J. Physiol. (1948) 107, 141–152 612.844.4–7

THE DISTRIBUTION OF REDUCING SUBSTANCES BETWEEN THE INTRA-OCULAR FLUIDS AND BLOOD PLASMA, AND THE KINETICS OF PENETRATION OF VARIOUS SUGARS INTO THESE FLUIDS

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(*Received* 20 *May* 1947)

The concentration of reducing substances (hereinafter referred to as glucose) in the aqueous humour is less than that in plasma (Adler, 1930; O'Brien & Salit, 1931); the concentration in the vitreous body is still smaller. In view of the tendency to ascribe differences in concentration between plasma and intra-ocular fluids to secretory activity it is important that the factors determining these differences be completely elucidated.

We may expect the relative concentrations of diffusible substances in plasma and intra-ocular fluid to be determined by three principal influences:

(*a*) The physico-chemical factors determining the relative compositions of a protein-containing solution in contact with its ultra-filtrate dialysate. If these factors operated alone, non-electrolytes would be equally distributed between the two fluids.* The concentrations of diffusible ions would conform to the Gibbs-Donnan relationship, the cations being more strongly concentrated in the plasma.

(*b*) The metabolism of the eye. The retina and the lens have an active metabolism and in so far as they derive materials directly from the intra-ocular fluids or modify the capillary blood concentration in the uveal tract, this metabolism must influence the observed distribution of solute between arterial blood plasma and intra-ocular fluids. We may expect the effect to be most pronounced on a non-electrolyte, like glucose, but the ionic equilibria can also be modified secondarily.

* That is, their *activities* should be the same in the two fluids. The observed concentrations need not necessarily be equal; thus the work of Weber & Nachmannsohn (1929) indicates that the concentration of glucose in plasma may be some 2% higher than that in its ultra-filtrate. When concentrations of a substance are compared in a protein-containing and protein-free solution it is important that they be expressed in terms of the weight of water in the solution rather than the volume of the latter; except where otherwise stated, 'concentration' in this paper means weight of substance in 100 g. H_2O.

(*c*) Secretory activity of the lining membranes. Our knowledge of the contribution of this factor is scanty, although the work of Friedenwald and his collaborators (e.g. Friedenwald & Stiehler, 1938; Friedenwald & Buschke, 1941 and Friedenwald, Buschke & Michel, 1943) is suggestive. Until the simpler physico-chemical and metabolic factors are completely elucidated, little definite can be stated.

In the present paper, the possible effects of these factors on the distribution of glucose between the intra-ocular fluids and blood plasma will be described; the experimental approach has been predominantly by way of kinetic studies, and these have led to tentative conclusions regarding the site of entry of dissolved substances into the eye, and the nature of the membranes separating the aqueous humour and vitreous body from the blood plasma.

EXPERIMENTAL

Static Studies. Great care was taken to avoid the hyperglycaemia associated with fear; nembutal was used as anaesthetic, intraperitoneally in the cat and intravenously in the rabbit. In the latter animal it is impossible to avoid hyperglycaemia, and before fluids were removed the animal was 'equilibrated' for some hours with its head projecting from a bleeding-box. For comparison of normal and aphakic eyes this equilibration was not so important and was generally omitted. Blood was withdrawn from the cat by arterial puncture, and from the marginal ear vein of the rabbit after vaso-dilatation with toluene. Sugars were determined in duplicate by the Hagedorn-Jensen technique (1923) on Somogyi (1930) filtrates of the various fluids; sucrose was determined by estimating the reducing value of the fluid before and after hydrolysis in 0·1 N-H_2SO_4 (15 min. at 100° C.). The difference between duplicates rarely exceeded 1%, except if the reducing value was low when it amounted to 2%. Removal of the lens was carried out by the standard surgical procedure for extra-capsular extraction.

Dynamic Studies. The general principle was to maintain a constant high level of a given sugar in the blood by continuous intravenous infusion of an isotonic solution in 6% gum acacia under nembutal anaesthesia. Rapid elimination of the injected sugar was prevented by tying the renal arteries. One eye was, in general, removed before the injection, to estimate the initial reducing value of the intra-ocular fluids, and the other after a known time interval. With sucrose, which is estimated independently of the reducing substances in the fluids, the preliminary removal of one eye is unnecessary. After enucleation, the aqueous humour was withdrawn and the eye was then frozen in solid CO_2. When hard, the eye was cut into two or more pieces as described later; the frozen pieces of vitreous body were filtered through glass-wool as they melted, in order to break down the gel structure. Blood and aqueous humour were immediately placed in tubes surrounded with ice.

