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The Factors which Determine the Production of Intraocular Fluid.

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In spite of the very numerous researches which have been made during the last half century on the seat and mechanism of production of intraocular fluid, ophthalmologists and physiologists are still far from an agreement on the subject, and a review of the literature reveals many discrepancies in the experimental evidence which it is impossible to clear away without a re-examination of the whole subject. The following paper contains the results of experiments made with the view of determining the weight to be ascribed to different experimental investigations.

As to the seat of production of the intraocular fluid, nearly all authorities are agreed that it is produced by the ciliary processes. From these processes a minute proportion travels backwards into the vitreous cavity, to be absorbed by the lymphatics of the optic disc, while by far the greater part makes its way between the lens and the ciliary processes, through the fibres of the suspensory ligament, into the posterior chamber, whence it passes round the margin of the iris into the anterior chamber. In addition to this mode of production, it has been suggested by Ehrlich that an appreciable amount of intraocular fluid may be secreted directly into the anterior chamber by the anterior surface of the iris. The experiments of Ehrlich (1) were made by the injection of a diffusible substance, fluorescine, and we agree with Leber (2) in regarding them as proving the possibility of diffusion between the vessels in the iris and the anterior chamber, but not the secretion of a normal intraocular fluid by this channel. At any rate, any fluid formed in this way is negligible when compared with that which is produced in the neighbourhood of the ciliary processes.

On the other hand, the place of absorption of the intraocular fluid is universally agreed to be the angle of the anterior chamber. Here the fluid is passed under pressure into the spaces of Fontana, whence it makes its way into the canal of Schlemm, between the endothelial cells lining this canal, and so is carried away into the venous system. This absorption is continuous, and its rapidity is largely determined by the height of the intraocular pressure. Since we have a constant absorption and a constant pouring out of fluid into the eyeball, it is evident that the intraocular pressure must be

a product of the two factors, formation and absorption, and that the maintenance of the pressure at a constant height must be determined by an accurate balance between these two processes. The problem which lies before us is to determine the mechanism of formation of this fluid.

The intraocular fluid is a clear, colourless solution containing a proportion of salts similar to that of the blood plasma, but having an osmotic pressure which is somewhat higher than the blood plasma, and containing the merest trace of proteids.*

I. *Methods of Research.*

The animals used were mostly cats. In a few cases dogs were employed, and in one experiment a rabbit. In the case of the cats the anæsthetic used was always ether, with the addition in some cases of a small dose of morphia. In a few experiments, after the induction of full anæsthesia, a small dose of curare was given. The administration of the anæsthetic was continued during the experiment by an air-pump connected with a cannula in the trachea. For the dogs the A.C.E. mixture was employed.

A record of the blood pressure was kept in all experiments. In some it was taken continuously, but in the greater number of experiments a short record was taken every few minutes in order to avoid trouble with clotting in the cannula. In the cats the blood pressure was taken in the lower part of the abdominal aorta, in the dog in the femoral artery.

The apparatus we employed for measuring the intraocular pressure was very similar to that described in a former paper (3). A graduated tube with internal bore of about 0·5 mm., and about 50 cm. long, is provided with a lateral tube near each end. One end of the tube is connected by india-rubber tubing, by means of a T-piece, with a reservoir containing Ringer's solution (or any other fluid the absorption of which is to be determined), and also with a manometer. The other end is connected by a second (glass) tube with a gilt steel hollow needle, which is introduced into the anterior chamber of the eye. The needle may be open at the end, or be closed at the end and provided with a lateral opening. To each of the side tubes a rubber capsule is attached. The capsule nearest the reservoir contains air, while that towards the eye is filled with fluid. By means of screw-clamps, fluid or air may be driven from either of the two capsules into the graduated tube. Before introducing the needle into the anterior chamber, the pressure in the apparatus is adjusted by raising the reservoir to about 25 cm. H_2O, which represents the average intraocular pressure. While the fluid is dropping from

* Full details of various analyses of intraocular fluid are given by Leber (2), p. 207, *et seq.*

the end of the needle, this latter is thrust through the lateral part of the cornea, so as to lie in the middle of the anterior chamber. A bubble of air is introduced into the graduated tube by compression of one capsule, and brought to the middle of the tube by relaxing the clamp on the capsule at the end towards the eye. The reservoir is then rapidly adjusted to such a height that the bubble remains stationary.

