The nature of the intra-ocular fluids / by W. Stewart Duke-Elder ; being the Sir Francis Laking Prize, 1926-1927, from the Biochemical Department, St. George's Hospital London.

Reprinted from

THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

OCTOBER, 1926

THE OCULAR CIRCULATION: ITS NORMAL PRESSURE RELATIONSHIPS AND THEIR PHYSIOLOGICAL SIGNIFICANCE

BY

W. STEWART DUKE-ELDER

PLIMMER RESEARCH FELLOW

From the Department of Physiology and Biochemistry, University College, London

THERE is no question in the whole of ophthalmology more important and fundamental than the vascular pressures of the eye. Not only must these form the only logical basis of a rational understanding of the pathology of many ocular diseases, but, inasmuch as the mechanism of the formation and absorption of the intraocular fluids depends primarily upon their magnitude and upon their relation to the intraocular pressure, their accurate determination is of paramount importance in the physiology of this organ. There is no question in the whole of ophthalmology which has excited more unnecessary controversy and received more varying answers. Estimates of the systolic arterial pressure vary from 60 to 120 mm. of mercury, of the diastolic, from a few mm. of mercury above the intraocular pressure to 70 mm. above it; within the last few years the pressure of the exit veins has been stated by one observer to be 10 mm. of mercury below the chamber pressure, by another to be 48 mm. above it. Consequently it is stated by one that an outflow of aqueous is brought about by hydrostatic forces, by another that its absorption is effected by osmotic energy; one affirms that the pressure gradient from capillary to aqueous is sufficient to allow the formation of the latter by a process of simple transudation, another, that the pressure relations between the two necessitate the intervention of a special secretory mechanism, involving an active expenditure of energy by the cells of the ciliary body. The unwieldy literature that has accumulated upon the subject is swollen with wearisomely

protracted and often acrimonious discussions of unnecessary hypotheses, with defective and confused experiments based on unsound physiological reasoning, with a multitude of theorizings and a paucity of facts. The present paper is an endeavour to point out the principles through whose neglect this disagreement has arisen, and to suggest what may approach more nearly the solution of a problem which forms the obvious preliminary to an inquiry into the nature of the intraocular fluids, and of the mechanism of their pressure changes.

I. The Ocular Circulation

It will simplify the subsequent discussion to consider at the outset two questions which are of importance throughout the following pages: the comparison of the vascular supply of the eye in man and in the lower animals, and the comparison of the uveal and the retinal circulations.

While in man the blood supply to the eye is derived wholly from the internal carotid artery, in the lower animals it arises from the external carotid. In the lower mammals, such as are used for experimental purposes (dog, rabbit, etc.), the transition stage between the two types occurs, and, although variations are frequent, as a general rule two ophthalmic arteries are present, one derived from either source, with a free anastomosis between them (Henderson, 1903; Parsons, 1903; etc.). The corresponding blood pressures in the various organs of the higher animals are generally accepted as comparable with those of man, but in considering the ocular circulation there may be some legitimate hesitancy in transferring experimental findings obtained in laboratory animals to the case of the human eye owing to the anatomical differences between the two. While it is very probable that they are approximately the same and in every way comparable, it would seem that the difference, if any, will be in the direction of a higher pressure obtaining in the ocular arteries of man. In him the ophthalmic artery is a direct branch of the internal carotid, virtually of the circle of Willis, a vessel which may be considered as the master vessel of the body inasmuch as the whole vasomotor mechanism is adjusted to maintain it continuously at a high pressure level. Immediately after this branch is given off the internal carotid constricts: its diameter proximal to the branching off of the ophthalmic artery averages 5.4 mm., immediately beyond this point it narrows to 3.8 mm., while the diameter of the ophthalmic artery averages only 1.5 mm. (Whitnall, 1921). The narrowing is therefore out of proportion to the cross section of the vessels, a provision which, by reducing the calibre of the main vessel and damming up the blood stream, will favour the passage of blood down this important branch, and ensure a high pressure in it.

ent. Art. Ret. ad o/art. - diam = 0·25 mm. Leber. pp. 2 Aufl.
Bd. II. S. 3. 1903

. . . centr. art. 0·23 - Schwalbe. q.s. 1 Aufl. B
S. 337 - 345. 18

iam. Thrombus ad disc. 0·1 mm. C. Hess. a.f.A. 84. 3. 19

" Ophthalmic art > 2 mm. - Knapp & Kalkins
q.s. Aufl 2. Bd 1. S 146.

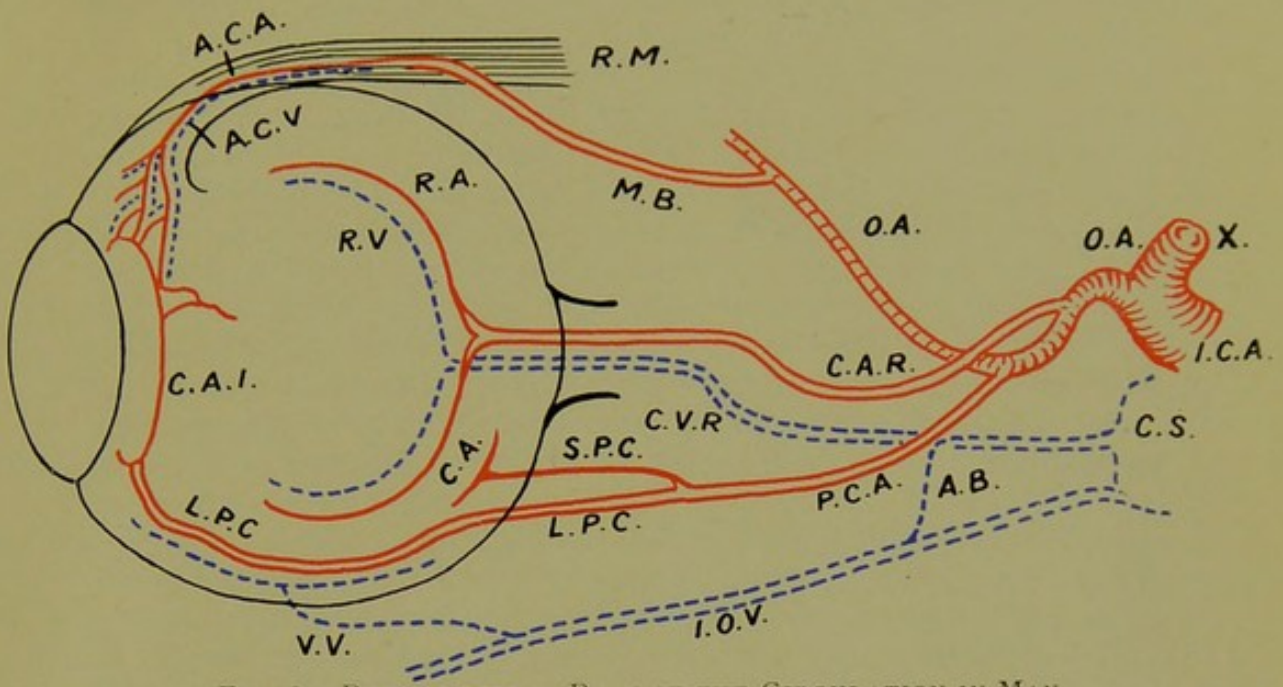


FIG. 1.—PHYSIOLOGICAL PLAN OF THE CIRCULATION IN MAN.

A diagrammatic plan of the circulation in the eye of man to emphasize the physiological principles dealt with in the text.

(I.C.A.). The internal carotid, which after giving off the ophthalmic artery (O.A.), bends round and narrows its lumen at (X). Diam. I.C.A — 5.4 mm.; diam. at X —3.8 mm.; diam. O.A. — 1.5 mm.

The branches of the ophthalmic artery involved are:

I. (C.A.R.), the central artery of the retina, breaking up into the retinal arteries (R.A.). These are accompanied by the retinal veins (R.V.), leading into the central vein of the retina (C.V.R), which enters (usually) the cavernous sinus (C.S.) directly. The central vein of the retina has always at least one anastomosing branch (A.B.), usually with the superior ophthalmic vein, here shown with the inferior. These may be considered to form, physiologically, a separate circulation.

II. The ciliary arteries comprising—

i. (P.C.A.) the posterior ciliary arteries, consisting of several short (S.P.C.) and two long (L.P.C.); the former supply the choroid, the latter terminate directly in the circulus arteriosus iridis major (C.A.I.).

ii. (A.C.A.) the anterior ciliary arteries derived from the muscular branches (M.B.) of the ophthalmic to the recti muscles (R.M.), also anastomosing with the circulus arteriosus iridis.

These two groups are to be considered as one system physiologically, the blood from which is drained away by the anterior ciliary (A.C.V.) and vortex veins (V.V.). For purposes of physiological comparison the long posterior ciliary arteries may be said to correspond to the central artery of the retina; the sub-divisions occurring in the anterior ciliary arteries prior to their entering the circulus arteriosus iridis are to be noted.

Physiologically, the vessels supplying the eye may be considered as forming two separate systems. The anterior and posterior ciliary arteries anastomose freely to form the uveal circulation, while normally the retinal circulation is anatomically apart except for a few and occasional anastomoses, which, being of little more than capillary dimensions (Leber, 1865), are of no importance from the physiological point of view: anomalous anastomoses, although they do occur, are rare (see Weizenblatt, 1926). Pathologically also, although there is some intercommunication (Kugel, 1863), a considerable amount of independence is manifested in the degree to which the two systems of vessels are involved (Coats, 1913). At the same time there is a large amount of evidence to show that, although they are anatomically distinct, in these two circulations the entrance and exit pressures are similar, that in both the same pressure gradient exists although it may be differently apportioned, and that they exhibit the same pressure variations under changing conditions.