RESULTS

The normal distribution. The concentrations of glucose in the aqueous humour, vitreous body, and blood plasma of rabbits and cats are shown in Table 1. The results on the cat amply confirm those of Adler (1930); the low glucose content of the vitreous body is striking.

There are two main loci of sugar utilization in the eye—the lens and retina. That the lens modifies the sugar content of both the aqueous and vitreous humours is shown in Table 2, in which some typical results on rabbits and cats are presented. The lens was removed from one eye, and at various intervals

TABLE 1. Glucose concentrations (mg./100 g. H_2O) in plasma and intra-ocular fluids

		Fluid			
	Plasma	Aqueous	Vitreous	R_A = aq./pl.	R_V = vitr./pl.
Rabbit	131	116	56	0·89	0·425
	133	118	66	0·89	0·495
	142	110	74	0·78	0·52
	149	128	87	0·86	0·58
	160	134	73	0·84	0·46
	163	145	82	0·89	0·50
Mean				0·86	0·49
Cat	125	95	64	0·76	0·51
	89	73	55	0·82	0·615
	92	78	52	0·85	0·565
	119	86	61	0·72	0·51
	104	67	44	0·64	0·425
	121	89	58	0·74	0·48
	103	89	64	0·87	0·62
Mean				0·77	0·53

TABLE 2. Glucose concentrations (mg./100 g. H_2O) in fluids of normal and aphakic eyes

	Interval after extraction (weeks)	Plasma	Fluid			
			Normal aqueous	Aphakic aqueous	Normal vitreous	Aphakic vitreous
Cat no. 1	4	89	64·5	83	—	—
	6	98	72	83	—	—
Cat no. 2	7	88	66·5	81	—	—
	9	104	66·5	83	44	57
Cat no. 3	3	95	76	81	—	—
	4	—	74	81	—	—
	6	88	76	82	45	53
Rabbit no. 1	3	214	165	149	—	—
	5	183	127	99	—	—
	6	185	166	147	—	—
	7	208	157	129	99	107
Rabbit no. 2	3	161	152	145	—	—
	5	126	103	105	—	—
	6	145	126	121	—	—
	7	178	162	158	99	111
Mean (9 rabbits), 7–14 weeks:		152	124	117	87	96

after the operation aqueous humour was withdrawn from both; finally, both eyes were enucleated. In the cat, the increase in the aqueous humour concentration after lens extraction was pronounced (20% or more) in two cases, whilst in the rabbit it was much smaller; in fact, there may be an actual *decrease*, as in rabbit no. 1. This seems to be due to diffusion backwards through the pupil into the vitreous body, since rabbit no. 1, in which this effect was most marked, had a wide iridectomy and dilated pupil, whereas rabbit no. 2 had no iridectomy, a constricted pupil, and a portion of dead lens partially covering the aperture. Similarly cats nos. 1 and 2 had portions of dead lens material remaining in the pupil whilst in cat no. 3 the pupil was wide and

completely unobstructed. The mean for nine rabbits shows a 6% decrease in the aqueous humour of the aphakic eye. The vitreous body showed a large increase in the cat (30%) and a smaller one in the rabbit. The normal eye of the rabbit contains a higher concentration of ascorbic acid than the aphakic eye (Goldman & Buschke, 1935) and, since this substance contributes to the reducing value of the aqueous humour, the increase in glucose concentration due to aphakia is partially masked by the decrease in ascorbic acid concentration.

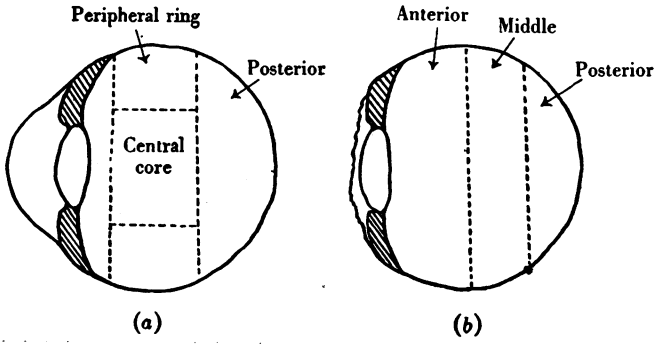

Fig. 1. (*a*) Approximate sectioning of the vitreous body before and after incubation. (*b*) Approximate sectioning of vitreous body before and after diffusion experiments; in this case the aqueous humour was removed before freezing.