In some of the later experiments a platino-iridium cannula, with a solid steel point made slightly conical, was found to be an improvement, as, in the event of any leaking occurring, it could be pushed in further.

In introducing the cannula great care must be used, as, should the needle catch in or tear the iris, or wound the lens, the eye would be rendered useless for the purposes of the experiment. The needle, being comparatively large and blunt, requires considerable force for its introduction. We have found it safer to make a small perforation with the point of a cataract knife and, without letting the aqueous humour escape, to introduce the cannula in the hole thus made. Should the exact spot be lost sight of, a little fluorescine will stain it. A fine silk thread passed through the episcleral tissue, as in the operation for advancement of a rectus tendon, gives a better hold than fixation forceps, and is somewhat less in the way.

The fluid employed in the apparatus was usually Ringer's solution, in some cases normal saline. Whichever fluid was employed, it was filtered through a Berkefeld candle before the experiment, in order that no foreign body might be present which could lodge in and block the filtration channels.

The intraocular fluid must play a twofold function in the eye. In the first place, by keeping up the intraocular pressure, it lends rigidity to the supporting structures of the eyeball, and furnishes therefore a fixed point for the intraocular muscles to contract against, besides maintaining the proper distances between the various refractive media. In the second place, it is the only source of nourishment to certain of the structures of the eye, namely, the middle and back part of the cornea, the lens and suspensory ligament, and the vitreous humour. The question that we have to decide is whether this fluid is formed by a process of secretion by the cells covering the ciliary processes, or whether it is a transudation similar to lymph. The question presents many analogies to that with regard to the secretion of urine. In each case we have a possible source of transudation in the capillary blood-vessel network and also an absorbing mechanism. We can only arrive at a conclusion by determining the physiological conditions under which we may alter either the production or the absorption of the intraocular fluid.

II. *The Effect of Changes in the Circulation on the Formation of Intraocular Fluid.*

If the production of intraocular fluid is dependent on a process of filtration through the blood vessels and the epithelium covering the ciliary processes, its rate must vary directly with the difference of pressure on the two sides of the filtering membrane. It must vary, therefore, directly with changes in the capillary blood pressure, and inversely with the changes in the intraocular pressure. In our first series of experiments we sought to eliminate the second factor, namely, that of absorption, by opening the anterior chamber, so that the intraocular pressure could be regarded as zero. A cannula was introduced into the anterior chamber and the fluid allowed to flow off into weighed porcelain capsules. These were changed every 10 or 20 minutes, and the amount of fluid secreted in the time determined by weighing. The fluid drained off during the first minute after insertion of the cannula was regarded as normal intraocular fluid, but the gradual emptying of the eye-ball continues during the first five minutes, so that the figures obtained during this time cannot be regarded as expressing the rate of secretion. In every case the total solids of the intraocular fluid were also determined.

The following experiment, p. 298, shows the results obtained while the blood pressure was approximately constant. It will be seen that there is a constant diminution in the amount of fluid obtained. In these experiments we were at first troubled by the formation in the anterior chamber of clots, which tended to plug the cannula. We found that this difficulty could be obviated by the injection of a dose of leech extract, not large enough to cause a permanent diminution of the blood pressure.*

