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THE DIALYSATION OF THE INTRA-OCULAR FLUIDS

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DURING the past few years a series of papers has been published by myself and my collaborators pursuing the hypothesis that a swelling of the vitreous gel might be responsible for the rise of intra-ocular pressure in chronic primary glaucoma, and it has been finally shown (*Brit. Jl. Ophthalm.*, Vol. XX, p. 520, 1936), that this hypothesis is wrong since the vitreous, either in the normal or glaucomatous eye, cannot originate pressures of anything like the required magnitude. Although its pursuit brought to light many facts of interest and importance, this hypothesis must, therefore, be discarded.

Before beginning the publication of a series of papers dealing with the next hypothesis, it is a good thing to look back and consider whether the theory upon which this work is based—that the intra-ocular fluids are a dialysate of the capillary blood—fits all the facts which have emerged since the time of its introduction. The more so does this seem advisable at the present moment since the appearance of a paper in a recent issue of this Journal (Vol. XXI, p. 401), by J. D. Robertson, in which, although the experimental work is limited to the osmotic interchange of tissue-fluids, the most far-reaching conclusions are deduced. Since, however,

he has gathered all the available arguments against the hypothesis of the dialysation of the intra-ocular fluids, it will be sufficient for the present purpose to consider the points raised by him.

The most important of these are as follow :—

(1) He contends that the intra-ocular fluids cannot be a dialysate since they are not stagnant but are subjected to a slow through-and-through circulation (pp. 416, 420). To a certain extent there is justification for this contention but it is essentially a terminological quibble which does not alter facts. Suppose a protein-free daughter fluid in a collodion thimble is immersed in a protein-rich mother fluid, in conditions of stagnation, everyone admits that the former is a dialysate in equilibrium with the latter. Suppose now that at intervals a drop of the dialysate is removed and thrown away; it is, of course, replaced by further dialysation. This is the position of the intra-ocular fluid. If it is not now to be called a dialysate, there is no available word in the language with which to label it; a new word will require to be coined and introduced into chemical terminology—to my mind, a quite unnecessary proceeding. An equilibrium need not be a static condition, but can also connote a dynamic state wherein a continually changing force is equally opposed by an opposite and similarly changing force. Moreover the term as generally used does not necessarily imply stagnation: when one “dialyses” a protein-salt mixture, the process is, in fact, the reverse.

(2) Robertson concludes (p. 440, *et seq.*), that my conception of the pressure-relationships in the canal of Schlemm is illogical and inconsistent with facts. My views upon this problem, supported by experimental facts which have never been disproved, have already been expressed in this Journal at considerable length (Vol. X, p. 513); but since they have been completely misunderstood in this instance, it may be well to point out again that the essential feature which enables this structure to function as a preferential drain for the fluids in the eye is that, while it (like the capillaries) has an endothelial wall through which fluid-traffic can take place, it is in direct connection with the intra-scleral veins, and therefore, being situated far down the venous pressure gradient, must have a pressure considerably less than the capillaries. It is thus a capillary (in the physiological, not the anatomical sense) in the venous system. Robertson complains, for example:—“one would have expected these (measurements) to be accompanied by an observation on the particular height of the intra-ocular pressure at which the venous pressure reversed its relationship to the chamber pressure.” The venous pressure referred to here must be the pressure in the intra-scleral veins of exit since they are the only veins which ever do show such a reversal. Such a criticism involves a misunderstanding of a view

which I thought I had expressed so clearly that misunderstanding was impossible. The answer is "at any and every pressure above the normal." To repeat my own words of 1926 (*Brit. Jl. Ophthal.*, Vol. X, p. 530):—"When the chamber pressure is raised the venous system is compressed. That part with the lowest lateral pressure will give way first, that is, the veins at their point of exit (from the chamber of the eye) will tend to become obliterated. (This can be seen clinically every day in the venous pulse so frequently observed on slight compression of the globe.) As soon as this occurs the blood flow will be checked, the *vis a tergo* from the arteries will pile up pressure, the constriction will be forced open, and the circulation will proceed at a higher level, the venous pressure in the eye rising with the intra-ocular pressure. While this is going on the pressure in the exit veins just inside the chamber of the eye has approximated the chamber pressure, the pressure gradient in the vessels traversing the sclera still obtains since their lumen is always kept open by the investing scleral tissue, and therefore, the pressure in the exit veins just outside the chamber of the eye will now fall below the intra-ocular pressure." These relationships can easily be demonstrated on a mechanical model, and were found to exist on direct experimental measurements.