In the arterial system, other things being equal, the pressure falls proportionately with the number of branchings and the size of the lumen of the vessels, and therefore, the central artery of the retina and the posterior ciliary arteries being both direct branches of the ophthalmic, both entering the eye directly, being both of the same order of size (Schwalbe, 1874; Henle, 1876), and being both subjected to the same external conditions along their course, we would expect them both to have approximately the same pressures. This anatomical deduction is substantiated by their physiological behaviour. Jacobi (1876) first observed the occurrence of an arterial pulse in the uveal vessels in a case of choroidal atrophy and noted that it appeared and disappeared under the same external pressure applied to the globe as did a synchronous pulse in the retinal vessels, an observation verified considerably later by Bailliart and Magitot (1925) under more exact conditions. Laqueur (1877) similarly noted the parallel behaviour of pulsation in the vortex veins and the central retinal vein, and Ulrich (1880) produced a pulsation in the former veins by finger pressure on the eye, correlating them in their behaviour with the similar pulsation produced in the central vein of the retina initially by Coccius (1853). Leber (1903) called attention to the parallelism in the pressure conditions in the choroidal arteries and those upon the disc, and Weiss (1911) brought forward evidence of the identity of the venous pressures in the two systems. Taking advantage of a case of vascularized pupillary membrane, Vossius (1921) correlated the behaviour of the vessels therein on increasing the intraocular pressure with that of those of the retina, and Bleidung (1924), compressing the globe with a pressure chamber through which ophthalmoscopic examination was possible, concluded that the pressures in the retinal and choroidal systems were the same

and varied together. The same relationship obtains in animals. Pulsation in the choroidal vessels has been known and studied in albino rabbits from the time of Waller (1856) and Liebreich (1858). Moreover, in most laboratory animals the circulus arteriosus major, instead of being placed inaccessibly at the base of the iris as in man, is situated in the substance of the iris, and is plainly visible under the magnification of the binocular loupe. The appearance and disappearance of pulsation in this vessel on applying pressure to the globe was first studied by Wegner (1866) in rabbits, and by Weber (1868) in dogs. The question was revived by Lepat (1920) who showed that in the dog the pressure changes in this vessel took place *pari passu* with similar variations in the retinal vessels; a similar relationship was noted by Bonnefon (1921) in the rabbit, and by Magitot and Bailliart (1921) in the cat. While the pressures obtained by these methods are not to be taken as correct absolutely, as will be seen later, the physiological and dynamical errors of the technique employed are common to the two cases, and do not invalidate their comparative value. We may therefore take it that the vascular pressures in the eyes of laboratory animals are comparable with those of man, and that in both, the entrance and exit pressures in the two systems of vessels—retinal and uveal— are of the same order of magnitude.

II. The Arterial Pressures of the Eye

Although several observers have claimed to have measured the arterial pressures in the eye, no one has yet succeeded in doing so. All the methods employed, with one exception, depend on raising the intraocular pressure, and observing at the same time the behaviour of the arteries of the eye and their pulsations. Before discussing these methods, therefore, it will be well to consider briefly the mechanics of the retinal arterial pulse and the conditions which determine its appearance and disappearance.

The Retinal Arterial Pulse

Since the pulse in the retinal artery was first noted by Jäger (1854) an unnecessary amount of discussion has taken place over the mechanism of its causation. There would seem to be no reason for assuming that the pulse in the arteries in the eye is in any way different from that in the arteries in the rest of the body, or that its behaviour with reference to the intraocular pressure involves principles other than those which apply to the vessels generally when they are subjected to external pressure applied by a sphygmomanometer.

In all the arteries of the body a pulse is always present, which extends throughout the entire length of the arterial system down to the capillaries with progressively lessening amplitude. In the retina a spontaneous pulse was early noted occurring in normal

Samojloff 1926. Choriodal [illegible] = (choroidal) = ciliary veins.
anat. 534.

eyes by Donders (1855) and Becker (1872); it is seen with the ophthalmoscope, according to Ballantyne (1913) in 36 per cent. of normal individuals, and it is often accompanied by locomotion of the vessels. It has been noted, also occurring spontaneously, in the choroid (Galezowski, 1916). With sufficient magnification it is always seen, either in the capillaries entoptoscopically (Onishi, 1913; Scheerer, 1924; Fortin, 1926), or extending down the arteries through to the veins, by the Gullstrand ophthalmoscope (Speyr, 1914; Kümmell, 1915).

Neglecting the disturbing factor of the rigidity of the arterial wall (Thoma, 1889) it is more easily seen, and can often be traced with the ordinary ophthalmoscope to the finest arterial ramifications if the arterial pulse is of large amplitude, as occurs in aortic insufficiency (Quincke, 1868; Mackenzie, 1875; Holloway, 1917; Wolff, 1917; Zentmayer, 1921), or in aortic aneurysm (Becker, 1872; Helfreich, 1882; Raehlmann, 1885), or in Graves's disease (Becker, 1873). In some of these cases it may be seen in the capillaries upon the disc (Quincke, 1868) as an alternate deepening and lightening of the normal tint. It becomes very marked if the intraocular pressure and the arterial pressure approximate; and when the diastolic pressure is reached it changes its character, and the "expansile" pulse becomes a "pressure" pulse at the disc, the arteries emptying and filling alternately, and the blood column flashing out of sight across the disc and filling up again suddenly. This occurs either when the intraocular pressure is high, as in glaucoma (v. Graefe, 1855; Jacobi, 1876; Ballantyne, 1913; Krämer, 1920; Bailliart, 1922), or on compressing the globe (v. Graefe, 1854; and others *vide infra*), or when the arterial pressure is low —either the general arterial pressure, as in debilitating diseases as anaemia (Pflüger, 1878; Becker, 1880; Raehlmann, 1885; Schmall, 1888; and others), or cholera (v. Graefe, 1866), or in syncope (Wordsworth, 1863; Ballantyne, 1913), or the local arterial pressure, as in embolism of the central retinal artery (Elschnig, 1892), or in the presence of retrobulbar orbital tumours (v. Graefe, 1864).

This pressure pulse is communicated by the incompressible ocular contents to the elastic sclera, where it becomes a volume pulse. In the normal eye this latter structure is so poorly distensible that the volume pulse is damped down beyond visible limits, but in conditions where the distensibility of the envelope of the eye is increased, such as in high myopia with a posterior staphyloma (Kyrieleis, 1925) or in keratoconus, or nearly perforating corneal ulcer, the pulse is readily seen (Javal, 1884; Gullstrand, 1891; Collies, 1891; Wagenmann, 1898; and others). When magnified by the lever of a tonometer, however, this volume pulse is always seen in the normal eye (Schiötz, 1905; Foster Moore, 1917; etc.), and again, if the continuity of the corneo-sclera is broken, and the contents of the eye are put into direct communication with an open manometer, the arterial pulse is imparted plainly and undiminished to the fluid in the latter. This was first observed by Weber (1850); and Bellarminoff (1886), registering the excursion of the fluid photographically, demonstrated its amplitude to be 1 to 2 mm. Hg, a finding confirmed by many subsequent observers.

This volume pulse is due to the intraocular arteries and is not communicated from the orbital vessels, since, on inducing local endocular hyperaemia (by subconjunctival saline injections, etc., Wessely, 1908) the ocular pulse increases proportionately, while a simultaneous carotid tracing remains unchanged. Inasmuch

as the choroidal vessels form eight-tenths of the entire circulation of the eye, the pulse will be largely due to their influence. This is demonstrated by the fact that clinically, in cases of embolism of the central artery of the retina, when this vessel is occluded, the pulsations of the eyeball as shown by the lever of a tonometer proceed as usual. As has been noted, the volume pulse communicated from the uveal vessels behaves in every way parallel with the pressure pulse seen in the retinal circulation.

THE MEASUREMENT OF THE ARTERIAL PRESSURE

In the normal eye therefore the arterial pulsation is very small, but on raising the intraocular pressure it becomes progressively larger until the diastolic pressure is reached; at this point the arteries are completely collapsed during a portion of the cardiac cycle, and the pulsation is at a maximum. On increasing the pressure still further, the amplitude of pulsation will progressively diminish until, when the systolic pressure is overcome, the blood flow ceases, pulsation stops, and the artery collapses.

In this way, it is to be noted, the eye is converted into a natural sphygmomanometer, and when the vessels are compressed the column of blood contained in them is partially or completely immobilized. The pressure thus registered is therefore not that of the vessels in the eye at all, but the lateral pressure at the most proximal arterial branching, that is, of the ophthalmic artery. Just in the same manner as a manometer in the carotid measures the lateral pressure in the arch of the aorta and not that in the carotid artery itself, or a sphygmomanometer over the brachial artery registers the pressure in the subclavian, so the lateral pressure in the ophthalmic artery is measured through the central artery of the retina by observing the retinal pulse, or through the posterior ciliary arteries by measuring the volume pulse of the globe.

In order to get a strictly correct interpretation from the pressures measured, there should be deducted from them the force necessary to overcome the resistance of the artery wall, a factor which varies with its rigidity and the degree of sclerosis. That such a consideration is not inconsiderable in many cases is seen in the observations of Foster Moore (1916) on the retinal arteries. A further correction factor should be applied depending on the length of the immobilized column of blood, on the acuteness of the angle at which the branch vessel leaves the parent stem (since, if it does not leave at right angles, in addition to the lateral pressure of the feeding artery, there is added to the pressure measured some of the kinetic energy of the forward moving stream), and depending further on the relative capacity of the occluded channels and the remaining channels (since, if the former be of any size, the pressure in the latter is increased correspondingly by engorgement), while in addition, if the vessels are large, the purposive action of the heart in attempting to overcome the obstruction thus caused must be allowed for. In the present case, however, these factors may be neglected for all practical purposes, and the pressures thus measured may be considered as representing the lateral pressure in the ophthalmic artery.

The intraocular pressure has been raised by two methods:

(1) *The Manometric Method.*—A manometer is inserted into the eye and the pressure therein raised by forcing in saline. Coincidently the behaviour of the retinal arteries has been studied,

the points of maximum oscillation and cessation of oscillation being taken as the diastolic and systolic pressures respectively. These points have been determined in two ways:

(*a*) By the Oscillatory Method.—By recording the points of maximum oscillation and cessation of oscillation as conducted to the mercury column of the manometer. The amplitude of these oscillations, first noted by Weber (1850), was correlated with variations in the intraocular pressure by Hippel and Grünhagen (1869), whose observations were substantiated by Hoelzke (1883), Bellarminoff (1886), Stocker (1887), and Koster (1895). Wessely (1908), recording the oscillations graphically with a membrane manometer, obtained the first reliable results. Weiss (1911), and more recently, Lullies and Gulkowitsch (1924) used the same method, or a modification of it. Their results are as in Table I.

TABLE I

	mm. Hg		
	Diastolic	Systolic	
Wessely (1908)	70	—	Rabbit
Weiss (1911)	50-70	—	,,
Lullies and Gulkowitsch (1924) ...	54-70	92-108	,,

(*b*) By the Ophthalmoscopic Method.—By observing the pulsations of the retinal artery with the ophthalmoscope. This method, adopted first by Schöler (1879), was carried out with a more refined technique by v. Schultén (1884).

TABLE II

	mm. Hg		
	Diastolic	Systolic	
Schöler (1879)	mean pr. 70		Rabbit
v. Schultén (1884)	90-120	100-130	,,

(2) *The Tonometric Method.*—The pressure in the eye is raised by external pressure applied to the intact globe. As in the first case, observations have been made by two methods:

(*a*) By the Oscillatory Method.—By observing the amplitude of the excursions of the tonometer lever on increments of pressure. The variations of the excursions with different degrees of pressure were first noted by Schiötz (1905); Bailliart (1919) registered the movements of the lever photographically. These movements, however, are so small, and their variations so inconsequential, that

this method cannot lay claim to any accuracy. The inherent fallacies which it involves are in large part common to the ophthalmoscopic method of Bailliart, in which connection they will be discussed in detail. To these is to be added the greater influence of the marked diminution of the distensibility of the sclerotic with increasing tension (v. Schultén, 1884; Koster, 1895; Wessely, 1908; Greeves, 1913). The amplitude of the ocular volume pulse varies with the volume capacity of the globe, a factor which varies with the elasticity of the sclera; on each pressure increment a condition of greater tension prevails in the eye, and therefore, in the higher pressure levels a proportionately smaller excursion is registered for the same increase of pressure. On raising the pressure, therefore, the amplitude of the oscillation not only varies with the increasing pressure in the eye, but is a function also of the decreasing distensibility of the sclerotic. To obtain readings which will correctly bear comparison, the continuity of the corneoscleral envelope must be broken, and the incompressible fluids of the eye put into direct communication with the fluid in a manometer.