The next question to determine was whether it was possible to alter the rate of production or the composition of the intraocular fluid by altering the blood pressure in the vessels of the eye-ball. The experiments on this point were all carried out on dogs. A diminution of the intraocular blood pressure was easily effected by ligature or obstruction of the carotid artery on the same side. In order to produce a maximal rise of pressure in the blood-vessels of one eye, the vertebral and subclavian arteries on both sides were tied. A loose ligature was placed round the thoracic aorta, so as to permit of its being obstructed at any given time. A cannula connected to the mercurial manometer was placed in the carotid artery on the right side. The production of intraocular fluid was determined in the left eye. By obstruction of the

* This procedure had been previously employed by Mr. E. Pflüger in some experiments carried out in this laboratory in 1902. An account of these experiments will shortly appear as a dissertation in the University of Bern.

aorta a large rise of blood pressure was produced in this eye, since all the blood had to pass through the one carotid artery in order to get back to the heart. On the other hand, an almost complete anæmia could be produced in the eye by obstruction of the one remaining carotid. We give below the results of one such experiment.

Cat, anæsthetised with Ether and the A.C.E. Mixture. A small dose of Curare was injected after anæsthesia was complete. The extract of 2 grammes of dried leech heads was injected.

Time.	B.P. in mm. Hg.	Weight of secretion.	Weight of solids after drying to a constant weight.	Percentage of solids.	Rate of flow per minute.
		grammes.	grammes.		grammes.
3.50 cannula inserted.					
3.51	130	0·689	0·009	1·3	
3.56	145	0·252	0·007	2·7	0·05
4.16	120	0·756	0·032	4·2	0·037
4.36	100	0·475	0·021	4·4	0·023
4.56	96	0·482	0·024	4·9	0·024

Dog. Weight, 7½ kilos. Anæsthetised with the A.C.E. mixture and morphia The extract of 2 grammes of dried leech heads was injected. Both subclavians and vertebrals were tied. Temporary ligature round aorta. Cannula in left eye. B.P. observed in right carotid.

Time.	B.P. in mm. Hg.	Amount of secretion in grammes.	Total solids in grammes.	Percentage of solids.	Rate of flow.	Remarks.
3·29	—	—	—	—	—	Cannula inserted. Aorta unobstructed
3·30	110	0·811	0·013	1·5	—	
3·35	110	0·432	0·014	3·2	0·086	
3·45	100	0·550	0·027	4·9	0·055	
3·55	205	1·153	0·068	5·9	0·115	Aorta obstructed. Fluid tinged red.
4·5	100	0·627	0·039	6·2	0·062	Aorta unobstructed.
4·15	198	0·816	0·053	6·6	0·081	Aorta obstructed.

It will be seen that in every case a rise of intraocular pressure caused an increase in the amount of fluid secreted. It is impossible, however, to deduce directly from these experiments that the intraocular fluid is a transudation. The opening of the eye-ball and the consequent diminution of the intraocular pressure to nothing have a serious effect on all the intraocular structures.

Great dilatation of the vessels of the ciliary processes and iris is produced. The fluid, which, in the normal eye, is free from fibrinogen and contains the merest trace of proteid, rapidly acquires the power of coagulation, and its proteid content rises to 3, 4, or 5 per cent. The serious alteration of the vascular structures is shown in many cases by the appearance of red blood corpuscles in the fluid dropping from the cannula, and Greeff has shown that if the lowered pressure be brought about suddenly and maintained for some time, the epithelium covering the ciliary processes may be raised from the surrounding tissue so as to form small blisters, which are filled with coagulable lymph. It has been suggested by Greeff (4) that the change in composition of the intraocular fluid ensuing on opening the eye-ball is determined by the separation of the epithelium, but Bauer (5) has shown that the proteid contents may be raised in the absence of these epithelial changes, and that, on the other hand, the epithelial changes may be well marked on the subsequent day, when the wound in the cornea has closed, and the intraocular fluid has regained its normal composition. He also points out that the amount of change produced depends entirely on the rapidity with which the intraocular pressure is lowered. The change in composition is probably due, as Leber suggests, to the great distension of the capillaries and the consequent separation of their endothelial cells. It represents in fact an alteration in permeability of the filtering membrane.

