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COMMUNICATIONS

SOME PHYSICO-CHEMICAL FACTORS INFLUENCING
THE INTRAOCULAR PRESSURE. EXPERIMENTS
ON THE "PERFUSED" EYE

BY

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IN a previous paper by one of us (1927) it was pointed out that the intraocular pressure is normally kept at a point of equilibrium as a result of the balancing of the hydrostatic pressure in the capillaries of the eye by the difference in osmotic pressure between the aqueous humour and the capillary plasma. It was also pointed out that variations in the intraocular pressure could be brought about in the following ways:

- A. By altering the equilibrium level.
 - 1. By raising or lowering the blood pressure in the capillaries.
 - 2. By varying the difference between the osmotic pressure of the capillary plasma and the aqueous humour.
- B. By varying the volume of the contents of the eye, a change which is readily transferred into an effective pressure variation by virtue of the small degree of distension of which the sclerotic is capable.
 - 1. By varying the state of the dilatation of the capillaries in the eye.
 - 2. By varying the quantity of the aqueous humour.
 - 3. By varying the volume of the vitreous and lens.

It will be seen that, apart from the factor of mechanical pressure on the globe of the eye, these considerations resolve themselves into two categories: (1) variations in the blood pressure, and (2) disturbances of the physico-chemical equilibrium in the plasma or in the ocular media. It is to elucidate further the effect of influences belonging to the latter category that the investigations detailed in this paper have been undertaken.

For the purposes of the present paper these physico-chemical influences will be dealt with only so far as they fall into the three following groups: firstly, changes in the osmotic concentration of the crystalloids of the plasma; secondly, changes in the osmotic concentration of the colloids of the plasma; and thirdly, changes in the volume of the vitreous and lens in so far as they are influenced by the hydrogen ion concentration of the plasma. Each of them has received attention already.

The effects of changes in the osmotic concentration of the crystalloids of the blood on the intraocular pressure were first experimentally investigated by Hertel (1914), and formed the subject of a series of experimental researches by one of us (1926) wherein the mechanism of the change was studied in detail and the appropriate literature was referred to. It was shown that when the osmotic concentration of the crystalloids was raised, as by the injection of concentrated saline, the intraocular pressure fell quite independently of the blood pressure. Further, it was shown that when the osmotic concentration of the crystalloids was decreased, as by the injection of hypotonic saline, the intraocular pressure rose—again quite independently of the blood pressure. That this pressure-variation depends largely upon the change in the quantity of the intraocular fluids was demonstrated by finding a difference in water-content in one eye before the experimental manipulations were commenced and in the other eye (of the same animal) after the experiment was completed. It was suggested that the main factor in determining these changes was the dehydration, or water-logging, respectively, of the eye, a process which accompanies all osmotic changes in the plasma of this nature, and which is necessitated in all the organs of the body, by simple physical laws. The length of time, however, over which the pressure-change extends, seems to point to the probability that this comparatively simple mechanism is complicated by more complex physico-chemical changes in the vitreous, the turgescence of which can be varied by alterations in the nature and concentration of the salts in the fluid bathing it.

The factor of the influence of the concentration of colloids in the plasma upon the intraocular pressure has been made the subject of special research by Dieter (1925) and one of us (1927). It can be shown that if the concentration of colloids is increased, the intra-

ocular pressure falls. We have seen that one of the factors maintaining the intraocular pressure at its normal equilibrium is the difference between the osmotic pressure of the plasma and that of the aqueous humour; and, since the capillary walls are freely permeable to crystalloids so that they rapidly equalize their concentrations in the plasma and the eye, any permanent difference between the osmotic pressure of the aqueous and the blood must depend on the relative colloid content of the two fluids. If the concentration of colloids in the blood is increased, this relative difference is correspondingly augmented, and the intraocular pressure, the level of which is determined by the capillary pressure less this difference, therefore falls. Conversely, if the concentration of colloids in the plasma is decreased, the intraocular pressure rises to approach more nearly the hydrostatic level in the capillaries.