(*b*) By the Ophthalmoscopic Method. — The pulsatory behaviour of the retinal artery as seen ophthalmoscopically on the application of pressure to the globe was first correlated by v. Graefe (1854) with the relation of the raised intraocular pressure to the arterial pressure. Bailliart (1909) and Black (1910) ascribed to the phenomena thus observed a clinical value, and Bajardi (1910) and Rubino (1911) attempted its assessment. So also did T. Henderson (1914), Bailliart (1917 *et seq.*), and Bleidung (1924). T. Henderson (1914), applying over the upper lid a Geneva lens measure, calibrated in mm. Hg instead of dioptres, noted that the arteries at the disc showed a pressure pulse at 15 to 25 mm. Hg (as recorded by his instrument) above the intraocular pressure. This, he claimed, represented the height of the diastolic pressure in the retinal arteries over the chamber pressure. Bailliart (1917) developed a more accurate technique, and since the procedure he has elaborated has been popularized clinically by its author and by Magitot (1922 *et seq.*), and has received a considerable amount of attention during the last few years, while the principles on which it is based have been generally accepted without question, I shall consider it in some detail.

The technique adopted by Bailliart is to apply to the sclerotic a piston working against a standardized spring ("dynamometer"), with which the tension of the eye is raised. While doing so the points of commencement and cessation of pulsation of the retinal artery are noted. A Schiötz tonometer is then applied to the eye, and the pressures as registered on the tonometer at these two points are taken respectively as the diastolic and systolic pressures of the branches of the retinal artery. The results obtained thus

<u>ianis method.</u>

Rasvan (1926) 30-45 mm. Hg — 70 mm Hg.

Lida & Adroqué (1926) 41-47 — 90-97 mm Hg.

mean of 50 normal indiv.

D/S = 50 / 80-100.

Abramowicz (192) D/S = 45-55 / 70-90.

iotz. (1927)

& Plancoulaine syst. Pulse watched &

using his terminale.

D/S = 50-56/70-80 mm Hg.

by different observers vary by more than 100 per cent., the majority of them being low. They are as given in Table III.

TABLE III

Author	Pressure. Interpreted as mm. Hg Diastolic	Systolic	Subject
Bailliart (1917)	25-30	50-70	Man
Velter (1920)	35	60	Man
Duverger and Barré (1920)	60	80-100	Man
Vossius (1921)	—	70	Man
Salvati (1922)	32-50	60-70	Man
Magitot (1922)	30-35	70-80	Man
Leplat (1920)	50-65	80-90	Dog
Magitot and Bailliart (1921)	45	130	Dog
Do. (1921)	45	100	Cat
Stasińska (1925)	30-35	67-70	Man
Lebensohn (1925)	30-35	65-75	Man
Vita (1925)	30-35	70-75	Man
Verway (1925)	=radial pr.	—	Man
Baurmann (1926)	54.9	80·1.	Man

The method of Bailliart, apart from registering, as has been pointed out, not the pressure in the branches of the central artery of the retina, as its author claims, but that of the ophthalmic artery, involves several fallacies in addition to incidental sources of error depending on the construction of the dynamometer, on the amount of force used, and the rate and manner of exerting it, on the nature and condition of the eye and the arteries, and on the very limited value of the tonometer as a means of recording pressures of any kind.

This last is a very important factor: see Priestley Smith (1917), and others. In the laboratory I have found that tonometric readings of the tension differ from manometric readings of the pressure of the same eye in living cats, dogs, and rabbits, in the most disconcerting manner, sometimes by as much as 10 mm. Hg, the variation being quite inconstant, rarely above, more frequently below. The same has been established in human eyes: compare Wessely (1916), MacLean (1919), Seidel (1922,b). The variation I find is more marked with Bailliart's instrument (1923) than with either Schiötz's or MacLean's, and the discrepancies occur with the first even in rabbits, on whose eyes the tonometer was calibrated. *The use of a tonometer as an instrument of accuracy is confined to the comparison of the two eyes of the same individual at the same time, or of the same eye at different times, provided that their condition is not widely different in the first case, or does not greatly alter in the second.*

The tension is not equal to the pressure, nor is it proportional to it in its variations. Inaccuracies are therefore involved in the method, and these to a certain extent Bailliart himself admits (1924). They are, however, greatly accentuated in the conditions of high tension which the manipulations involve, and would seem to be accentuated beyond all reason by the simultaneous use of two instruments both pressing heavily upon the eye at the same time, since the force exerted by the dynamometer must considerably

deform the curvature of the globe, upon which the tonometer largely depends for any accuracy it may have.

Further, in the application of the pressure, the eye is rendered tense and hard, and is pushed back into the orbit, kinking in doing so the central artery of the retina, and compressing the ophthalmic artery, thus partially occluding the blood flow in both. This probably accounts for the lowness of the results obtained, and would seem to provide an explanation for the much higher readings which Bailliart and Magitot (1921) obtained in animals than in man. It has been already suggested that everything points to the reverse relation holding in fact. In these animals, however, with their double and anastomosing arterial supply, it is possible for the intraocular circulation to be maintained in the absence of one or the other of the ophthalmic arteries. On compression, therefore, it is probable that this error will be largely eliminated, and that the higher results obtained in these animals will indicate a closer approximation to the correct measurement than the readings obtained in the case of man.

The explanation offered, for example by Gaudissart (1921), to explain this discrepancy found by Bailliart and Magitot—namely, that the pressure in man is less than in animals because of the erect attitude and the greater length of the arteries—will not bear examination. The effect of attitude upon the blood pressure of animals which habitually adopt the erect posture is very efficiently compensated (L. Hill, 1895; Hill and Barnard, 1897), or even over-compensated (Barach, 1913) by reflex action. Further the length of the artery involves practically no fall in pressure. This last decreases proportionately with the diminution in the size of the lumen of the vessels, and the number of branchings. In point of fact the work of Bazett (1924) seems to show that normally, both in the dog and in man, the femoral pressure is higher than the brachial by an amount, according to Burdick (1925) varying from 20 to 40 mm. Hg; while L. Hill (1909) and others have demonstrated that the systolic pressure in the peripheral arteries may under certain conditions be higher than that in the aorta. The phenomenon doubtless depends among other things upon the transference of the kinetic energy of a fluid in rapid motion into stress when the flow meets with resistance (Bazett, 1924), upon the formation of "breakers" in the transmission of the pulse wave (Bramwell and A. V. Hill, 1925), and upon the "conductance" of the arterial wall (L. Hill, 1912), but such considerations serve to illustrate the inadequacy of the explanation here offered.

Further, according to Bailliart, the diastolic pressure is only some 10 to 15 mm. Hg above the intraocular pressure: this is important from the sweeping deductions some writers have drawn from this low value regarding the impossibility of the formation of the aqueous without the intervention of a special secretory mechanism. Reasoning that whenever the pressure on the external side of the artery is equal to the internal pressure, the arterial wall so placed in equilibrium begins to vibrate, he takes (if I understand him aright) the first clearly visible pulsation in the retinal artery as the diastolic pressure.

Thus Bailliart (1917, p. 265): "l'apparition du premier battement artériel, facilement constatable à l'ophtalmoscope"; (ibid., p. 265): "pour provoquer le premier battement artériel, c'est à dire, pour équilibrer la pression diastolique." The pressure is taken (ibid., p. 656): "au moment où le premier battement artériel à été noté."

But we have already seen that under the influence of the pulse pressure the arteries all over the body vibrate, and that the same

thing is always seen in the eye under sufficient magnification. This pulse increases under increments of external pressure until it reaches a maximum when the diastolic pressure is overcome. The first appearance of a pulse "which is easily made out by the ophthalmoscope" is therefore not an index of the diastolic pressure but of the magnifying power of the instrument used to observe it. The point at which the lumen of the artery is obliterated, that is, the point of maximum pulsation, is the diastolic pressure.

An illustration from Bailliart and Magitot's own measurements (1921) is illuminating. They record the diastolic-systolic pressures in the aorta of a dog as 170-195 mm. Hg, and the diastolic-systolic pressures in the retinal arteries of the same animal as 45-130 mm. Hg. Throughout the whole arterial system the tendency is for the intermittent flow in the larger arteries to be converted into a more constant flow peripherally under the influence of the elasticity of the arterial walls, an effect which in the present case is further increased by the damping influence of the elasticity of the sclerotic and the intraocular pressure. On travelling to the periphery, therefore, the pulse pressure progressively decreases, until in the smaller vessels the difference between the diastolic and systolic pressures becomes very limited; it is difficult to conceive how a pulse pressure of 25 mm. Hg in the aorta becomes converted into one of 85 mm. Hg in the eye.

A further illustration of the fallacies of the method is seen in the conclusion of Bailliart that the retinal arterial pressure ascends and descends parallel with the intraocular tension and this without variation in the general arterial pressure. Thus he states that the two retinal arteries of the same individual of whom one eye is glaucomatous differ largely in their pressure (1921); in a case of unilateral traumatic glaucoma the entrance pressure in the retinal artery rises in the injured eye only; and on the relief of a glaucoma by an iridectomy it falls coincidently with the intraocular pressure: thus: I. O. P., 50 mm. Hg, D./S. pr., 50/80 mm. Hg; subsequently, I. O. P., 10, D./S. pr., 26/40; later I. O. P., 35, D./S. pr., 39/65. While it is admitted that the venous pressure in the eye varies with the intraocular it is difficult to imagine what influence would make the pressures in the entering arteries vary up to 100 per cent. with it, and when it is remembered that the pressure actually measured is not the pressure in the arteries in the eye, but is an incorrect reading of the pressure in the ophthalmic artery, it is impossible to believe that any changes in the eye would exert an influence of this extent. The obvious deduction is that the method involves the introduction of a relative and indeterminable error, which is a function of the intraocular pressure and the state of tension of the sclerotic.

It would appear, therefore, that the technique elaborated by Bailliart is a fallacious method of estimating the lateral pressure in the ophthalmic artery; and that, whatever clinical value its results may be interpreted to have if considered in this light, merely as figures with a comparative and no absolute significance, they can give no indication whatever of the pressure in the branches of the retinal artery, nor of the relation between the blood pressures in the eye and the intraocular pressure.