III. *Amount of Intraocular Fluid Produced under Normal Circumstances.*

In any investigation of the factors determining the production and absorption of intraocular fluid, it is important to get some idea of the amount of this fluid secreted under normal circumstances, that is at normal intraocular pressure. Since the intraocular pressure is maintained constant so long as the blood pressure is steady, the amount of fluid produced at a given intraocular pressure must be equal to the amount of fluid absorbed at the same pressure. It is therefore a matter of indifference whether we measure the amount formed or the amount absorbed at any given pressure. Le Plat (6) sought to abolish the absorption of the intraocular fluid by filling the anterior chamber with oil or vaseline. A cannula was placed in the vitreous cavity, and the pressure in the cannula maintained at the normal intraocular pressure. It was found that the obstruction of the absorbing angle of the eye-ball carried out in this way caused a rise of intraocular pressure if the eye-ball were closed, or a flow outwards of intraocular fluid by the cannula if the pressure in this was maintained at the normal intraocular pressure. The amount of this outflow was measured, and was regarded by Le Plat as representing the normal rate of formation of intraocular fluid. He arrived at

the conclusion that the amount of fluid normally secreted by the ciliary processes is in the rabbit about 4 c.mm. per minute. We found considerable difficulties in applying this method, chiefly determined by the tendency of the cannula in the vitreous to become blocked. We therefore adopted a method similar to that already employed by Niesnamoff, (7) under Leber's direction. The arrangement of the experiment was as follows:—

The hollow needle, connected by the capillary tube (containing an air bubble as index) to the reservoir and manometer, was introduced into the anterior chamber. The height of the reservoir was then adjusted until the bubble was stationary, showing that the intraocular pressure was exactly balanced by the pressure of the fluid in the tube leading to the reservoir. This intraocular pressure was of course maintained by a constant secretion of intraocular fluid, exactly equal to the amount escaping by filtration through the anterior angle of the eye. The animal was then killed by dividing the heart. This procedure at once stopped the production of intraocular fluid. The intraocular pressure, however, was maintained at its previous height by the connection of the eye with the reservoir of Ringer's fluid; the escape of fluid by the anterior angle was therefore the same as before. The rate of this escape could be determined by noting the rapidity with which the air bubble moved along the capillary tube towards the eye, and this rate must be equal to the rate of *production* of fluid previously obtaining in the eye under normal conditions of circulation. The following table gives the rate of production of intraocular fluid, determined in this way, with varying intraocular pressures:—

Animal.	Intraocular pressure in mm. Hg.	Inflow, after cessation of circulation, in cubic millimetres per minute.
Cat.....	20	12
Cat.....	15	11
Cat.....	26	12
Cat.....	28	10
Cat.....	14	5
Cat.....	20	15
Average.....	20·5	10·8

It will be seen that there is a considerable difference in the case of filtration in various eyes, and therefore a corresponding difference in rate of production of intraocular fluid.

IV. *The Factors Determining Absorption of Intraocular Fluid.*

In the last set of experiments we determined the rate of absorption of intraocular fluid at the normal intraocular pressure, and regarded this as representing the rate of production of this fluid under normal circumstances. In the same experiment it was possible to alter the intraocular pressure by raising or lowering the reservoir, and so to determine the effect of the height of the intraocular pressure on the rate of absorption. The results of two such experiments are given below, and show conclusively that the rate of absorption is determined, in the absence of disturbing factors which we shall have to consider later on, solely by the height of intraocular pressure.

(1) Cat, anæsthetised with Ether. While the anæsthesia was maintained, a small dose of morphia and curare was injected. Atropine was instilled locally into the conjunctival sac.

B.P. in mm. Hg.	I.O.P. in mm. Hg.	Rate of inflow in cubic millimetres per minute.
115	22	0
115	30	4
115	46	7
130	62	8
	Heart divided.	
0	22	12
0	36	16
0	46	19
0	62	22

(2) Cat, anæsthetised with Ether. Atropine and cocaine instilled locally into the conjunctival sac.