With regard to the third question—the concentration of hydrogen ions in the blood—very much less unequivocal experimental work has been done. Experimenting on the eye *in vitro*, Fischer (1908-10) found that on immersing it in acids, pressures of a very considerable magnitude were generated; but the results of his work, as he interpreted them, must be accepted with reserve, since, in the first place, the concentrations of acid which he used were far above any that could occur within the limits of variation compatible with life, and, in the second place, he omitted to take into consideration the swelling of the sclerotic which occurs simultaneously. von Fürth and Hanke (1913), von Ruben (1914), and, at a considerably later date, Nakamura (1925) and Heesch (1926) repeated his work, and suggested that this swelling of the sclerotic, with the diminution in volume of the eye which it entailed, was sufficient to account for the changes which Fischer had found. In confirmation of this, Mawas and Vincent (1926) found clinically that glaucomatous patients showed an increased acidity, an observation which was confirmed by Kubik (1928). Baurmann (1924), on the other hand, experimenting on the vitreous *in vitro*, concluded that its volume decreased in hydrogen ion concentrations less than normal and increased in conditions of alkalosis. Similarly, Meesmann (1924) obtained a diminution of pressure on injecting the eye with isotonic solutions of a low pH, and an increased pressure on using solutions of high alkalinity. He verified those results by clinical observations on glaucomatous patients, and he was confirmed in his opinion by Gala (1925), who also found the ocular media alkaline in these subjects. In contra-distinction to these, Oguchi (1924) found an increase of pressure on injecting both acid and alkaline solutions into the eye, and Dominguez (1926) arrived at the same conclusion in the enucleated eye. At the same time a very large number of observers have investigated the reaction of the blood or of the intraocular fluids in glaucomatous patients, and on comparing them

with the normal, have found little or no difference: Hertel (1921), Schmelzer (1927), Seidel (1927), Kubik (1927), Jasinski (1927), Gala and Melka (1928), and Schmerl (1928); while Schmelzer (1927), and Wegner and Endres (1928), after raising the pH of the blood by over-ventilation of the lungs and by the exhibition of large quantities of sodium bicarbonate, failed to find any alteration in the pressure of the eye. Finally, Nakamura (1926) has injected animals with solutions of varying pH and recorded the changes in the intraocular pressure. He found a fall of pressure with acid solutions and no observable alteration with alkalis, but he concluded that the former change was accounted for by the accompanying derangement of the osmotic concentration of the plasma which followed upon the injection of the solutions which he used. At the same time, the disorganisation of the essential functions of the experimental animals by the change of the pH of the body fluids which he brought about, produced quite abnormal conditions and frequently resulted in their death.

This last is an extremely important point. On the attempt to change the physico-chemical equilibrium, the whole vital mechanism of the animal strives to counteract the extraneous influences and to maintain the normal level. A very small change, for example, in the pH of the blood at once upsets the circulatory centres and the respiratory centres, and a change of any magnitude very rapidly results in death; it is obvious that in these circumstances the recording of changes in any detail which may be brought about by the experimental variant, will tend to be completely masked and obscured by the general metabolic upset. With these considerations in mind it was determined to isolate the eye completely from the influence of the vital centres by maintaining its circulation by means of an artificial heart and an artificial lung, so that the effects of physico-chemical changes in the blood could be studied without the intervention of unnecessary disturbances.

The principles of the technique employed can be gathered from the accompanying diagram (Fig. 1.) Throughout all the experiments dogs were employed. A dog was anaesthetized by chloroform and ether, and artificial respiration was maintained from the commencement of the experiment through a tracheal tube simultaneously feeding with anaesthetic. An artery was then opened and the dog was slowly bled, the blood being immediately whipped and maintained at constant body temperature in a thermostat. The dog was then killed, and a second animal similarly anaesthetized. In this animal the femoral artery of one leg was opened and the femoral vein of the other, and the animal was bled and simultaneously transfused with the whipped blood of the other; this was continued until the blood of the two animals had been thoroughly

whipped and retransfused, care being taken in the meantime that the general condition of the second dog was maintained. A quantity of this blood was then placed in the vessel (a) where it was maintained at a constant temperature by a thermostat jacket, and

FIG. 1.

The apparatus employed for perfusion of the eye. For explanation see text.

was kept oxygenated by a slow stream of a mixture of 95 per cent. oxygen and 5 per cent. carbon dioxide, fed through the tube (*om*) from the gas cylinder (*c*). Meantime, with the animal in the position *D'*, the right carotid artery was opened and a cannula (*A'*) was inserted into it, while the circulation through the head was maintained by way of the left carotid and the vertebral arteries. This cannula was connected by tubing (*PC*) to the pump which formed the artificial heart.