Bleidung (1924) employed an air chamber connected with a manometer as a means of compression. This he fitted hermetically over the eye, and as the pressure in it was raised, the ocular circulation was observed ophthalmoscopically through a window in front of the cornea. His results average D./S. pr., 64 - 75/96 - 117 mm. Hg in man. Although herein some of the mechanical errors of Bailliart's technique are avoided, others are introduced: the air pressure in the chamber is not equal to the tension, still less to the pressure in the compressed eye. Here again many of

the same criticisms as I have already considered equally apply; and here again the pressure registered depends on the pressure in the ophthalmic artery, and is not, as Bleidung claims, that in the retinal and choroidal vessels.

The Pressure in the Anterior Ciliary Arteries has been measured by Seidel (1924,a) and Hiroishi (1924) by applying a small pressure chamber over them connected to a manometer. The pressures appeared as diastolic systolic: 35-45/65-75 mm. Hg.*

Seidel argues that since these vessels supply the ciliary body, the arterial pressure therein, that is, the arterial pressure associated with the formation of aqueous, must be less than this, and that consequently the aqueous is a secretion. He, however, compressed the arteries just at their entrance into the globe; the pressure registered was therefore that at the most proximal branching, that is, almost immediately at the limbus. Here these vessels are very minute, and have undergone several sub-branchings since leaving the ophthalmic artery; their pressure will consequently be considerably less than that of the long posterior ciliary arteries which run to the ciliary body directly from the ophthalmic artery (see Fig. 1).

That the anterior ciliary arteries are of secondary importance, and that the uveal circulation is determined largely by the posterior vessels is seen in the fact that the former are absent in some animals; when they are present, their obliteration would seem to lead to little or no deleterious effects, while ligation of the posterior arteries leads to hypotony and widespread degenerative changes extending even to structures as near the distribution of the anterior arteries as the cornea. This was demonstrated experimentally by Wagenmann (1890) and Siegrist (1900), and has been noted clinically after their operative obliteration in an optico-ciliary resection by Knapp (1874) and Löhlein (1910), or after their pathological obliteration (Coats, 1913). Further, an observation by Serr (1926) is interesting: measuring the pressures in these vessels by Seidel's technique, he finds that in glaucoma the intraocular pressure is frequently higher than the systolic pressure in them. Thus I. O. P.=61 mm. Hg, D./S. pr., ant. cil. art.=40/57 mm. Hg; I. O. P.=74, D./S. pr., ant. cil. art.=45/61, etc. In these cases the intraocular circulation was still proceeding and therefore the capillary pressure in the eye must have been still higher than the intraocular. Obviously, as Seidel's technique itself reveals, the pressure in these vessels is, or at any rate, can be, less than

* I gather from an abstract that Bauermann (*Versam. d. Nordwestdeutsch. u. d. Neidersachs. Augenärzte-Verein.*, May, 1926) has recently repeated Seidel's experiments, using the same technique. His results appear to be S./D pr.—53.7/80.1 mm. Hg. He also finds the diastolic pressure by Bailliart's method to be 54.9 mm. Hg. While it is impossible to assess adequately experimental results from an abstract, and dangerous to attempt to do so, these values appear to me to be more reasonable than those obtained by Seidel.

v. g. a. f. o. 118. 118, 1925.

systolic 70 to 95 av. 80.1
diastolic 46.6 to 60 av. 53.7.
Ant. Cil. Arteries

Seidel's technique "Pelotte".
nterior ciliary arteries by
Bauermann (1925) see footnote. p.324
Samojloff. (1927). D/S. = 34 to 46/50-65
(normal people).
(Samojloff hence concludes that filtration impossible.)
agree c̄ Seidel.
Since cap. pr. must be less than 30-46

the general blood pressure in the vessels of the eye, and it is obviously wrong to assume that its measurement is indicative of the pressure in the latter.

Incidentally, it may be noted in passing that T. Henderson (1910) claims that the anterior ciliary arteries are veins: this is merely mentioned because it seems to have passed without being directly contradicted hitherto. This decision was arrived at after the study of "literally hundreds of sections" (ibid., p. 73), and provides an excellent example of the futility and danger of basing physiological conclusions as to function upon purely anatomical or histological data, another example of which is seen in the functions sometimes ascribed to the ciliary epithelium. To keep to the present case in the meantime, these vessels are directly given off from the muscular branches of the ophthalmic artery, they contain blood at a pressure of 75 mm. Hg, while their companion veins have a pressure of 10 to 15 mm. Hg, and the blood in them flows in a centrifugal direction from the heart to the eye, as can be seen by compressing them in man and watching the direction from which they refill, or by dividing them in animals and watching the blood flow from the proximal end. This, the physiological method of inquiry, was that which enabled Harvey to establish the fundamentals whereupon our knowledge of the circulation rests: see his MSS. lectures to the Royal College of Physicians (1616)—"WH . . . constat per ligaturem transitum sanguinis ab arteriis ad venas. . ." It is a method of inquiry a little less time-consuming and a great deal more conclusive than that adopted by Henderson.

EXPERIMENTAL TECHNIQUE

(1) *The Pressure in the Branches of the Retinal Artery.*—The pressure in the branches of the retinal artery was measured directly by the insertion into their lumen of a micro-pipette as used by Barber in his bacteriological work (1914). This is made by drawing out capillary glass tubing over a micro-burner into a needle with a rapidly tapering point, and converting the needle into a pipette with a sharp point by jamming its tip against a cover-slip until it breaks off. In this way it is possible to make pipettes with an orifice of a few micra in diameter, and relatively easy to make one of such a size as will enter the branches of the retinal artery (diam. at disc, 0.1 mm.: Hess, 1919), and at the same time allow the circulation therein to proceed unimpeded. So long as the tip of such a pipette is surrounded by air, the pressure of the internal liquid is kept in check by capillarity, but on immersing the tip in blood this error is eliminated. A theoretical error remains depending on the difference between the surface tension of the two fluids, but its magnitude is so small that it can be neglected. The pipette was controlled by a micro-manipulator designed after the type elaborated by Chambers (1922) for the injection and dissection of single cells. It was provided with adjusting devices worked in three planes, controlled by finely-threaded screws opposed by springs, so that accurate and continuous control of the pipette was obtained in every direction, and its tip could be maintained in any desired position.

The animals used in the investigation were cats. In the dog the retinal vessels are ensheathed and to a large extent obscured by neuroglia, only fine branches being visible upon the optic disc. The fundus of the rabbit is traversed by opaque nerve fibres

running in two large sheaves out from the disc. But the retina of the cat closely resembles that of man, and in it the retinal vessels are easily differentiated against a bright, glistening background, and their relation to variations in the pressure conditions are readily observed: usually three, and sometimes four, large arteries run out from the disc, each flanked by a vein.

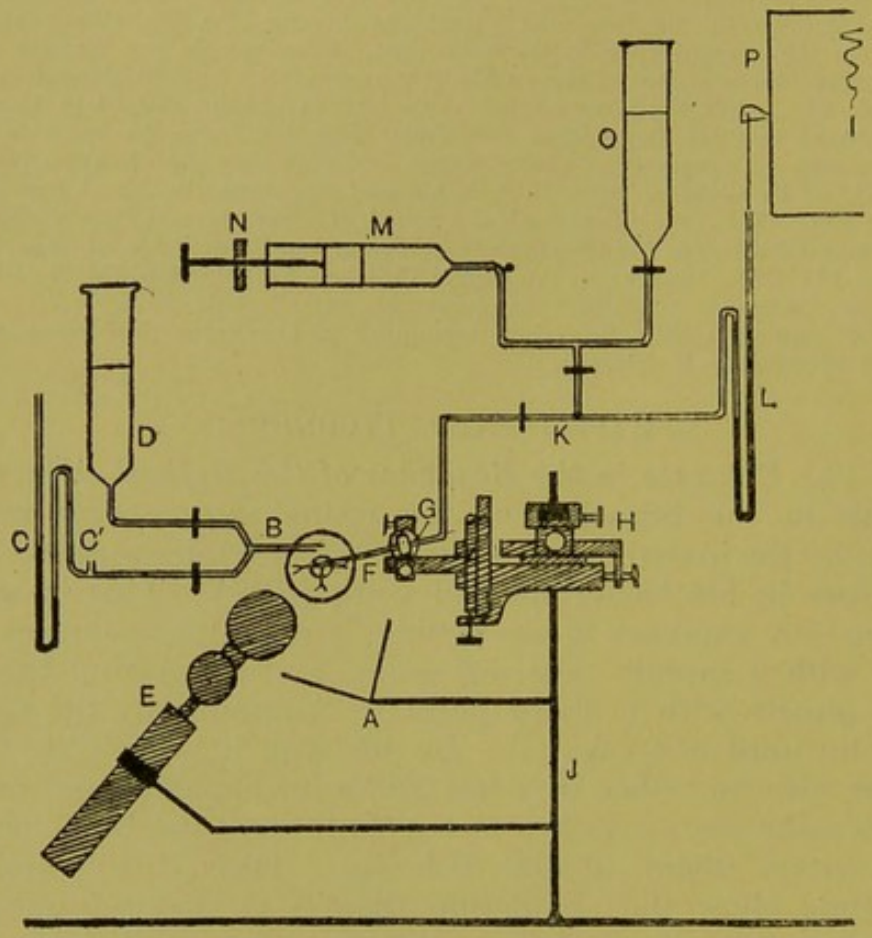


FIG. 2.
(Reproduced from the *Journal of Physiology*.)

I have elsewhere (1926,c) described the technique employed. Anaesthesia was induced with ether, and maintained by intravenous chloralose. The lower lid was reflected along with the soft tissues, the periosteum elevated, a V-shaped piece of bone removed from the lower orbital margin, and the under surface of the globe exposed. The animal's head was then securely clamped (A, Fig. 2) in a suitable position. A hollow needle (B) of large bore to prevent any valvular action, and provided with a side-arm, was inserted into the vitreous, and connected to a compensated mercury manometer (C) with an attached reservoir (C′) by means of a capillary tube with an air bubble to serve as an index of equilibrium. The side-arm of the needle was connected to a second reservoir filled with normal saline (D). The normal intra-

ocular pressure was then taken as described in a previous paper (1926,a) by means of the compensated manometer; the reservoir (D) was then raised to a corresponding height and its connection with the eye opened—by this means the intraocular pressure was maintained at its normal level throughout all the subsequent manipulations.

A self-illuminating ophthalmoscope (E) was then adjusted so as to obtain a good view of the fundus by the direct method, and was clamped into position. The sclerotic was then pierced post-equatorially by a fine metal needle, and the micro-pipette (F), carrying a collar (G), was inserted immediately on the withdrawal of the needle through the hole thus made. Under the guidance of the ophthalmoscope the tip was then made to approximate closely the branch of the artery on the side of the disc opposite to that at which the pipette was inserted, and when in this position, the micro-manipulator (H) was brought into position, and the collar securely fixed by a screw. The animal's head, the manipulator, and the ophthalmoscope were all clamped to the same support (J) in order to secure rigidity of adjustment. Under observation through the ophthalmoscope the tip of the pipette was then made to enter the lumen of the artery by adjusting the screws on the manipulator. The micro-pipette was connected by tubing (K) to a mercury manometer (L), the whole system being filled with a solution of methylene blue in physiological saline. Any desired fluid pressure was made to act on the pipette tip by means of a syringe (M), whose movements were accurately controlled by a milled screw adjustment (N) on the piston, the pressure being simultaneously recorded on the manometer (L); while a constant supply of solution was maintained by re-charging the syringe from a reservoir (O) and suitably adjusting the stop-cocks.