B.P. in mm. Hg.	I.O.P. in mm. Hg.	Rate of inflow in cubic millimetres per minute.
124	32	0
124	44	5
124	52	11
110	20	0
116	44	10
116	52	20
	Heart divided.	
0	52	22
0	44	15
0	20	12

In a previous paper we have shown that the intraocular pressure varies directly as the blood pressure in the vessels of the eyeball. We must therefore conclude that the rate of absorption of intraocular fluid is also determined by the height of the blood pressure, and since the absorption must keep pace exactly with the formation of this fluid, it follows that the formation of the intraocular fluid must also be determined by the height of the intraocular blood pressure. So far then the conditions which we laid down as necessary to be fulfilled in order to justify the filtration theory of the production of intraocular fluid have been fulfilled, and we might conclude with Leber that the formation of this fluid is exactly analogous to that of lymph, and is determined by the difference of pressure between the blood in the vessels and the fluid outside the vessels. There are, however, certain difficulties in this assumption which have so far not been considered by previous workers, but which must be met satisfactorily before we can come to any definite conclusion on the subject.

It has hitherto been assumed by Leber, Niesnamoff, and others, that a fluid having the composition of intraocular fluid might be formed by a process of filtration through the blood vessels of the ciliary processes under any difference of pressure. In this assumption they have neglected the question of the different proteid content of blood plasma and intraocular fluid. It was shown by one of us (E. H. S.) that, in order to separate a proteid-free transudate from a fluid such as blood serum, a certain amount of work had to be done, and that for this separation a minimum difference of pressure on the two sides of the filtering membrane of at least 28 mm. Hg was necessary. The intraocular fluid has such a small content in proteid that it may be regarded as analogous in all respects to the fluid which is supposed to be separated by the glomeruli of the kidney. In order therefore that any fluid shall be poured out in the eyeball, a minimum difference of 30 mm. Hg must be present between intraocular pressure and capillary blood pressure. If this pressure difference is not present, work must be done by the cells forming the filtering membrane, and the formation of intraocular fluid must be regarded in the light of a secretion rather than in that of a transudation. A definite decision on this point could be reached if we had any means of determining the blood pressure in the capillaries of the eyeball. A method for this purpose has been devised by Niesnamoff, (7) and this observer states that the normal intraocular capillary pressure is about 50 mm. of mercury. His arguments, however, involve several fallacies. In his experiments he connected a cannula, attached to a reservoir of salt solution, with the eyeball of a living animal. He found that the fluid neither ran in nor out at 25 mm. Hg, which was therefore the intraocular pressure. He then

determined the rate of inflow when the pressure in his cannula was raised to 50 mm., 75 mm., and 100 mm. Hg. He then killed the animal, and again determined the rate at which the fluid would flow in under these various pressures. He found that above 50 mm. Hg the rate of inflow was the same in the dead as in the living animal. He therefore concluded that 50 mm. Hg represented the intracapillary pressure. In coming to this conclusion he was guided by the assumption that, when the intraocular pressure was raised so as to be equal to the intracapillary pressure, the transudation of intraocular fluid would cease, and above this pressure the rate of inflow for his reservoir would be, therefore, the same in the living and dead eye. It is impossible, however, by this method to determine intracapillary pressure. The globe of the eyeball is practically rigid. As the intraocular pressure is raised, the intraocular fluid will press upon the veins of the ciliary processes, and the blood pressure will therefore rise in the capillaries and in the veins until it is greater than the intraocular pressure. With successive rises in the intraocular pressure the pressure in capillaries and veins must get larger and larger in order that any circulation of blood may be maintained, and the circulation through the capillaries will cease only when the intraocular pressure is very nearly as high as the arterial pressure. If the circulation in Niesnamoff's experiments ceased at 50 mm. Hg, it is evident that the normal intracapillary pressure, when the intraocular pressure is 25 mm. Hg, must be considerably below 50 mm. Hg. How then are we to explain the very definite figures obtained by Niesnamoff? This observer apparently performed very few experiments. In his paper he gives the results of only one such experiment as that here described. On repeating his experiments we found it impossible to obtain anything like such definite figures—and this for various reasons. In the first place, a considerable rise of intraocular pressure, such as to 50 or 70 mm. Hg, exercises an abnormal stretching effect upon the filtering apparatus of the eyeball, so that the channels at the anterior angle of the eye are gradually opened up, and in many experiments we observed a consequent gradual increase in the rate of inflow of the fluid. In most experiments, for example, the rate of inflow was greater with descending pressures than with ascending pressures. This is well shown in experiment No. 2, on p. 301.