The pump, which was modelled on the perfusion pump of Dale and Schuster (1928), consisted essentially of a rubber valve enclosed within a glass dome (V). This was controlled by a crank-shaft (X) driven by a pulley (Y), connection being made by a connecting rod and rocking lever. The stroke of the lever had a sleeve-adjustment controlled by a screw (Z) so arranged that in the most forward position of the screw no motion was imparted to the pump rod, but when it was screwed back, the arms of the lever became of approximately equal length and a stroke of about $5/8$ in. was given to the pump rod. In intermediate positions the stroke could be varied with great delicacy. The pump rod controlled a rubber diaphragm (I), the chamber above which, as well as the interior of the valve, was filled with water. The glass dome outside the valve was filled with blood (or other perfusion fluid). When the diaphragm rose, water was forced into the valve, which expanded and drove blood out of the glass dome; when the diaphragm fell the reverse process occurred, and blood was sucked into the dome. In order to provide for the passage of the blood in the required direction, two tubes were blown into the sides of the dome, one connected to a one-way inlet valve (U) and the other to a one-way outlet valve (T). Each of these worked in a valve-chamber provided with exit-tubes to allow the air to escape when filling the apparatus, and each was connected with a coil of glass tubing (S.R.) The whole was contained in a tank filled with water, and this, like the containing vessels (*a* and *b*), was kept at constant body temperature. The temperature regulation was maintained by long electric glow-lamps housed in brass tubing running across the tank and soldered into its sides, the heat adjustment being controlled by a thermostat (W) working a magnetic relay.

When the pump was in action blood was sucked up from either of the reservoirs (*a*) or (*b*), as desired, by the tubes *kg* and *lg*, into the heating coil S, where its temperature was again adjusted, into the pump-chamber (V), and was driven out through the second heating coil (R) and the outlet tube (*h*). From *h* a side-tube (E) led off to a mercury manometer (F) which recorded a tracing of the blood-pressure on the kymograph (N). The tube was continued on to C, where it was made to divide into two branches (A and B).

At the start of the experiment, whipped blood, normally oxygenated and kept at constant temperature, was placed in the reservoir (*a*), and drawn up through the pump until it presented at the tube C. One outlet tube (B) was then shut off by a valve (*n*), and the blood flowed through C, to the end of which a rubber tube (P) led into the cannula inserted into the right carotid. The head of the animal was thus perfused artificially through this artery, while at the same time the normal circulation took place through the left carotid. Meantime, blood was withdrawn from the femoral

artery to prevent any over-engorgement, and the pump was adjusted so that the rate and excursion of the artificial " heart-beat " and the height of the blood-pressure as seen on the kymograph tracing coincided with the normal.

Once the artificial circulation was thus started, the left carotid was clamped, and a second cannula (B) was inserted into it : at this moment the whole of the circulation of the head was undertaken artificially without at any time having suffered a cessation. The head of the dog was then rapidly cut off and clamped in the position D. The cannula B was then connected to the tube B and the valve *n* was opened, so that the circulation proceeded directly through the left carotid. The valve *m* was then closed, the tube P disconnected, and the cannula A connected directly to the tube A. The valve *m* was now opened, and the isolated head was thus perfused equally through both carotid arteries directly from the tube C without any hiatus in the circulation having taken place. In this position the head was kept warm by a powerful lamp (L), the temperature being adjusted by means of a thermometer thrust into the dog's mouth.

Immediately the head was in position the obvious bleeding points were ligated and the vertebral arteries were occluded by stout wiring. This prevented any short-circuiting of blood, and ensured that it was forced through the capillary circulation. Returning in this manner through the veins, the blood was caught by a funnel (*p*) placed underneath the head and fell by gravity into either of the two reservoirs *a* or *b* through the tubes *e* or *f* which were fed by a two-way tap. The blood fell upon a rotating disc (*d*) kept spinning round at a rapid rate by a pulley and was thus thrown out centrifugally as a fine stream to the sides of the reservoir. In this way, trickling down the sides of the reservoir, it became aerated, the efficiency of which process was further increased by constantly bubbling through the blood as it lay in the reservoir a stream of oxygen-carbon dioxide from the gas cylinder *c*, through the tubes *om* and *on*.