While the pipette was being manipulated into the artery the system was kept at the normal intraocular pressure, so that none of the methylene blue escaped into the eye and obscured the field. When it was introduced, blood was seen to flow up into it from the artery. The pressure was then raised by means of the syringe until the methylene blue flowed continuously into the artery: the flow was easily seen ophthalmoscopically. At this point the pressure in the system, registered by the manometer, was higher than the blood pressure at its highest point in the cardiac cycle. The pressure was then lowered until a slight stoppage of this flow occurred periodically, when a small amount of blood tended to enter the tip of the pipette: this point marks the pressure required to equilibrate the highest pressure level reached in the artery in the cardiac cycle, that is, the crest of the systolic pressure. On lowering the pressure further the dye and the blood fluctuated in the tube of the pipette, and no continuous flow took place, until a point was reached when an almost steady flow of blood into the

pipette occurred, with a periodic stoppage at diastole, when a small spurt of the dye entered the vessel. These two pressure levels were recorded by marking their height on the kymograph (P). Several readings were taken in each experiment, the mean of which is given in Table IV, a correction factor being added to allow for the influence of a column of saline equal to the difference in level between the manometer and the eye.

TABLE IV

No. of Cat	Intraocular Pressure mm. Hg	Pr. Retinal Artery mm. Hg		
		Systolic	Diastolic	Mean, interpreted as S. + D./2
1	22	91	65	78
2	25	88	59	73.5
3	29	94	69	81.5
4	20	86	65	75.5
5	23	83	63	73
Average	24	88.5	64	76

(2) *The Pressure in the Ophthalmic Artery.*—The pressure in the ophthalmic artery was measured by a method modified from that adopted by previous workers, by making use of the eye as a natural sphygmomanometer. In the criticism of their technique, it was pointed out that any interference with the circulation behind the globe by pressure applied to the intact eye entirely vitiated the results. Further, we have seen that unless the continuity of the corneo-sclera is broken and the incompressible fluids of the eye put into free communication with a rigid fluid system, owing to the progressive damping of the pulse by the decreasing distensibility of the sclerotic with increasing tension, any method which purports to compare the variations in the amplitude of the ocular pulse becomes progressively more inaccurate as the tension rises. A manometric method of raising the pressure was therefore adopted; and the pulse was both observed by the ophthalmoscope, and recorded by the oscillatory method.

A manometer needle (A, Fig. 3), of large bore (1 mm.) to ensure free communication of the oscillations, and provided with a side-arm, was inserted through the cornea, the point of the needle being kept in the periphery of the anterior chamber to allow ophthalmoscopic examination of the fundus. From the side-arm a tube (B) was connected with a compensated mercury manometer (C) with an attached reservoir (C′), and communicated with a syringe (D) whose piston was controlled by a screw adjustment (E). The whole was filled with saline, a constant supply of which

was obtained from a reservoir (F). The straight end of the manometer led directly into a very fine capillary tube (G) lying horizontally, to which was attached a scale graduated arbitrarily. The capillary was connected by stout pressure-tubing to a glass tube (H) which served as a reservoir filled with saline, and which could be raised and lowered by a pulley. It was made as small as was convenient in order to reduce the inertia of the fluid in the capillary (G), and thus make the oscillations as large as possible. When

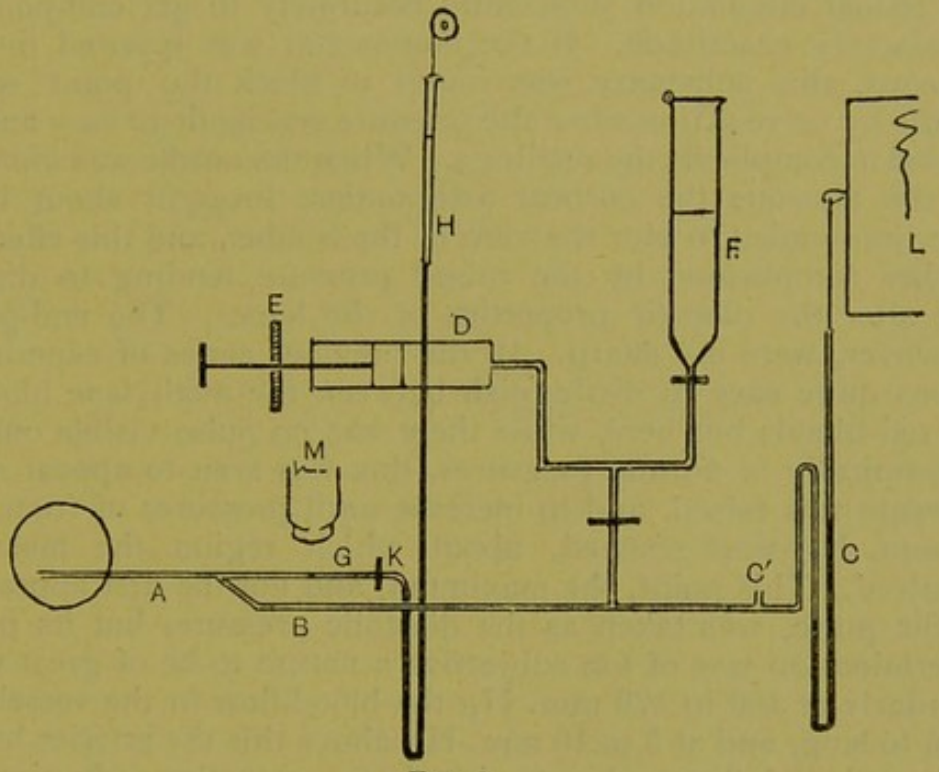


FIG. 3.

(Reproduced from the *Journal of Physiology*.)

the manometer was inserted, the reservoir (H) was shut off by a stop-cock (K); an air-bubble was then introduced into the tube (B) by a fine hypodermic syringe, and the pressure in the system adjusted by raising and lowering (C′) until the bubble was stationary, the normal intraocular pressure being thus recorded on the manometer. Communication with the reservoir (C′) was then closed, and, after the height of (H) had been adjusted to correspond with that registered on the manometer, communication between it and the eye was established by opening the stop-cock (K). The pressure in the syringe was then slightly increased, while the level in the reservoir (H) was kept unaltered, so that the air-bubble travelled slowly down the tube (B) and along the capillary (G). Having arrived here, it was kept constantly in the same place by raising or lowering (H) coincidently with any subsequent manipulations of the syringe. When the pressure in the eye was varied by means of the syringe, the behaviour of the

retinal artery was observed ophthalmoscopically, and the excursion of the air-bubble in the capillary was noted simultaneously through a microscope (M). The pressures at the points of maximum oscillation and cessation of oscillation were marked on the kymograph (L), and were subsequently measured, corrections being applied to compensate for a column of saline equal to the difference in level between the eye and the manometer.

With the ophthalmoscope it was not always easy to observe the retinal circulation sufficiently accurately to get end-points of satisfactory exactitude. If the manometer was inserted into the vitreous, this substance was found to block the point of the needle by valve action when the pressure was made to vary and this tended to complicate the readings. When the needle was immersed in the aqueous the corneal astigmatism brought about by its insertion tended to blur the view of the fundus, and this effect was further complicated by the raised pressure tending to displace and alter the dioptric properties of the lens. The end-points, moreover, were not sharp. In the previous series of experiments it was quite easy to distinguish between the methylene blue and the red blood; but here, while there was no pulse visible ophthalmoscopically at normal pressures, this was seen to appear as the pressure was raised, and to increase until pressures of from 70 to 80 mm. Hg were reached, about which region the maximum occurred. This point, the maximum, and not the first appearance of the pulse, was taken as the diastolic pressure, but its precise determination was of too subjective a nature to be of great value. Similarly at 100 to 120 mm. Hg the blood-flow in the vessels was seen to stop, and at 5 to 10 mm. Hg above this the arteries became collapsed and flattened out; but here again the end-point was indefinite, and did not lend itself to objective exactitude. Greater reliance was therefore placed upon the oscillatory method.

There follows the protocol of a typical experiment (Table V); the figures expressing the amount of oscillation refer to divisions of the scale, and are therefore arbitrary and of purely comparative significance.

Taking the point of maximum oscillation as the diastolic, and that of cessation of oscillation as the systolic pressure, the results of a series of six experiments are given in Table VI.

(3) *The Pressure in the Aorta.*—The lateral pressure in the aorta was registered by a mercury manometer connected with a cannula inserted into the lumen of the carotid artery. To obtain an idea of the pulse pressure in the carotid the technique used in the estimation of the pressure in the retinal arteries was attempted, by which a pipette was inserted into its lumen. The systolic pressure is easily obtained in this way as the point at which blood just starts to come up from the artery into the pipette; but the determination of the diastolic pressure proved

to be more difficult. The pulse pressure in this artery is too large and the oscillations too free to allow accurate readings to be made by this method; and with a large artery with opaque walls making it is impossible to see the dye inside the

TABLE V

Intraocular Pressure mm. Hg	Ophthalmoscopic Appearances	Amplitude of Oscillation (Scale Divisions)
26	Vessels normal	4 – 5
28	Venous pulsation at disc; arteries normal ...	4 – 5
40	Veins engorged; arteries pulsating slightly ...	6 – 7
60	Veins beginning to become constricted; ... arteries pulsating.	8 – 10
70	Arterial pulsation increasing	11 – 12
75	Do.	14 – 15
78	Arterial pulsation maximal	18 – 20
80	Arterial pulsation marked	14 – 17
90	Arterial pulsation less	9 – 12
110	Veins constricted; arteries filling only at systole	6 – 7
120	Blood stream segmented; arterial pulsation ceased.	0
125	Arteries barely visible	0

Mean aortic pressure – 114 mm. Hg

TABLE VI

No. of Cat	Intraocular Pressure mm. Hg.	Pressure Ophthalmic Artery mm. Hg			Mean Aortic Pressure mm. Hg
		Systolic	Diastolic	Mean, interpreted as S. + D./2	
1	26	78	120	99	108
2	29	85	129	107	118
3	26	74	106	90	96
4	23	81	110	95.5	100
5	25	73	116	94.5	108
6	20	80	109	94.5	104
Average ...	25	78.5	115	97	106

vessel an end-point is not easy to decide upon. A mean aortic pressure of 110 mm. Hg corresponds to a systolic crest of 150 mm. Hg in the carotid, and the diastolic level is probably in the region of 70 mm.