The fact that the fluids of the aphakic eye do not show sugar concentrations equal to that in plasma suggests that the retina is utilizing glucose. If glucose is consumed by the retina of the enucleated eye, the concentration of glucose after incubation should be less in the periphery than in the centre of the vitreous body. The two eyes of a cat were removed; one was frozen immediately, whilst the other was placed in a boiling tube in the bottom of which there was cotton-wool moistened with 0·9% NaCl; the tube was immersed in a bath at 38–40° C. After 2 hr. the eye was frozen. The eyes were sectioned as indicated in Fig. 1 (*a*), giving a large central disk and a thinner posterior cap of vitreous body. With a cork-borer the central disk was divided into a core and peripheral ring, the latter about 3 mm. wide. The differences in the glucose contents of the aqueous humour and of the various parts of the vitreous body before and after incubation were as follows:

		mg./100 g.
Vitreous body	Core of central disk	15
	Periphery of central disk	40
	Posterior cap	30
Aqueous humour		27

The result leaves little doubt that the retina is responsible for at least a part of the glucose consumption in the posterior cavity of the eye; if the lens only were consuming glucose, the core of the central disk would have shown the greatest loss since it was in immediate contact with the lens. In the eye,

immediately after enucleation, the glucose is apparently not uniformly distributed through the vitreous body; Adler (1930) has shown that in the frozen eye the anterior half of the vitreous body contains more sugar than the posterior. In a series of nine rabbits we have found that if the middle disk (Fig. 1 (*a*)) of the frozen vitreous body was divided into a central core and a peripheral ring, the latter invariably contained the higher glucose concentration. It is possible that these differences in concentration are, at least in part, artefacts resulting from the freezing process, so that it is not justifiable to draw definite conclusions from the observed concentrations regarding the relative extents to which glucose is utilized in the different parts of the eye. The lower concentration in the central core is, however, reasonable, since it is in immediate contact with the lens; on incubation, this relationship is invariably reversed, both in the cat and rabbit; in these circumstances the retina draws on the glucose in the vitreous body owing to the absence of retinal and uveal circulation, and this upsets the normal picture of glucose distribution.

If the lens consumes glucose from the anterior chamber, it may be expected that by reducing the area of lens exposed to the aqueous humour, by miosis, the glucose content should rise. One eye of a cat was treated with eserine and the other with atropine; after about 2 hr. the aqueous humours were withdrawn from both eyes. The mean results for four cats (two of them kittens) were as follows:

	mg./100 g.
Atropinized eye	70
Eserinized eye	75
Plasma	107

Again, it may be expected that the aqueous humour formed immediately after the emptying of the anterior chamber (paracentesis) should have a higher concentration of glucose since the lens will not have had time to re-establish a steady state. The results of a typical experiment are as follows, the 'second' re-formed aqueous humour being the fluid formed after the successive withdrawals of the original and 'first' re-formed aqueous humour:

	mg./100 g. H_2O
Normal aqueous humour	62·5
First re-formed humour	83·5
Second re-formed humour	85·5
Plasma	89

In no instance, however, did the glucose concentration in the re-formed fluid equal that in the plasma exactly.

Kinetic Studies. The permeability of the eye membranes to the following sugars was investigated: glucose, galactose, 3-methyl glucose, xylose and sucrose. 3-Methyl glucose is a synthetic compound which is apparently not phosphorylated in vivo (Campbell, unpublished) and was thought, on this account, to be unlikely to be secreted.