A complete circulation was thus maintained indefinitely through the head providing in its circuit an artificial heart and an artificial lung. Moreover, no matter what changes are made in the perfusing blood, the respiration and the rate and output of the heart could either be kept constant or varied at will. The whole of the substitution was made without stopping the blood-flow at any time, and the circulation in the eye itself could be verified by ophthalmoscopic examination of the fundus, or by recording the pulse beat communicated to the intraocular pressure. Indeed, the experimental conditions were found to remain so nearly normal that a winking reflex could be easily elicited if the cornea of the decapitated dog was touched for a moment. In this way normal

blood could be put in one reservoir (a), and altered blood, either with its osmotic concentration or its pH changed, could be put into the second reservoir (b), the circulation could be switched over from one to the other without any hiatus, and the effects examined in the isolated eye.

A mercury manometer was used for recording the changes in intraocular pressure, since in this series of experiments only slow and gradual changes were to be expected. A modification of the type employed by one of us in previous work (1925, etc.) was employed, consisting essentially of a graduated capillary tube (J) connecting a cannula (G) and a mercury manometer (M). Between the cannula and the capillary tube was connected a reservoir of Ringer's solution (H), and between the capillary tube and the manometer itself, a syringe (K), the piston of which was controlled by a very fine screw. In the capillary tube was an air-bubble. The reservoir (H) was raised until the pressure in the system had attained the level of the normal intraocular pressure (about 25 mm. Hg), as recorded by the writing point on the kymograph drum (N). While in this position the small tap opening into the cannula was opened, and the solution was allowed to escape from the point of the cannula under this pressure. This was then immediately inserted through the cornea in such a way that it lay across the anterior chamber without touching the iris or lens, the reservoir H was shut off, and the pressure in the system was adjusted by means of the syringe so that the air bubble in the capillary tube remained constant. In this way the pressure of the eye was recorded without losing any aqueous and without disturbing its equilibrium more than was necessary; and, provided the air bubble was kept constantly at rest, the variations of this pressure were exactly duplicated and recorded by corresponding variations in the manometer (M).

The following series of experiments were conducted :—

A. *Controls.*

1. As a control the perfusion was allowed to run on for a space of three hours, the intraocular pressure and the blood pressure being recorded simultaneously. The constancy of the tracing shown in Fig. 2 is evidence of the constancy of the experimental conditions attained.

2. *Variation of the intraocular pressure with the blood pressure.* Again as a control, the composition of the blood was kept constant, but the blood pressure was varied by varying the output of the pump. The close manner in which the intraocular pressure followed the course of the blood pressure within the limits of the inertia of a mercury manometer provides a criterion whereby to judge the subsequent experimental results (Fig. 3).

B. *Variation of the intraocular pressure with the osmotic pressure of the crystalloids of the blood.* In the intact animal the

FIG. 2.

Control experiment ; all experimental conditions being normal.

FIG. 3.

Control experiment; variation of the intraocular pressure with the blood pressure.

curves showing the variation of the intraocular pressure with changes in the concentration of the crystalloids of the blood were published by one of us in this Journal (1926). In the perfused eye the curves, which correspond closely, are seen in Figs. 4 and 5. In this series of experiments an increase in the concentration of crystalloids was obtained by perfusing from the second reservoir a mixture of two-thirds blood and one-third 20 per cent. saline :

FIG. 4.

The fall of intraocular pressure on increasing the concentration of crystalloids in the perfusing blood. At a, a mixture of $\frac{2}{3}$ blood and $\frac{1}{3}$ 20 per cent. saline was perfused.

it will be seen that the intraocular pressure falls (Fig. 4). A decrease of concentration in crystalloids was obtained by similarly perfusing with a mixture of four-fifths blood and one-fifth distilled water: the consequent rise of pressure is evident from Fig. 5, even although in the experiment illustrated the blood pressure was somewhat lowered.

C. *Variation of the intraocular pressure with the osmotic pressure of the colloids in the blood.* In the intact animal curves showing this variation were published by one of us in the *Jl. of Physiol.* (1927), and two of the illustrations therefrom are included in the present paper for purposes of comparison. Fig. 6 shows the variation of the intraocular pressure on altering the composition of the blood, the osmotic conditions remaining constant; it therefore

serves as a control. At (a) in the figure blood, to which was added normal physiological saline and gum arabic in proportions isotonic with normal blood, was commenced and continued until the end of the experiment. It will be seen that the intraocular pressure follows approximately the blood pressure. In the intact animal an injection of concentrated (15 per cent.) gum arabic increases the colloid osmotic pressure of the blood, and causes the

FIG. 5.