Only in one case were the four measurements taken in the same animal; as a general rule the length of time occupied by the

manipulations and the consequent change in the animal's condition, rendered comparative values of little account. In this case the measurements are given in Table VII; and of these, the pressure taken in the carotid, being taken last, is probably somewhat too low.

TABLE VII

	Pressures in mm. Hg		
	Systolic	Diastolic	Mean
Pressure in carotid (aortic) (Rt. side)	—	—	104
Pressure in ophthalmic artery (Rt.)...	119	80	99.5
Pressure in retinal arteries (Lt.) ...	86	65	75.5
Intraocular pressure	—	—	20

It is seen that while the systolic crest has fallen very largely, the mean pressure in the ophthalmic artery is only about 10 mm. Hg below that measured in the carotid, that is, below the mean aortic pressure; and that in the first branching in the eye a larger fall of about 25 mm. Hg, or approximately 30 per cent. of the total pressure, has occurred. Between this and the veins a fall of 54 mm. Hg takes place. This distribution of the pressure gradient is in conformity with that encountered in other parts of the body, where the arterial pressure is maintained at a fairly constant high level throughout the larger arteries until the smaller vessels are reached. This has been recognized since the time of Poiseuille (1828). It is well illustrated in the pressure gradient in the arm: Müller and Blauel (1907) showed that the pressure in the volar digital arteries was only 8 per cent. less than that in the brachial, and Oliver (1916) found no appreciable fall in the arterial pressure down to the forearm, and only a fall of 5 to 15 mm. Hg to the forefinger. Tigerstedt (1919) places the commencement of a marked fall in pressure about the region where the diameter of the artery becomes less than approximately 2 mm. The diameter of the ophthalmic artery averages 1.5 mm. (Whitnall, 1921) to 2 mm. (Merkel and Kallius, 1910); we would therefore expect its pressure to be little less than that of the aorta. The central artery of the retina has a diameter at its commencement of 0.28 mm. (Henle, 1876) and at its termination in the eye of 0.23 mm. (Schwalbe, 1874); a fall of pressure will therefore take place here. The branches of this artery at the disc are about 0.1 mm. in diameter (Hess, 1919); and here again a further fall will occur.

III. The Venous Pressure

HISTORICAL SURVEY

In the estimation of the venous pressure of the eye five different methods have been employed. The inadequacy of the various

Sea. f orh. I 681

forms of technique which have been adopted to meet the requirements of what is admittedly a difficult problem is seen in the complete lack of agreement in the results which they have produced. Not only do their findings differ from each other, but some of the measurements obtained by the same observers using the same method involve a variation in themselves of over 100 per cent.

These experimental procedures may be divided into three categories according as they ascribe to the venous pressure a value higher than, or equal to, or less than the intraocular pressure.

1. *Methods showing a venous pressure higher than the intraocular pressure*

The direct manometric method.—Weiss (1920), experimenting on rabbits, inserted a cannula directly into the superior vortex vein as it comes into relation with the superior rectus muscle, and thus measured the pressure directly. He obtained results varying from 33 to 63 mm. Hg, and he found the venous pressure invariably considerably higher than the intraocular, the ratio between them varying from 12 :10 to 19 :10. Lullies (1923), using the same technique in dogs, came to the same conclusion. His results vary from 21 to 39 mm. Hg : in two cases the venous and the intraocular pressures were approximately equal, in the remaining four the venous pressures were considerably higher.

The blockage of a vortex vein, however, by a manometer involves the production of a hyperaemia with which the collateral venous channels are unable to cope, and the normal pressure equilibrium is thus completely disturbed. In the rabbit the vortex veins are easily ligated without further disturbance by passing a ligature subconjunctivally round the tendinous insertion of the corresponding rectus muscle. A ligature passed in this way round one of the vortex veins thus stopping the circulation in the same manner as an end-on manometer, involves a rise of tension of about 20 mm. Hg, a result which occurred with great consistency in my experiments. The inadequacy of the anastomosing channels can be easily seen in the albino in the marked hyperaemia which comes on immediately thereafter, limited to the segment of the iris drained by the vein in question. If the operation is repeated on the inferior aspect of the eye large tensions up to 70 and 80 mm. Hg are obtained, while at the same time the anterior chamber becomes shallow, the pupil dilated, the iris becomes hyperaemic, and the vessels of the fundus engorged and swollen; later the cornea becomes opaque, and further examination is impossible.

In the dog the same reaction occurs, although it is less pronounced : ligature of the superior veins induces a rise of tension from 23 to 30 mm. Hg, of the two sets, to 50 mm. Hg. In the cat a somewhat intermediate result is obtained, the tension

rising from 25 mm. Hg to 40 in the first case, and 60 in the second. It is to be noted that, correspondingly, Weiss working on the rabbit got higher figures than Lullies on the dog. The difference is due to a difference in the efficiency of the venous anastomoses in these animals. In the dog there is a direct anastomosis between the anterior ciliary venous system and the vortex veins, in the rabbit there is not; on obliterating one efferent channel in the dog, therefore, more anastomotic avenues are available for carrying on the circulation than in the rabbit, and the reactionary hyperaemia is less marked. The results of both observers thus involve a large error; Lullies's measurements are more nearly correct than those of Weiss, and of these the lowest are the nearest to the truth.

2. *Methods showing a venous pressure lower than the intraocular*

(*a*) *The compression method.*—Seidel (1923,b) and Hiroishi (1924) estimated the pressure in the episcleral veins as they are seen under the conjunctiva near the corneo-scleral junction by applying over them a pressure chamber connected with a manometer, and observing the point at which they were obliterated. Their results were:—

7 to 11 mm. Hg in the rabbit.
11 to 18 mm. Hg in the dog,
10 to 14 mm. Hg in man,

the intraocular tension in each case being about 25 mm. Hg (Schiötz). The measurement here made, however, is that of the pressure of the veins outside the eye—virtually in the orbit, and to assume that it represents the intraocular venous pressure, as Seidel does, is quite unjustified.

(*b*) *The method of injection.*—A very large number of experimenters from the time of Schwalbe (1868) and Leber (1873) have drawn conclusions as to the mechanism of the exit of the intraocular fluids and the relative levels of the pressures in the eye and in the veins from experiments involving the injection of dyes. The great diversity of the conclusions arrived at is alone sufficient for the condemnation of this method of approaching the question. Most of the earlier experimental work was complicated by the fact that the injection material used was of such nature as to bring into play such disturbing factors as the forces of diffusion and osmosis and the phagocytic activity of the endothelial cells lining the anterior chamber, but the method has lately been taken up with greater care by Seidel (1922,a) and Hiroishi (1924). These investigators made use of non-diffusible dyes made up in solutions isotonic with and hypertonic to blood, and injected them into the eye under "normal" and "sub-normal" pressures. Since the dye was seen in the episcleral veins in a very short time, its appearance

mojloff (1926) - Seidel's technique and found ※
That the venous pressure at the limbus was
greater than the I.O.P.
By Bailliart's method P. C.V.R > I.O.P.

iliary arteries at limbus (Seidel's m. chamber) 27-30/80-85.
ciliary veins - " " - 23-27 mm Hg
I.O.P. 16-18 mm Hg.
Radial artery - 65/95.
(C.a.R. (Bailliart) 35/60-70.
cuco-ciliary veins at disc. (choroidal) 23-27 mm Hg.

there was taken as necessarily indicating a fall in hydrostatic pressure between these two points.

The very large amount of work which has been done on the intraocular injection of dyes lends itself readily to criticism, and the physiological deductions that have been drawn from it are only to be accepted with reserve. The introduction of a needle into the eye, and the injection thereinto of any material profoundly alters the pressure equilibrium, and completely changes the circulatory conditions. No matter how sharp the needle employed, a considerable amount of force is required to transfix the tough cornea, and the immediate result of this impounding force will be to raise the intraocular pressure considerably.

The great pressure disturbance which follows the application of a small amount of external force to the globe is well seen in the effects produced by the contractions of the orbital musculature. (See the work of Parsons, 1903; Halbern, 1909; Lederer, 1912; Levinsohn, 1916; Wessely, 1916).

The pressure will be further raised temporarily once the needle is introduced into the globe by the additional volume required to accommodate the needle—a small volume in itself, but, when translated into terms of pressure, its influence becomes by no means inconsiderable when the very small distensibility of the sclerotic is borne in mind. The effect of the temporary rise of pressure conditioned by these two factors will be to compress and force out some of the fluid contents of the globe; the readiest exit will be found by the blood in the exit veins, and this will be supplemented by a considerable part of the blood in the turgescent venous reservoir of the choroid which they immediately drain. When the needle has entered, pressure equilibrium will rapidly tend to re-establish itself, and the elasticity of the sclerotic will tend to make the eye resume its normal state. At this point there will be a very much lower pressure than normally in the depleted exit veins, and fluid will tend to be drawn into them by hydrostatic forces from all available sources, including the aqueous with any dye-stuffs injected into it. Further the transfixion of the cornea with the needle is a severe trauma to a highly innervated structure, and is a procedure which causes a considerable reflex vasomotor disturbance, with a further disturbing effect on the intraocular pressure. This effect, which forms part of the reflex noci-ceptive syndrome (Bayliss, 1923), can be produced by the mere pricking of the cornea with the point of a needle (Magitot, 1923).

The complete dislocation of the circulation thus brought about by the summation of these three influences—an immediate anaemia followed by a marked hyperaemia—can be easily observed by introducing a needle into the eye of an albino rabbit, the behaviour of whose vessels can be readily seen. Any immediate results of injections, therefore, must be neglected as far as physiological conclusions regarding the normal conditions are concerned, and

after the initial disturbance has subsided, if any of the injection material at all flows into the eye, the pressure in the feeding reservoir is obviously higher than the intraocular pressure: to speak of injecting fluid under "normal" pressure into the anterior chamber is a contradiction in terms. Seidel further claims that a flow occurs from the anterior chamber into the veins with a pressure head as low as 10 mm. Hg below the normal intraocular pressure, *i.e.*, at 15 mm. Hg; this, therefore, he argues, represents the venous pressure. This result was obtained by withdrawing a small quantity of aqueous from the eye, and then observing the flow of dye-stuff from the reservoir adjusted to a height of 15 mm. Hg. But the withdrawal of a small quantity of aqueous reduces the intraocular pressure to the atmospheric level, and as will be shown later, when the chamber pressure falls, the venous pressure falls likewise; it will certainly fall below 15 mm. Hg. The flow of fluid as observed by Seidel will then necessarily take place, but it is a flow occurring in greatly reduced pressure conditions, and it can give no information at all about the pressure relationships which normally obtain.