Against this Robertson argues (p. 442): "As the intra-scleral veins drain the blood from the iris, ciliary body, and choroid, it must surely follow that the venous pressure must be higher than the chamber pressure to allow drainage to take place without collapse of their walls." (This is not correct.)* "The canal of Schlemm joins the anterior ciliary veins within the sclera and thus it follows that the pressures in canal of Schlemm, anterior ciliary veins (intra-scleral) and vortex veins (intra-scleral) must equal one another and vary with one another." (This is correct.) "In view of (the inter-anastomoses in the eye) it would follow as a natural conclusion that at all times the pressure in the canal of Schlemm must equal the pressure in the intra-ocular veins and exceed the intra-ocular pressure. . . . If the pressure in the retinal veins exceeded the intra-ocular pressure, as it must do, then so must also the pressure in the canal of Schlemm." This argument seems to me to be absurd. The pressure in the intra-ocular veins does exceed the chamber pressure (as I have demonstrated); but the intra-ocular venous pressure cannot equal the intra-scleral venous pressure (and the pressure in the canal of Schlemm), for in this case the blood could not flow out of the eye. If the circulation is to be maintained the pressure in the intra-scleral veins

* The statement is correct for the intra-ocular veins. Since the intra-scleral veins are outside the chamber of the eye and their lumen kept open by the investing scleral tissue, they do not collapse if their internal pressure should fall below the intra-ocular pressure.

must be less than the pressure in the intra-ocular veins, and on measurement I found it so. Robertson says that these measurements are to be accepted "with a certain amount of caution." The facts of physiology are open to everyone to verify by experiment, and form a more satisfactory basis of reasoning than argument which can be shown to be illogical.

(3) Robertson concludes that "there is no chemical equilibrium between the aqueous and the blood plasma," the conclusion being based, not on original work, but on the findings of others. He criticised my earliest analyses (1927) because they compared the pooled intra-ocular fluid of many animals with the serum of one—a perfectly legitimate criticism to which I have drawn attention myself. In an analysis, however, involving minute amounts of materials which are extremely difficult of micro-estimation, such a scheme provided, I think, a useful starting point for future work. The three most easily estimated substances are sodium, potassium and chloride; and in a later estimation of these, in association with Davson and Benham (*Biochem. J.*, Vol. XXX, p. 733), wherein the aqueous humour of cats was compared with its corresponding plasma, we showed that their concentrations were such as would be expected if the intra-ocular fluids were a dialysate. A considerable number of confirmatory analyses by others makes it necessary to accept this as an established fact. With regard to some of the other constituents the position is not so clear, and the majority of investigators have found the quantities of phosphate, sulphate, and organic diffusible substance less in the aqueous than one would expect if a simple equilibrium existed. Robertson cites particularly the case of urea, quoting the work of Walker (1933), (*Jl. Biol. Chem.*, Vol. CI, p. 269), who, "with technique and material far in advance of any hitherto," found that the urea concentration averaged only 68 per cent. of that of the plasma. The subsequent history of this (which Robertson does not note) is extremely interesting as showing how little anyone knows of these questions. Actually the method employed by Walker (an aeration titration method) is not sufficiently accurate for such small quantities of material, a fact indicated by the enormous variation in his results (from 49 to 95 per cent.). The most accurate method known to-day for the estimation of small quantities of this substance in organic mixtures, so far as I am aware, is the conductivity method based on the measurement of the liberation of electrolyte by the hydrolysis of urea, and using this method under my direction, and employing aqueous and serum from the same animal, Benham (*Biochem. J.*, Vol. XXXI, p. 1157), found that the ratio varied from 80.5 to 95.7, with an average of 90 per cent. The first point I wish to make is that at the moment chemistry is not in a position to

estimate accurately minute quantities of organic substances in the complexity of the body-fluids. The passage of four years has changed a variation of 49 to 95 with an average of 68 per cent. to a variation of 80.5 to 95.7 with an average of 90 per cent. What will the next four years bring? I am far from claiming finality from Benham's method.