Detailed results of seven experiments with glucose are presented in Table 3 in order that the animal-to-animal variations may be appreciated. Constants indicating the rate of penetration into both aqueous humour (K_A) and vitreous body (K_V) have been calculated in accordance with the equation of Davson & Quilliam (1940).*

TABLE 3. The rate of penetration of glucose into the aqueous humour and vitreous body of the cat

Plasma (mg./100 ml.)	Aqueous (mg./100 ml.) A_1	Aqueous (mg./100 ml.) A_2	Time (hr.)	$100K_A$	$100K_V$	K_A/K_V
280	94	254	2·0	38	11	3·45
290	140	188	0·5	33	16·5	2·0
265	92·5	144	0·75	20·5	12	1·7
266	130	232	2·0	30	10	3·0
280	104	202	0·62	57	7	8·1
597	112	238	0·47	31	10	3·1
439	88	233	0·75	30·5	9	3·4
Mean				34	11	3·1

A_1 is the initial concentration in the aqueous humour; A_2 the concentration in the aqueous humour after the blood concentration, P, had been maintained for t hours. K_A is given by the equation:

$$K_A = \frac{kA}{V} \times \frac{1}{2{\cdot}303} = \frac{1}{t} \log \frac{P - A_1}{P - A_2}$$

where k is the true permeability constant, and A and V are the area and volume of the system respectively. K_V represents a similar constant derived from the concentrations in the vitreous body.

TABLE 4. Penetration of different sugars into the eye fluids of cats

Sugar	No. of cats	$100K_A$	$100K_V$	K_A/K_V	P_S
Glucose	7	34 ±2·2	11 ±0·8	3·1	0·125
Galactose	9	33·5±2·3	9·5 ±0·9	3·5	0·006
3-Methyl glucose	5	36·5±2·9	11 ±0·5	3·3	0·02
Xylose	6	37 ±2·7	16·5 ±1·5	2·2	—
Sucrose	9	4·9±0·6	0·29±0·05	17	—

K_A and K_V have the same meaning as for Table 3. P_S is the probability that the value of Student's t, computed from the mean xylose K_A/K_V and the hexose K_A/K_V, would occur by chance (Yule & Kendall, 1940). Standard errors are also shown.

Table 3 shows a consistent difference in rates of penetration into the aqueous humour and vitreous body, the rate for the aqueous humour being some three times greater. In Table 4 the results for the remaining sugars are presented in the form of the constants, K_A and K_V, only. The following points may be noted: (*a*) The rates of penetration of the pentose (xylose) and of the hexoses into the aqueous humour are not significantly different; the disaccharide, sucrose, on the other hand, penetrates very much more slowly. (*b*) The

* The equation is only approximate, especially owing to the utilization of sugar by the eye, but in view of the large animal-to-animal variations refinements seem unnecessary. When the plasma reducing value is raised by several hundred % the steady state finally achieved tends to equality of concentration expressed as mg./100 ml. as opposed to mg./100 g. H_2O (i.e. the true concentration in the plasma is about 7% higher than in the aqueous humour), and for this reason the former unit has been used in these kinetic studies.

rates of penetration of the hexoses into the vitreous are all about one-third of those into the aqueous humour ($K_A/K_V = 3{\cdot}1 - 3{\cdot}5$); with sucrose the factor is one-seventeenth ($K_A/K_V = 17$). With the pentose, xylose, the ratio was 2·2, due to an increased value of K_V. Owing to the impossibility of obtaining further supplies of this sugar no more than six experiments could be carried out; consequently Student's '*t*-test' for the differences between means of small samples was applied successively to the mean values of K_A/K_V for xylose and the individual hexoses; the values of P_S (Yule & Kendall, 1940), indicating the probability that the values of t so computed would occur by chance, are included in the table. With 3-methyl glucose and galactose the differences in the ratios are significant; with glucose, where greater variability was encountered, the difference is not significant. The large increase of the ratio K_A/K_V on passing to the disaccharide is clearly significant.

The results suggest that the membrane separating the vitreous body from the blood plasma is more selective than that separating the aqueous humour; thus the latter apparently does not discriminate between a hexose and pentose, whereas the former appears to do so; as the molecular size is increased, the greater selectivity of the barrier separating the vitreous body from the blood is reflected in an increasing value of K_A/K_V.