The following experiment of my own, which has been repeated several times under conditions approximating as closely as possible those described by Seidel, is of interest. Two needles were introduced into the anterior chamber each of which was connected with a reservoir, one containing saline, and the other a solution of indigo-carmine, the former communicating with the eye by means of a tube containing an air-bubble. Both reservoirs were kept at the level of the normal intraocular pressure for some time after the initial disturbance subsequent to the insertion of the needle had subsided. That this state existed was made clear by the fact that no fluid either entered or left the eye as was indicated by there being no movement of the air-bubble. The bulb containing the coloured solution was than raised 1.0. cm., and the other lowered 0.3 cm., thus allowing a slow circulation of coloured fluid from the first, through the eye, into the second, governed by a pressure head of 1.3 cm. water (1 mm. Hg). The episcleral veins were illuminated by a powerful beam of direct light and observed through a dissecting microscope, but in no case was there any sign of this discoloration, even after some time. If, as Seidel claims, there is a pressure gradient of 10 mm. Hg between the aqueous and the veins, it would seem to follow that some of the fluid would follow this path, rather than flow down a gradient of only 1 mm. Hg.

It is evident, therefore, that it is impossible to deduce any conclusions of physiological value from the method of injection. The most cogent commentary that can be made upon it is to quote the results of three investigators who have used it. In order to get filtration, Hamburger (1914) considered he required a pressure of 30 to 40 mm. Hg, Leber (1903) a value "a little above" the intraocular pressure, and Seidel (1922) 10 mm. Hg below it. All three experimented upon living rabbits' eyes, all three used indigo-carmine, and all three took as the index of flow the discoloration of the espiscleral veins.

(*c*) *The formation of a fistula.*—With a view to determining the relative pressures of the aqueous and the venous exits, Wegefarth (1914) introduced a fine needle into an episcleral vein in the dog, pushed it down through the sclerotic into the anterior chamber, and then withdrew it and ligated the vein. Since no

blood flowed into the eye, he concluded that the chamber pressure was slightly greater than the venous pressure. The fistula was, however, made when the normal pressure relations were completely dislocated by the introduction of the needle, it was made through raw tissues, and immediately thereafter the vein was ligated, thus stopping the blood flow and providing every opportunity for the formation of clots in the eddy thus formed. Wegefarth satisfied himself of the patency of the channel so formed after 48 hours by demonstrating a flow of blood from the fistula on paracentesis, and by tracing an injection mass injected into the anterior chamber directly up the track. Neither of these tests is conclusive. On paracentesis in the normal eye, owing to the withdrawal of the supporting pressure of the aqueous a capillary engorgement is induced, so great as to lead sometimes to minute haemorrhages, and always to considerable haemorrhage if a small stimulus, as pressing on the abdomen, is added (L. Hill, 1912); if normal vessels are ruptured under these conditions, a clot recently deposited at the time of fistulization will be readily dislodged. Conversely, we would expect the same result to follow the injection of any quantity of fluid into the anterior chamber.

A similar argument has been employed at various times derived from the behaviour of the operative fistula left after an iridectomy. Fuchs (1896) pointed out that after cutting the iris tissue no cicatrization took place, and that after the operation of iridectomy, the lumen of the iridic veins appears histologically to be potentially open; Fuchs's observations were later corroborated by T. Henderson (1907) and McBurney (1914). Since such an operation can be conducted without any haemorrhage it is therefore argued that the blood pressure in the veins may be slightly less than, but is more probably equal to the intraocular pressure. The argument exposes itself to a *reductio ad absurdum*: when the wound is made the eye is open and therefore at atmospheric pressure, and for some considerable time afterwards the intraocular pressure is subnormal; the arteries as well as the veins are cut across; since there is no bleeding it follows that the arterial pressure as well as the venous must be equal to the atmospheric pressure. Clearly the explanation is to be sought, not on any lines of pressure difference, but in the fact of the spongy tissue of the iris allowing the vessel walls to retract immediately on section, a process aided by the temporary anaemia brought on by the mechanical traction upon the iris, and the vaso-constriction induced by the manipulation of a structure so highly innervated. Moreover, at a later date, when normal pressure conditions have been restored, a considerable amount of haemorrhage may occur from such a wound, an occurrence which usually takes place in infective cases, when presumably a thrombus formed at the time of operation becomes softened. This brings about the formation of a fistula under conditions of pressure more nearly approaching the normal, and an opposite result is demonstrated.

3. *Methods showing the venous pressure sometimes greater than and sometimes less than the intraocular pressure*

The dynamometric method of Bailliart.—With a technique analogous to that which he elaborated for the measurement of the pressure in the retinal arteries, Bailliart (1918,b) has made use of his dynamometer to estimate the pressure of the retinal veins relative to the intraocular pressure. On compressing the eye, the veins at the optic disc are observed simultaneously. In a certain proportion of eyes there is a spontaneous pulse in the veins just at their exit at

the optic nerve; the increase of pressure on the globe necessary to abolish this pulse is a measure of the height of the venous pressure over the intraocular. In others which show no spontaneous pulse, if the globe is compressed, a pulse is sometimes induced: again the pressure increment represented by the amount of force required to induce the pulse gives the value of the venous pressure over the intraocular. In the remainder, in whom no pulse can be elicited on pressure, the venous pressure is constantly below the intraocular. These deductions Bailliart formed on very little evidence. I shall suggest presently that I have obtained experimental proof that they are wrong. In the meantime, they lay themselves open to criticism, for many factors other than mere pressure differences enter into the mechanics of the venous pulse of the eye.

The Venous Pulse.—The venous pulse in the eye is in every way comparable with the arterial pulse, of which it is essentially a direct continuation. The essential factor in its mechanism would appear to be a centrifugal pulsatory wave from the arteries which is continued through the capillaries into the veins. This was early noted ophthalmoscopically by Wadsworth and Putman (1878), and verified by Haab (1897) and Türk (1899); with the magnification afforded by the Gullstrand ophthalmoscope, it is apparently constantly seen in normal eyes as a widening and narrowing of the retinal reflexes, which may be traced from the finest venous ramifications up to the disc, occurring post-systolically (Kümmell, 1915). In pathological conditions, as in aortic insufficiency, where the arterial pulse is exaggerated, this "progressive peripheral venous pulse" may be very apparent (Quincke, 1868; Raynaud, 1874; Helfreich, 1882; Rählmann, 1885; Osten-Sacken, 1890), and in those cases of cardiac lesions where the contractions of the right auricle and left ventricle are dissociated, Kümmell (1925) found that the venous pulse in the eye follows the ventricular rhythm, thus demonstrating its dependence on the arterial pulse, as well as its non-dependence on the activity of the right auricle as transmitted up the jugulars. The continuation of this "expansile" pulse into the venous stream depends on two factors: first, the physiological constriction of the veins at or near their exits (Holtz, 1889), and secondly, the fact of the incompressible ocular contents enclosed under tension by the elastic sclera tending to make the circulatory system react to pressure variations more after the manner of a series of rigid tubes than occurs elsewhere in the body (Türk, 1899).

At the exit of the veins from the eye a further factor comes into play. The pressure wave of the arteries at systole is conducted directly by the intraocular contents and rhythmically compresses the veins (Donders, 1855). Elsewhere in the eye one part of a vein cannot dilate to allow another to collapse owing to the increased intraocular pressure acting equally, but at the exits a

sudden expulsion of blood is possible, for here the vein is passing from a region of high pressure (the eye) to a region of low pressure (the optic nerve and orbit) (v. Graefe, 1854). A "pressure" pulse may therefore occur at the exits synchronous with arterial systole (Comberg, 1924). At the disc the occurrence of this pulse is probably aided by the greater distensibility of this part of the wall of the globe (the lamina cribrosa) under pressure (Jacobi, 1876), the influence of which factor is seen in the occurrence of a spontaneous "pressure" pulse at a distance from the venous exits in cases of posterior staphyloma (Thorner, 1902).

Since this pressure pulse was first noted by van Trigt (1853) and Coccius (1853) it has been remarked and discussed by numerous observers. It occurs at the disc in a large proportion of normal eyes—70 to 80 per cent., Lang and Barrett (1888), 58 per cent., Bailliart (1918), 46 per cent., Elliot (1921). It occurs similarly in animals: sheep and pigs (v. Graefe, 1854; Helfreich, 1882), dogs (Michel, 1881), and cats (Howe, 1885). On increasing the intraocular pressure slightly by the application of external pressure to the globe its amplitude is usually increased, or a non-spontaneous pulse may be elicited, as was first noted by v. Graefe (1854) in the retinal veins, and by Laqueur (1877) and Ulrich (1880) in the vortex veins. Sometimes a non-spontaneous pulse is not thus elicited—in the retinal vein of man in 30 per cent. of cases (Bailliart, 1918), or in 25.5 per cent. (Elliot, 1921); or in the vortex veins, both in man (Jacobi, 1876) and in animals (Becker, 1872; Helfreich, 1882). It would seem, however, unjustifiable to assume, as Bailliart and many others do, that the behaviour of this pulsation is indicative only of the pressure relations between the eye and the veins. (Compare Priestley Smith, 1917; Bauermann, 1925.)

In the first place a pulsatile flow at the exit does not necessarily imply an equality of pressure on both sides of the venous wall: if a rhythmic force is acting on the vein at the exit, a rhythmic outflow of blood will be produced even if the external force (the intraocular pressure) is less than the internal (venous) pressure, particularly if its action be enhanced by a centripetal pulse derived from the arteries. Such a phenomenon can readily be demonstrated on a simple mechanical model.

In the second place, although depending primarily on pressure differences, many other factors must be considered in the occurrence of the pulse, and in the variation of its occurrence. In the eye itself, the state of rigidity of the sclerotic is a source of variation; the less distensible this structure is, the less "give" before the arterial pulsation, and the more likelihood of the production of a venous pulse. Similarly the state of the arteries is a determining factor, depending on the degree of sclerosis of their walls; with extreme sclerosis there is often no demonstrable ocular pulse at

all (Foster Moore, 1917). Further, the arrangement of the arteries exerts an influence: the compression of a vein near the disc by an artery favours the collapse of the former distal to its crossing, the pressure here being lowered since the stream is dammed back (Priestley Smith, 1891; Marcus Gunn, 1892). A high blood pressure without accompanying sclerosis may involve a more ready and marked pulsation (Basch, 1876), so also do all the conditions which lead to an increased amplitude in the arterial pulse, as well as any factor which leads to the freer communication of this pulse through to the veins, as for example, capillary dilatation (Lieger and Forster, 1881).

Further, since pulsation implies the displacement of fluid, the amount of pulsation and its incidence will be influenced by the ease of the exit afforded the fluid—a very variable condition.