The rise of intraocular pressure on decreasing the concentration of crystalloids in the perfusing blood. After a, a mixture of 4/5 blood and 1/5 distilled water was perfused.

intraocular pressures to fall (Fig. 7); while exsanguination and subsequent restoration of the blood volume with physiological saline, decreases the colloid osmotic pressure of the blood, and brings about a rise of intraocular pressure (Fig. 8). Similarly, in the perfused eye, the addition of 15 per cent. gum arabic to the perfusion fluid brings on a fall of intraocular pressure (Fig. 9), and the addition of isotonic saline a rise (Fig. 10).

D. *Changes in the intraocular pressure with change of the reaction of the blood.* Controls of this physico-chemical variant carried out in the intact animal are, we think, of less value than in the other conditions treated in this paper, because of the difficulty of altering the hydrogen ion concentration of the blood and at the same time keeping the animal in a condition which in any way

FIG. 6.

Control experiment ; showing the absence of variation in intraocular pressure on perfusing equal quantities of blood and physiological saline with gum arabic in isotonic proportions. The perfusion was started at a.

FIG. 7.

The variation of the intraocular pressure in the intact animal on increasing the colloid osmotic pressure of the blood. At a, the femoral artery was opened ; at b, the bleeding was stopped ; at c, an injection of 15 per cent. gum arabic was commenced ; at d, the injection was stopped. The intra-ocular pressure, after following the blood pressure initially, tends to fall. (cat.) (*Journal of Physiology*, 1927).

FIG. 8.

The variation of the intraocular pressure on decreasing the colloid osmotic pressure of the blood in the intact animal. At a, femoral artery was opened; at b, physiological saline was slowly injected; at c, the saline was injected rapidly. The intraocular pressure, after following the blood pressure initially, tends to rise. (cat). (*Journal of Physiology*, 1927).

FIG. 9.

The fall of intraocular pressure with an increase in the concentration of colloids in the blood in the perfused eye. The perfusion fluid consisted of a mixture of normal whipped blood and 15 per cent. gum arabic.

FIG. 10.

The rise of intraocular pressure with a diminution in the concentration of colloids in the perfused eye. Perfusion was performed with a mixture of 2/3 normal whipped blood, and 1/3 isotonic saline.

FIG. 11.

The fall of intraocular pressure in the perfused eye with acidified blood, the reaction of which had been decreased to pH 6 by the addition of lactic acid.

approached the normal. Any attempt to do so over the length of time necessary to affect the physico-chemical state of the vitreous humour leads to extreme dyspnoea, cardiac disturbances, and death. The conditions of artificial perfusion, however, allow of these difficulties being overcome. In order to render the reaction of the perfusing blood more acid, a small quantity of lactic acid

FIG. 12.

The rise of intraocular pressure in the perfused eye on perfusion with alkaline blood, the reaction of which had been raised to pH 8 by sodium hydroxide.

was added to the blood in one of the reservoirs slowly, drop by drop, until the reaction showed a pH value to electrometric readings of about 6; in this way the change of reaction is brought about without any significant osmotic change. A curve of the tracing showed a distinct drop in the intraocular pressure. (Fig. 11). Conversely an alkalosis of the perfusing blood was induced by the similar cautious addition of sodium hydroxide until the reaction was in the neighbourhood of pH 8. The curve here showed a slight rise in the intraocular pressure (Fig. 12).

Conclusions

From these experiments on the surviving perfused eye it is seen, in conditions wherein the effects of systemic influences are eliminated, that:

1. The intraocular pressure falls with an increase in the osmotic

concentration of the crystalloids in the blood, and rises with a decrease in their concentration.

2. The intraocular pressure falls with an increase in the osmotic concentration of colloids in the blood, and rises with a relative decrease in their concentration.

3. *Within the limits of the changes in the reaction of the blood which were used in these experiments* the intraocular pressure falls with a decrease in pH and rises with an increase of pH. As was pointed out in the earlier part of this paper the mechanism of this change and the part it may play—if any—in the production of pathological changes in the intraocular pressure is still a matter of dispute. We do not think that these questions can be satisfactorily answered in the meantime; nor is it likely that they will be, until more fundamental research is done on the chemical constitution and the physical properties of the vitreous body and its reaction to physico-chemical changes. It may be suggested that the conditions are not so simple as these experiments might indicate. It is hoped to make this the subject of further publications in the near future.

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