The following experiment shows the dilatation consequent on a preliminary raising of the intraocular pressure:—

Cat, anæsthetised with Ether. Eserine applied locally to conjunctival sac. Pupil moderately contracted.

B.P. in mm. Hg.	I.O.P. in mm. Hg.	Rate of absorption in cubic millimetres per minute.
110	16	0
110	32	5
110	48	8
108	64	9
112	16	0
112	32	8
112	48	13
112	64	18

Another disturbing factor is the size of the pupil. We shall have to consider this factor more in detail later on, but unless atropin be given at the beginning of the experiment, the observations on the living eye are made with a somewhat contracted pupil, whereas those on the dead eye are made on a widely dilated pupil. Other factors being equal, the filtration in the eye with dilated pupil is always slower than in the eye with contracted pupil. In certain of our experiments we observed an equality of inflow between the dead and living eye at some pressure above 40 mm. of mercury, but on further raising the pressure this equality disappeared, showing that we were dealing with yielding tissues and altering membranes. This fact rendered it impossible to obtain by such methods any definite information of the intracapillary pressure in the eye-ball, or of the level of intraocular pressure at which transudation or formation of intraocular fluid would definitely cease. One other factor which would aid in disturbing the results obtained is the effect of a high intraocular pressure on the general circulation through the eye-ball. If we succeed in raising the pressure to such a height that the circulation is entirely abolished, changes must rapidly take place in the apparatus both for formation and absorption of intraocular fluid, and subsequent results cannot be compared with those obtained before such a cessation of circulation. The raising of the intraocular pressure in itself may act as a stimulus and cause reflexly alterations in blood flow, in the general blood pressure, or in the state of contraction of the pupil. The co-operation of these various factors suffices to explain the varying results obtained in the very many experiments we performed upon this subject, including those of which we have already given details. We are of opinion, therefore, that the results obtained by Niesnamoff must be regarded as accidental, and that a greater number of experiments would have convinced this observer of the fallacies of his method.

Although it is impossible at present to determine the intracapillary pressure in the ciliary processes, we may at any rate inquire whether there is, in all experiments on the subject, the possibility of a difference of pressure of 30 mm. Hg between intracapillary blood pressure and intraocular pressure. In the case of a similar question in the kidney, we have been accustomed to compare the aortic blood pressure with the ureter pressure, and have regarded a difference of 40 mm. between these two pressures as satisfying the necessary conditions for filtration through the glomeruli. A similar comparison of arterial blood pressure and intraocular pressure leads to the same result. Below we give the intraocular pressure and arterial pressure as determined in a series of 20 experiments. It will be seen that in every case there is a difference between the two pressures of at least 48 mm. Hg, the average difference of pressure in all the experiments being 84·8 mm. Hg.