The differing values of K_A and K_V for any given sugar suggested that, contrary to accepted belief, substances could enter the eye from other parts than the ciliary body; if penetration takes place only from the ciliary body it would be expected that after maintaining the blood sugar level at a high value for, say an hour, the concentration in the part of the vitreous body most remote from the ciliary body would be smaller than in that closest. In thirteen different experiments, the eyes, after removal of the aqueous humours, and freezing, were cut approximately as in Fig. 1(*b*), giving as mean volumes for the various sections: posterior 0·35 ml., middle 0·43 ml., and anterior 0·63 ml. The different parts were analysed and the results are shown in Table 5. It will

TABLE 5. Concentrations of sugar (mg./100 g. H_2O) in three sections of vitreous body after maintaining a high blood concentration for a definite period, compared with the concentrations in the control eye. Mean results of thirteen experiments

	Section of vitreous body		
	Posterior	Middle	Anterior
Control	73	67	75
Test	124	98	113

be seen that, for the control eyes, the mean concentration in the middle section was 67 mg./100 g. H_2O, being 92% of that in the posterior section; after a high blood-sugar had been maintained for about 1 hr. the average concentration in the middle section was 98 mg./100 g. H_2O, being only 78·5% of that in the posterior section. The results certainly suggest that the locus of diffusion into

the vitreous body is not confined to the ciliary body, but it must be remembered that deductions from the concentrations of dissolved material in the frozen eye are to be accepted with caution; conditions of freezing were, however, kept as uniform as possible so that disturbances in distribution would operate to the same extent in control and test eyes.

These results prompted an inquiry into the site of entry of substances into the aqueous humour; if diffusion takes place entirely from the ciliary body, they must enter through the pupil and a variation in the size of the latter might modify the rate of appearance. Diffusion experiments were carried out as before, but one eye of the cat was eserinized and the other atropinized. If diffusion takes place only by way of the ciliary body the rate of entry should be less in the eserinized eye with its slit-like pupil. The results are shown in Table 6; invariably the eserinized eye contained the greater amount of sugar,

TABLE 6. The rates of entry of sugars into atropinized and eserinized eyes compared

Sugar	Time (min.)	Atropinized eye	Eserinized eye
Galactose	40	152	214
Galactose	27	215	239
Glucose	60	242	257
Xylose	41	191	199
Galactose	62	150	164
Sucrose		18	28
Sucrose	110	38	51

Figures represent sugar concentration in the aqueous humour, in mg./100 g. H_2O, after maintaining a high sugar concentration in the blood for a given time.

although the effects were, in general, not large. The results strongly suggest that the pupil size is of no importance in so far as rate of penetration of sugars into the aqueous humour is concerned. The increased rate of penetration into the eye with the constricted pupil is most probably due to an increased capillary permeability resulting from direct action of the drug on the vessels and possibly also a mechanical stretching, since when both galactose and sucrose were studied in the same animal (the bracketed results in Table 6) the effect was much more pronounced on the larger molecule; moreover the eserinized eye generally, but not always, contained a trace of protein.

DISCUSSION

The membranes lining the eye are readily permeable to hexoses and we may therefore expect that, if physical factors of diffusion alone were operative, the concentrations of glucose in the ocular fluids and the capillary plasma would be equal. The large discrepancy between the concentrations in plasma and ocular fluids has been shown to be primarily due to metabolic influences, and it may well be asked whether the factor of active secretion need be invoked at all. The influence of the lens can be studied in aphakic eyes, and in these the

aqueous humour and plasma levels still differ by a factor of at least 10% in the cat. The activity of the retina cannot be excluded, however, and it may well be that removal of the lens permits a ready diffusion of glucose from the anterior chamber into the vitreous body. The experiments with rabbits strongly support this view. The immediately re-formed aqueous humour, after paracentesis, has a glucose concentration differing by only about 5% from that of plasma; here the effects of lens activity and diffusion through the pupil are minimized, and one might expect to find the concentrations equal. Two other factors must, however, be taken into consideration. The blood used for comparison is arterial; the eye is an organ with a very high metabolism and we may therefore expect an arterio-venous difference in sugar concentration (differences as large as 39 mg./100 g. between carotid artery and vortex vein have been reported; the greater portion of this discrepancy is probably due, however, to activity in the more posterior parts of the eye). The glucose concentration in the capillary plasma may therefore be, on the average, less than that in arterial plasma. Again, the non-sugar reducing substances in the plasma represent a considerable fraction of the whole (27 mg./100 ml. according to Somogyi, 1927); the membrane separating the aqueous humour from the plasma has a high degree of selectivity in respect to nitrogenous compounds (unpublished), and it is possible that the re-formed aqueous humour, formed by a rapid process of ultra-filtration and therefore not necessarily equivalent to a dialysate, contains a lower concentration of non-sugar reducing substances than would be the case if time were permitted for dialysis to proceed to completion. The behaviour of sucrose is a case in point; if a high sucrose concentration is maintained in the blood of the cat, it is found that the re-formed aqueous humour after paracentesis has a sucrose concentration only 60% of that in the blood.