The second point of importance is that no one knows the exact state or activities of many of these substances in the body-fluids. There is, for example, less sugar in the intra-ocular fluid than in the plasma. In the first place no one is yet quite clear how the sugar behaves in the blood. There is a considerable amount of evidence (so far as I am aware not yet conclusive) that a moiety is "bound" to the proteins of the serum, in which case it could not dialyse into the eye. Such a supposition—if correct—could account for some of the discrepancy, but not for all. In the second place, no one knows what happens to it in the eye. Thus Adler (*Arch. of Ophthalm.*, Vol. VI, p. 901), found that when the optic nerve was sectioned and allowed to atrophy the glucose content of the aqueous humour increased, a finding which suggests that the metabolism of the retina accounted for some. Again such substances as lactic acid (Fischer, *Ergeb. de. Phys.*, Vol. XXXI, p. 533), or hexuronic acid (Müller, *Arch. f. Augenheilk.*, Vol. CVIII, p. 41), are found in considerable quantity in the aqueous of the normal eye, but only in minute quantity in that of the aphakic eye, suggesting that the metabolism of the lens has to be taken into consideration also. Again, in cases of malignant melanoma of the choroid Rados (*Arch. f. Ophthalm.*, Vol. CIX, p. 342), found the amino-acid content of the aqueous humour increased up to ten times. Until our almost non-existent knowledge of these questions has increased out of all bounds it is extremely dangerous to argue about fine differences in minute quantities of substances participating in metabolic activity.

A conclusion that the relatively inert substances which can be accurately estimated are in equilibrium, while those which are subject to metabolic interference and which cannot yet be adequately assessed are not, would not, however, be just and would be merely begging the question. The evidence to-day points, I think, to the conclusion that a membrane exists (other than the capillary walls) capable of maintaining concentration gradients. A considerable body of experimental work which is yet unpublished has led me to think that this membrane may be of extreme physiological and pathological importance.

In 1936 I wrote (*Biochem. Jl.*, Vol. XXX, p. 773): "As a main conclusion, then, it may be taken that the aqueous humour is a dialysate from the blood plasma, showing the ionic distribution characteristic of such a system; superimposed on this simple

system is the phenomenon of selective absorption which manifests itself in concentration gradients to certain molecules, but most probably not of Na^+ , K^+ , and Cl^- ." The paper from which this is quoted is referred to by Robertson; in his critical analysis why are the conclusions of 1927 alone insisted on and the modifications of 1936, necessitated by subsequent and more accurate experiment, ignored? The function of any theory is to correlate all the known facts into a comprehensible system; it is to be unhesitatingly modified to suit new facts; and if it cannot embrace them, it is to be as unhesitatingly discarded.

(4) Robertson concludes that my earliest measurements (1927) of the osmotic pressure of the intra-ocular fluids were open to criticism. I agree. He has, however, omitted to mention that this also has been repeated (Benham, Davson, and Duke-Elder, *Jl. Physiol.*, Vol. LXXXIX, p. 61), by the newer and most accurate method available—the vapour pressure method of A. V. Hill as modified by Baldes (*Jl. Sc. Instr.*, Vol. XI, p. 223). The results of the second method corroborated those of the first.

Incidentally here Robertson (pp. 422-3) says: "From these observations (the isotonicity of the aqueous and plasma) he (Duke-Elder) concluded that a further argument had been brought forward in favour of the theory of dialysis . . . if the deduction is necessarily followed, then gastric juice, pancreatic juice, and hepatic bile are also dialysates, for all these secretions are isotonic with blood plasma." I cannot follow the deduction. My argument is that, if the aqueous humour is osmotically equilibrated with the plasma, it can be a dialysate, if it were not, it could not be. The one fact constitutes no proof in itself; it merely forms one link in a long chain of evidence.

(5) Robertson quotes a series of my experiments on the variation of the intra-ocular pressure with variations in the osmotic equilibrium of the blood, and concludes in general terms that my results demonstrate that the intra-ocular fluids are not a simple dialysate from the blood. With this conclusion I agree, and my agreement is in no way altered by the fact that I did not appreciate the significance of the discrepancies at the time at which the experiments were done and the results published. To a certain extent the conclusions which he deduces are too sweeping, because most of these experiments were done *qualitatively* rather than quantitatively and cannot bear the far-reaching deductions which he draws. Thus in the experiments on exsanguination and replacement of the blood withdrawn by solutions of different osmotic content, the injections were made merely so that the blood pressure remained at its original level without the determination of the quantities of fluid employed, time-relationships, blood volumes, and so on, the idea being merely to determine in which direction (if any) the intra-ocular pressure would move independently of the blood-pressure. Moreover, the pressure was recorded by the mercury manometer which is quite inaccurate for fine measurements. The experiments provided all the information I

required at the time, but in no sense will they bear quantitative criticism. If such be desired they will have to be repeated. Such analysis as they will bear, however, brings out one point of extreme importance, that, in comparison with tissue-fluids, there is a definite time-lag in the reaction of the eye. The importance of this is that it corroborates the chemical evidence of the possibility of the presence of some complicating membrane in the dialysation system.

