far from being suitable for stabilizing the intra-ocular pressure, is suitable for stabilizing the rate of flow of aqueous instead. What kind of physiological function could such a mechanism fulfil?

The answer lies near at hand if we once stop to consider the aqueous as merely something that causes intra-ocular pressure. The aqueous is the blood of the lens. What we have stumbled upon is a mechanism by means of which a fairly constant circulation of aqueous could be maintained in spite of the changing intra-ocular pressure.

In the "architecture of bodily function," a hierarchy of regulations exists. We have a regulation of blood pressure by the baroreceptors, but this regulation is subordinated to the need for adequate blood flow through vital and working organs. In case of conflicting purposes, the blood pressure regulation just gives in.

This simile may be extended to the eye. There is possibly a regulation of the intra-ocular pressure to which the drainage mechanism could possibly contribute. But this regulation seems to be subordinated to the need for a constant aqueous flow, which gives the lens a constant environment. In the cataracts which accompany various disturbances of intra-ocular pressure and aqueous flow we see what may perhaps be the result of overtaxing this mechanism. In fact, it is tempting to go even further: might not the glaucomatous pressure rise be considered, at least in some cases, as an adaptation, securing an adequate circulation of aqueous in face of impaired drainage facilities?

Summary

1. A new method of studying the dependence of aqueous outflow on intra-ocular pressure in the completely intact eye is described and applied to the rabbit. It is based on determinations in the aqueous of equilibrium concentration and rate of entrance of a substance at different levels of intra-ocular pressure.
2. Unilateral carotid occlusion does not change the equilibrium concentration of radiosodium. This shows that the change in aqueous outflow caused by the operation and the concomitant eye pressure drop is proportionally equal to the change in rate of entrance of radiosodium into the aqueous humour.
3. Unilateral carotid occlusion reduces the rate of entrance of radiosodium into the aqueous humour by only about 7 per cent., probably somewhat less. This shows that the reduction in aqueous outflow is percentually smaller than the reduction in intra-ocular pressure and hydrostatic pressure head. Thus, there must be some kind of relative stabilization of the rate of aqueous flow.
4. The influence of the hydrostatic driving force would be less if osmotic forces participated in the aqueous drainage mechanism.

Mathematical treatment of fluid absorption by a vessel under combined osmotic and hydrostatic action shows that if the diluting effect of the absorbed fluid is not insignificant, a certain absolute as well as relative stability of fluid absorption will obtain, in spite of changes in the hydrostatic pressure relations.

5. The results indicate the existence of an aqueous drainage mechanism which tends to keep the rate of aqueous flow constant even at the expense of the stability of the intra-ocular pressure. Such a mechanism could be significant from the point of view of the lens.

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A CASE OF BILATERAL GENUINE IRIS-ATROPHY*†

BY

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A lady, aged 24 years, came to the clinic complaining of intolerable headache and bad vision of the right eye. The left eye was always blind. Clinical findings: sight of right eye finger counting 1 metre,—8·0 D = 1/3: left, no light perception. Pressure on both sides 56 Hg mm. Right eye: eccentric pupil directed to 3 o'clock, roughly triangular in shape reaching almost to the iris-root. Pigment border nasally below and above is intact. Iris tissue very atrophic, the iris-frill can be seen only above and below. Temporally

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