The concentration of glucose in the aqueous humour may thus attain a 'steady state' in which the lens consumption is made good by diffusion through the anterior surface of the iris; it is possible to calculate, from the observed concentrations and the constant, K_A, for glucose, the rate of absorption of glucose from the anterior chamber; it amounts to about 0·15 mg./hr., a figure not inconsistent with the known sugar utilization of the lens (Kronfeld & Bothman, 1928).

From the posterior cavity of the eye the lens and retina may both extract glucose, and the concentration in the vitreous body is therefore less than in the aqueous humour. The regional distribution of glucose in the vitreous body is explained by this dual consumption.

The kinetic studies tend to confirm this view of the steady state; the barrier between the plasma and the aqueous humour shows no special selectivity towards glucose but permits galactose, the synthetic 3-methyl glucose, and the pentose, xylose, to pass at about the same rate. If any secretory activity were

involved, one might expect, by analogy with intestinal absorption, to find appreciable differences in rates. The slow rate of penetration of sucrose is in agreement with some earlier preliminary work on the dog (Weld, Feindel & Davson, 1942) in which it was shown that this molecule represents the limiting size for sugar penetration, the trisaccharide, raffinose, not penetrating at all.

The striking difference in selectivity between the barriers separating aqueous humour and vitreous body from the blood is of some significance; hitherto it has been considered sufficient, in the interpretation of intra-ocular dynamics, to study the penetration of substances into the aqueous humour only. The existence of this more selective membrane lining the posterior cavity of the eye may well mean that it is the composition of the vitreous body that predominantly determines the intra-ocular pressure; if there is any secretion into the eye it will obviously be more effective in modifying the osmotic pressure difference between the ocular fluid and plasma if the secreted substance does not leak away very rapidly.

It may reasonably be asked whether the differences in K_A and K_V represent actual differences in permeability constants. The constants K_A and K_V contain the factor A/V, the ratio of area of membrane to volume of fluid, and if this is not the same for the two compartments of the eye the constants are not directly comparable. In the cat, the volumes of aqueous humour and vitreous body are roughly in the ratio of 1:1·5, but it is impossible to state the effective areas of membrane; in view of the large number of ciliary processes, it would appear that the area available for diffusion into the vitreous body is considerably the greater, in which case the difference between the true permeability constants would be greater still. However, it is not necessary to know the values of A/V in determining whether the differences in K_A and K_V represent differences in permeability constants; if the membranes had identical characteristics we should expect the ratio K_A/K_V to be the same for different molecules; as we have seen, this is by no means true, the ratio increasing with increasing size of molecule. In a similar way the effects of different viscosity and different rates of mixing in the two fluids should manifest themselves to approximately the same extent for different molecules.

It is of interest to assess the actual value of k, the true permeability constant for hexoses, from an assumed area-to-volume relationship. k is given by:

$$k=\frac{KV}{A}\times 2{\cdot}3 \text{ (Davson \& Quilliam, 1940).}$$

Conventionally, k is expressed as the number of g.-mol. of the substance penetrating $1\mu^2$ of surface in 1 sec. when the concentration difference is 1 mol./l. If the volume of the aqueous humour is taken as 1 ml. and the diffusing surface as 1 cm.^{2}, k comes out at approximately 2×10^{-15}. This compares with a value of

$7{\cdot}8 \times 10^{-16}$ for the penetration of urea into the ox erythrocyte, an instance of high permeability. The effective area of diffusing surface for the anterior chamber is, of course, likely to be very much higher than 1 cm.^{2}; if the area-to-volume relationship were comparable with that in the erythrocyte where 1 ml. of cells has an area of about $1 \times 10^{12} \mu^2$ (Ponder, 1934), k becomes 2×10^{-19}. Such an extreme instance of area-to-volume relationship is unlikely to apply to the eye, but even this value of k suggests that the rate of penetration is comparatively high when it is appreciated that the penetration of the smaller molecule, erythritol, into plant cells gives constants ranging from 7×10^{-21} to $1{\cdot}3 \times 10^{-19}$ (vide Davson & Danielli, 1943). It therefore seems likely that the penetration of hexoses into the eye is a rapid permeability process; this fact, and the absence of a significant difference in rate between hexoses and the pentose, might suggest a penetration by way of water-filled pores, e.g. through the intercellular spaces of the iris capillaries and iris endothelium, but evidence derived from a study of the penetration of some other substances is against this simple mechanism and it is more probable that the comparatively rapid rate of penetration of sugars is an instance of cell membrane specialization of the kind described by Davson & Reiner (1942).