From this evidence Robertson draws the abrupt conclusion that the aqueous humour is formed by a process of secretion at the ciliary body. But if A is not B, it does not necessarily follow in logic that it is C, nor should it do so in scientific reasoning. In his paper there is no positive experimental proof that it is a secretion, and he does not consider the evidence that it is formed elsewhere in the eye than from the ciliary body. As an alternative I would suggest an hypothesis which experimental work done during the last two years has prompted. It is, of course, quite rash and premature to present such a hypothesis in the meantime, since it depends on work partially completed. It is, therefore, stated with diffidence, and in its final form it will probably be unrecognisable from its presentation at this moment. This, however, is the unfailing interest of all physiological work, that as knowledge grows our views on all bodily processes are continually being changed and amplified to suit new facts which have come to light owing to the application of more elaborate and more exact experimental methods. Moreover, its premature introduction here illustrates that although A is not B, it may perhaps be D.

In my monograph on "The nature of the intra-ocular fluids" (1927), after suggesting that the intra-ocular fluid dialysed from the capillaries into the tissue-spaces of the eye and passed thence into the chambers of the eye, I wrote with due consideration of possible future developments necessitated by more exhaustive research: "it must be remembered that in its course . . . fresh membranes have to be traversed, each involving a new series of stresses with the corresponding adjustments that these entail." Suppose that lining the chambers of the eye there is such a physiological (not an anatomical) membrane, and suppose that this membrane has a selective and uni-directional permeability (a not uncommon thing), all the facts which we have yet been able to examine experimentally have been shown to be explained.

Reasoning from the facts of the intra-ocular pressure in 1927, I stated that such a membrane must exist. Reasoning from the chemistry of the aqueous humour in 1936 I found fresh evidence for it. Working on the physico-chemistry of the pathological intra-ocular fluid we are gathering evidence which seems impossible of denial.

The work of Fischer has already demonstrated that such a uni-directional flow (or irreciprocal permeability) exists in the cornea for water, sodium chloride, and gases. The phenomena depend on relative inhibitory power, electrosmosis, and so on, affecting especially the epithelium and endothelium. No one, so far as I know, considers the cornea a secretory gland. In the present case the rôle of the endothelium is of importance. The presence of such a membrane lining the eye can answer many of the questions raised by Robertson (and others) in criticising the conception of a simple dialysate; it could account for the residual pressure in the excised eye, it could account for the existence of concentration-gradients, it could account for such facts that, while the sugar concentration in the aqueous humour is slightly low, it varies passively with the concentration in the blood, but that the rate of exchange is greater in descending than in ascending hyperglycaemia; it could account for a lag in osmotic equilibrium; and it would explain the irreversible permeability for water, electrolytes, and dyes found by Friedenwald and Pierce (*Bull. Johns Hopkins Hosp.*, Vol. XLIX., p. 259) in the ciliary epithelium. What is much more important and much more interesting, its presence seems necessitated to explain the physical and chemical condition in the eye which we are finding in chronic glaucoma; these changes will be made the subject of subsequent papers. Changes of an opposite nature will, I think, be found to explain the hitherto inexplicable facts of hypotonic conditions. Whether or not it can explain the interesting pressure condition in the eyes of oedematous nephritics, pointed out by Robertson, can only be decided after much more fundamental work has been done on the fluid-traffic of the eye in these states than a few tonometric measurements.

In summary it may be stated that the aqueous humour is not a simple dialysate as I originally hypothesized. On the other hand there is no positive evidence for the theory that it is a secretion of the ciliary epithelium. An hypothesis which I had already adumbrated eighteen months ago is advanced, admittedly on experimental evidence which is yet insufficient for its full development, that, having dialysed from the intra-ocular capillaries and before reaching the chambers of the eye, the fluid passes through a physiological membrane the properties of which maintain a concentration gradient to some molecules, a degree of uni-directional permeability to other molecules, alterations in the properties of which may account for many obscure but important pathological phenomena. As our knowledge stands at the moment I can see little value in further arguments which must be based on insufficient premises: the sensible course is to continue in the search for further and more accurate experimental facts.