Animal.	B.P. in mm. Hg.	I.O.P. in mm. Hg.	B.P. – I.O.P.
Cat.....	130	16	114
Cat.....	140	25	115
Cat.....	138	20	118
Cat.....	94	24	70
Rabbit	74	16	58
Dog	112	14	98
Cat.....	104	15	89
Cat.....	106	19	87
Cat.....	106	18	88
Cat.....	120	20	100
Cat.....	150	22	128
Dog	84	12	72
Dog	58	10	48
Dog	70	16	54
Cat.....	115	23	92
Cat.....	124	32	92
Cat.....	110	16	94
Cat.....	138	22	116
Cat.....	94	27	67
Cat.....	110	24	96

So far then our observations tend to support in every particular the view laid down by Leber, namely, that intraocular fluid is produced in the ciliary processes by a process of filtration, and that the sole factor determining the amount of transuded fluid is the difference of pressure between the blood in the capillaries and the fluid in the eye-ball.

V. *Influence of the Proteid Content of the Intraocular Fluid on the Intraocular Pressure.*

The fact that the intraocular fluid has to be filtered through the intercellular channels of the endothelium bounding the spaces of Fontana and lining the

canal of Schlemm, in order to escape from the eyeball, suggests that the resistance will be greater if the viscosity of the filtering fluid be increased in consequence of raised proteid content. Indeed, one form of raised intraocular pressure, the glaucoma accompanying inflammation of the ciliary region, has been ascribed to the greater proteid content of the intraocular fluid secreted by the inflamed vessels, and the consequent greater resistance to the filtration of this fluid through the anterior angle of the eye. So far as we are aware, there are no direct determinations of the relative rates of filtration of normal salt solutions with and without proteid. We have, therefore, in a series of animals, determined the intraocular pressure under the two conditions:—

(*a*) With normal intraocular fluid.

(*b*) After replacing this fluid by blood serum.

We have also compared the relative rates of filtration of normal salt solution and of serum in the living and dead eye.

In our experiments one eye of the animal was connected with a reservoir and manometer containing Ringer's saline fluid, while the other was connected with a similar apparatus filled with filtered blood serum.

In order to determine the intraocular pressure in an eye, in which the normal aqueous humour had been replaced by serum, after introduction of the hollow needle, the aqueous was allowed to escape through the side opening in the cannula. Serum was then allowed to flow in for a time, and then the contents of the anterior chamber again allowed to escape. The side tube was then closed, an air bubble introduced into the capillary tube, and the pressure determined at which the bubble moved neither backwards nor forwards.

In nearly every experiment the intraocular pressure, during the first 5 or 10 minutes after the insertion of the cannula, was higher in the eye filled with serum than in the eye filled with normal fluid. The difference, however, rapidly diminished, so that 15 to 20 minutes after the beginning of the observation the pressures were practically identical in the two eyes, and remained so throughout the rest of the experiment. It must be remembered that with the zero method used by us there is no movement of fluid into the eye. Hence the fluid necessary to replace the loss by filtration and to maintain the intraocular pressure is being constantly secreted by the ciliary processes, and is probably of the normal composition, *i.e.*, practically free from proteid. We should therefore expect a gradual decline of the intraocular pressure in the eye with serum, although hardly so rapid an equalisation of the pressures on the two sides as we actually observed in our experiments.

After the determination of the intraocular pressure, the animal was killed by opening its heart, and the inflow of serum and saline fluid respectively observed, first under the normal intraocular pressure, and then under raised pressures.

The results of two such experiments are given below. It will be seen that there is a marked difference in the rate of filtration of the two fluids, that of serum being, as one might predict, very much slower than that of saline.*

Experiment 1.—Dog, A.C.E. Morphia. Curare. Vagi cut.

Time.	Blood pressure.	Intraocular pressure.	
		Salt eye.	Serum eye.
4.15	70 mm. Hg.	26·2	29·4 cm. water.
4.20	70 ,,	24·2	27 ,,
4.45	100 ,,	29·2	29 ,,
Animal killed	by opening heart.		

Pressure.	Inflow per minute in cubic millimetres (after 10 minutes).	
	Salt.	Serum.
29 cm.	11·5	6
—	11·5	6
—	11·5	6

Experiment 2.—Cat. Ether, morphia, curare.