It is common, in describing studies on the intra-ocular fluids, to discuss them in relation to dialysis or secretion theories; we are convinced that this sort of discussion is now unprofitable; the problem, as indicated in the introduction to this paper, is to study each constituent of the intra-ocular fluids and to determine whether its concentration and the dynamics of its penetration are in accordance with simple diffusion theory, and next to determine the influence of the internal metabolism of the eye on these factors. Only when these physico-chemical and metabolic factors fail to explain the observed facts does it become necessary to invoke specific secretory activity.

SUMMARY

1. In the cat and rabbit, the glucose concentrations in the aqueous humour and vitreous body are lower than would be expected on the basis of a simple diffusion equilibrium with the plasma. Experiments indicate that the metabolism of both the lens and retina causes this glucose deficit.

2. The rates of penetration of glucose, galactose, 3-methyl glucose, xylose and sucrose into both aqueous humour and vitreous body of the cat's eye have been measured, and constants, K_A and K_V, proportional to these rates, have been calculated. No significant differences in rate of penetration into the aqueous humour were found with the first four sugars, but sucrose penetrated much more slowly. With the vitreous body the penetration rates were consistently smaller, and an analysis of the results indicates the existence of a more selective barrier to diffusion into this part of the eye than that separating the aqueous humour from the blood. The possible physiological significance of this

difference is discussed and the importance of including the vitreous body in any study of intra-ocular dynamics is stressed.

3. The rate of penetration of sugars into the aqueous humour seems to be independent of pupil size and it seems likely that the bulk of diffusion into the anterior chamber takes place from the iris. Some evidence is presented which suggests that the locus of diffusion into the vitreous body is not confined to the ciliary body.

4. By assuming limiting values for the area-to-volume relationship for the aqueous humour, it is possible to calculate the true permeability constants for the hexoses in the conventional units; the computation suggests that penetration is rapid in comparison with that of analogous, lipoid-insoluble, molecules diffusing into plant cells.

We are grateful to the Medical Research Council for a grant to one of us (H.D.) and for defraying the whole cost of this work. We should also like to thank Prof. Lovatt Evans for extending us the hospitality of his laboratory.

REFERENCES

Adler, F. H. (1930). *Trans. Amer. ophthal. Soc.* **28**, 307.
Davson, H. & Danielli, J. F. (1943). *The Permeability of Natural Membranes.* Cambridge Univ. Press.
Davson, H. & Quilliam, J. P. (1940). *J. Physiol.* **98**, 141.
Davson, H. & Reiner, J. M. (1942). *J. cell. comp. Physiol.* **20**, 325.
Friedenwald, J. S. & Buschke, W. (1941). *Amer. J. Ophthal.* **24**, 1105.
Friedenwald, J. S., Buschke, W. & Michel, D. (1943). *Arch. Ophthal., N.Y.*, **29**, 535.
Friedenwald, J. S. & Stiehler, R. D. (1938). *Arch. Ophthal., N.Y.*, **20**, 761.
Goldman, H. & Buschke, W. (1935). *Klin. Wschr.* **14**, 239.
Hagedorn, H. C. & Jensen, B. N. (1923). *Biochem. Z.* **135**, 46.
Kronfeld, P. & Bothman, L. (1928). *Z. Augenheilk.* **65**, 41.
O'Brien, C. S. & Salit, A. W. (1931). *Amer. J. Ophthal.* **14**, 582.
Ponder, E. (1934). *The Mammalian Red Cell and the Properties of Haemolytic Systems.* Berlin, Borntraeger.
Somogyi, M. (1927). *J. biol. Chem.* **75**, 33.
Somogyi, M. (1930). *J. biol. Chem.* **86**, 655.
Weber, H. H. & Nachmannsohn, D. (1929). *Biochem. Z.* **204**, 215.
Weld, C. B., Feindel, W. H. & Davson, H. (1942). *Amer. J. Physiol.* **137**, 421.
Yule, G. U. & Kendall, M. G. (1940). *An Introduction to the Theory of Statistics.* London, Griffin.