Time.	Blood pressure.	Intraocular pressure.	
		Salt.	Serum.
3.0 P.M.	120	14·8	15·1
3.10	116	10·8	12·5
3.20	110	9·2	11·5
Animal killed.			

* Although serum filters more slowly than normal intraocular fluid or saline, the difference is not sufficiently great to cause any marked variation in the intraocular pressures on the two sides. One cannot, therefore, in view of these observations, ascribe any large part in the production of any form of glaucoma to possible differences in the composition of the aqueous humour which might be determined by inflammatory conditions of the blood vessels.

Inflow three minutes later at same intraocular pressures—

Salt.	Serum.
6	3
5	3·5
5	6
5	4
4	4

Fifteen minutes later—

3·5	1·5
3·0	1·5
3·5	1·5
etc.	etc.

This difference in the rate of filtration of the two fluids becomes greater the higher the intraocular pressure is raised.

VI. *The Effect of the Size of the Pupil on the Absorption of Intraocular Fluid.*

In the experiments we made to decide this point, one eye of the animal under observation was treated with eserine and the other with atropine. The instillation of these drugs should be begun before the induction of anæsthesia, as the action of eserine is very uncertain if only instilled after anæsthesia.

We have found, as a result of these experiments, that the intraocular pressure in the two eyes remains the same during the time of observation, but that, if the pressure in the apparatus be raised, the rate of filtration in the eye under eserine is much greater than in that under atropine.

It is difficult to give a precise explanation as to the cause of this difference. Stretching of the filtration spaces at the angle of the anterior chamber may possibly account for it all. If this, however, is the case, we should expect to find the intraocular pressure at a lower level in the eye with the contracted pupil, for the intraocular pressure must of course be the product of the rate of secretion and the rate of absorption of the intraocular fluid. The same objection applies to the explanation of this phenomenon by Grönholm (9), who states that in his opinion it is due to diminished intraocular secretion as a result of the contraction of the intraocular vessels. It may also be possible that at these raised pressures other channels of filtration are opened up—such for instance as the surface of the iris. An important, perhaps the most important, factor, however, must be the crushing of the dilated flaccid iris

into the filtration angle of the eye, thus causing a mechanical obstruction, which will be more marked the greater the intraocular pressure. Hence the smaller amount of filtration in the atropinised or dead eye with dilated pupil, as compared with that in the eye which has been put under the influence of eserine.

The figures of a typical experiment are given.

Cat, anæsthetised with Ether. Blood pressure average 138 mm. Hg, with only trifling variations throughout the experiment.

Intraocular pressure in mm. Hg.	Rate of filtration in eserine eye in cubic millimetres per minute.	Rate of filtration in atropine eye in cubic millimetres per minute.	Rate of filtration in atropine eye *post-mortem*, in cubic millimetres per minute.
20	0	0	15
35	11	8	20
50	16	11	25
65	23	14	31

Summary of Conclusions.

1. The intraocular pressure represents the pressure at which the rate of formation of intraocular fluid is exactly balanced by its rate of escape through the filtration angle of the eye.

2. The production of intraocular fluid is strictly proportional to the difference of pressure between the blood in the capillaries of the eyeball and the intraocular fluid.

3. No satisfactory method of measuring the intracapillary pressure in the eyeball has been yet devised. The fallacies of Niesnamoff's method are pointed out. Judging, however, from a comparison of the arterial pressures and the intraocular pressures in a large number of animals under different conditions, there is probably always a difference between the intracapillary pressure and intraocular pressure, which is sufficient to account for the production of the intraocular fluid, without assuming any active intervention on the part of the cells of the capillary walls or of the ciliary processes.

4. An increased proteid content of intraocular fluid slows its rate of absorption in consequence of the mechanical hindrance of the proteid to filtration.

5. Filtration, *i.e.*, the absorption of intraocular fluids, at high intraocular pressures is favoured by constriction of the pupil and hindered by dilatation of the pupil. The difference, however, is barely perceptible with normal or low intraocular pressures.

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