Having left the eye the retinal vein runs along the optic nerve alongside the retinal artery, often sharing a common sheath with it; the pulsation of the artery in systole will oppose the free expansion of the vein as it simultaneously seeks to accommodate the pulsating out-flow of blood (Jäger, 1854), and the proximity of the two will introduce a variable factor. Further, the retinal vein usually runs directly into the cavernous sinus: here there is a positive pulse, also at systole—the cerebral venous pulse—which will oppose the ocular venous pulse, and the ready exit of blood from the eye (Helfreich, 1882). That the influence of such back-pressure is not negligible is seen in the congestion which occurs in the frontal and ophthalmic veins on laughing, or coughing, or in conditions of cerebral pressure. A further variation depends on the mode of termination of the vein: if the retinal vein does not communicate directly with the cavernous sinus, it joins the superior, or more rarely, the inferior ophthalmic vein; in this case the opposing pulse from the cavernous sinus will be less markedly felt; and a further variation in the conduction of the pulse will depend on whether the superior ophthalmic vein is dilated into an ampulla or constricted at its junction with the cavernous sinus. Again, at systole, blood is driven both from the eye and the cerebral sinuses, and room is found for it in the anastomosing orbital veins; at the end of systole this excess of blood will tend to return to the eye, and this helps to form the ocular pulse by distending the veins near their exit at the commencement of diastole (Haab, 1897); a further variable depends on the efficiency of these anastomoses which are by no means constant. All these variables are further complicated when it is remembered that the pulse is induced by pressing the eye backwards into the orbit, thus obstructing the venous outflow by a variable amount.

Whenever the outflow from the veins is sufficiently obstructed the venous pulse will not occur, no matter what the pressure relations are. This is seen experimentally in the abolition of a pulse in any condition of venous engorgement, as by prolonged expiration (Trigt, 1853; Donders, 1855), on raising the arms above the head (Manz, 1874; Laqueur, 1877), on compressing the jugulars or the thorax (Helfreich, 1882), or on kinking the vein by rotating the eyes to the side (Graves, 1922).

The occurrence or non-occurrence of a venous pulse is therefore no indication whatever of the relative pressures in the eye and the veins; nor is the artificial pressure necessary to be applied to the eye to induce a non-spontaneous pulse any accurate measure of the normal pressure difference between the two, for since, as will be shown, the venous pressure varies with the intraocular, the latter cannot be approximated to the former without altering it

also, thus leaving the initial difference between them quite unknown. *In any technique for the measurement of the venous pressures of the eye it is absolutely essential that the normal intra-ocular pressure be undisturbed, and that the normal circulation be in no way interfered with.*

EXPERIMENTAL TECHNIQUE

In the investigation of the venous pressure dogs were employed, since they are the most convenient laboratory animal with tolerably large veins, and in them the anastomoses of the venous channels,

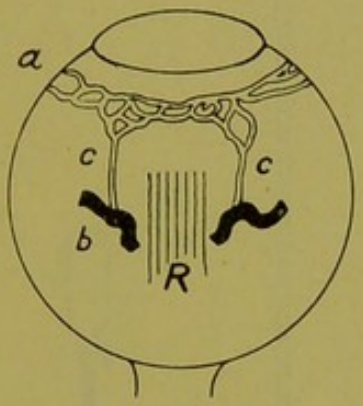


FIG. 4.—THE SCLERAL VEINS OF THE DOG.

The scleral veins of the dog from an injected specimen.

a. The circle of Hovius.

b. The vortex veins leaving the eye post-equatorially in relation to the rectus muscle R.

c.c. The anastomosing veins between the two.

a. and *c*.—drawn in open lines—lie within the scleral tissues.

b.—drawn black—come outside of the sclera.

as we have seen, are very efficient. In them the venous blood from the choroid is drained by two systems (Fig. 4) : (*a*) from the anterior part of the choroid, the ciliary body, and the iris by a complicated, inter-anastomosing ring plexus in the substance of the sclerotic which takes the place of the canal of Schlemm, emptying into a second ring plexus running round the corneo-scleral junction, near the surface of the sclerotic but still in its substance, being covered by a thin layer of scleral tissue through which it is clearly visible; (*b*) from the main body and posterior part of the choroid by four or five vortex veins which leave the eye post-equatorially, and are carried away *via* the recti muscles. The anterior plexus—the circle of Hovius—is drained by two veins or groups of veins running forwards to join the orbital veins, and by intra-scleral vessels, usually one above and two below, running backwards to anastomose with the vortex veins,

lying, like the circle of Hovius itself, in the outer layers of the sclera, and visible through its outermost fibres.

(1) *The Pressure in the Intra-scleral Veins.*—The technique employed in the measurement of the pressure in the intra-scleral veins was a modification of the micro-pipette method already

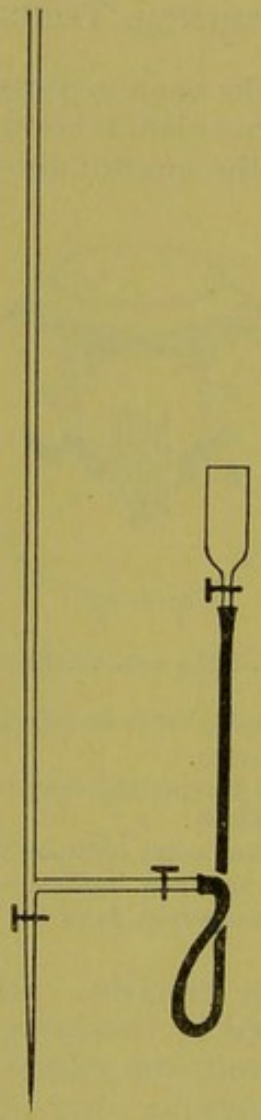
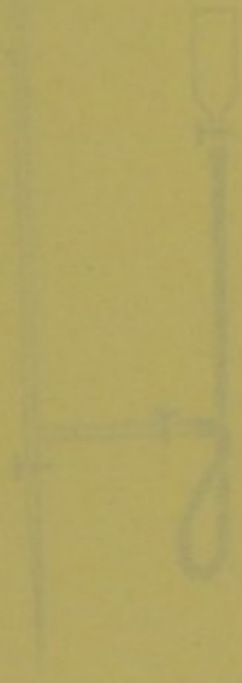


FIG. 5.—PRESSURE IN THE INTRA-SCLERAL VEINS.

described in the measurement of the arterial pressure. Anaesthesia was induced by chloroform-ether, and maintained by intra-venous chloralose. The scleral veins were reached by slitting the lids back to the orbital margin in the mid-line, and keeping them retroverted by stitches. The conjunctiva was then opened behind the limbus and dissected back until the veins were exposed. A dissecting microscope was then focussed on the exposed sclera, direct illumination being obtained from a strong light concentrated by a lens system.



A piece of glass tubing (Fig. 5) 4 mm. in diameter was drawn to a fine point at the end, the process being repeated several times so as to obtain a short and sharp tip. A side arm near the point was connected by a rubber tube to a reservoir filled with physiological citrate solution; as this was raised and lowered the water column in the tube followed suit, and a pressure was therefore exerted at the capillary tip equal to the height of this column. When the pipette is inserted into the lumen of a vein blood will flow into the tube if the venous pressure is higher than the pressure of the citrate column, if the venous pressure is lower, citrate will flow into the vein. By raising and lowering the reservoir and observing the capillary point through the microscope, a very exact end-point can be reached. The scleral veins of the circle of Hovius and the anastomosing veins just described are ideal for the method, since under the microscope they appear large enough for the point of the capillary pipette to be introduced into them without hesitation and for it to be held in their lumen for some time; meantime the investing scleral tissue, by keeping the vessel patent, ensures the ready entrance of the point, and at the same time allows perfect freedom for the continuance of the circulation, thus preventing any hyperaemia or damming up of the stream. The lateral venous pressure is thus measured, while retaining a free and undisturbed circulation and leaving the intraocular pressure conditions wholly unaffected.

Precautions were taken to record the intraocular pressure accurately with as little disturbance as possible. In the first experiment it was taken by a compensated saline manometer, using an air-bubble inserted into a horizontal capillary tube as an index of equilibrium, and no measurements were taken until 30 minutes after the pressure reaction following its introduction into the eye had settled down. In the second experiment the tensions in the two eyes were taken by a tonometer, and were found to be equal; although as we have seen this cannot be considered as accurate for absolute measurements construed as pressures, especially as applied to the eye of a dog, under the conditions of the experiment they may be accepted as comparative measurements, and the pressures in the two eyes may be taken as identical. The pressure was then taken in the second eye by the compensated manometer, and the reading transposed to the first. In the third experiment the tension was taken by the tonometer, and the corresponding manometric value determined in the other eye. The venous pressure in the first eye was then measured; the manometer was then inserted, and after equilibrium had been established at the original intraocular pressure for some time, the venous pressure was again taken, and readings similar to the first were obtained.

The results of three experiments are given in Table VIII.

TABLE VIII

No. of Dog	Intraocular pressure	Venous pressure	Difference V.P — I.O.P.
1	22 mm. Hg (300 mm. saline)	23.5 mm. Hg (320 mm. saline)	1.5 mm. Hg
2	26 mm. Hg (350 mm. saline)	28 mm. Hg (380 mm. saline)	2 mm. Hg
3	25 mm. Hg (340 mm. saline)	26 mm. Hg (350 mm. saline)	1 mm. Hg

The venous pressure in the intra-scleral veins is therefore slightly above the intraocular pressure, the pressure difference averaging 1.5 mm. Hg.

(2) *The Pressure in the Extra-scleral Veins.*—In the measurement of the extra-scleral venous pressure, the compression method of v. Recklinghausen (1906) and Hooker (1911) was used, as had been adopted by Seidel (1923,*b*). The pressure was determined by placing over the vein a glass cylinder (*a*, Fig. 6) whose base was formed by a membrane of softened cellophane, and which was placed in communication with a manometer tube (*b*) and reservoir (*c*) containing warmed saline. The intraocular pressure was taken as in the previous experiments both by manometer and tonometer. The estimation was made in the subconjunctival veins near the corneo-scleral junction, that point when the vein was first definitely obliterated being taken as standard of measurement : this precaution is necessary in order to eliminate the factor of hyperaemia, since if the pressure be maintained on the vein for any length of time, the vessel, originally emptied of blood, refills and begins to pulsate, and a vein which originally required 15 mm. Hg to obliterate it, now requires a pressure of 20 mm.

Over a series of twelve experiments in dogs results comparable to those of Seidel were obtained, although they were on the average slightly higher. The pressure in the episcleral veins soon after their exit from the eye varies from 5 to 8 mm. Hg below the intraocular pressure, the average being 7.2 mm. It may be repeated, however, that the interpretation put upon these results by this observer is not admitted—that this represents the intraocular venous pressure.

The rapid drop in magnitude is only to be expected after leaving the eye, the pressure level falling quickly to that obtaining in the veins of the orbit and head. This, even in man in the upright position, is always a small positive pressure, although above the level of the heart—a physical consequence of the flow of liquids through collapsible tubes. The venous pressure is determined by the hydrostatic difference of the point under con-

sideration and the thoracic cavity, and the frictional resistance, which is governed by the cross-section of the veins and the rate of flow. On any excess of pressure from outside the readily yielding veins collapse, and this entails a diminished sectional area and an increased frictional resistance. The negative hydrostatic pressure which would obtain in a rigid tube above the level

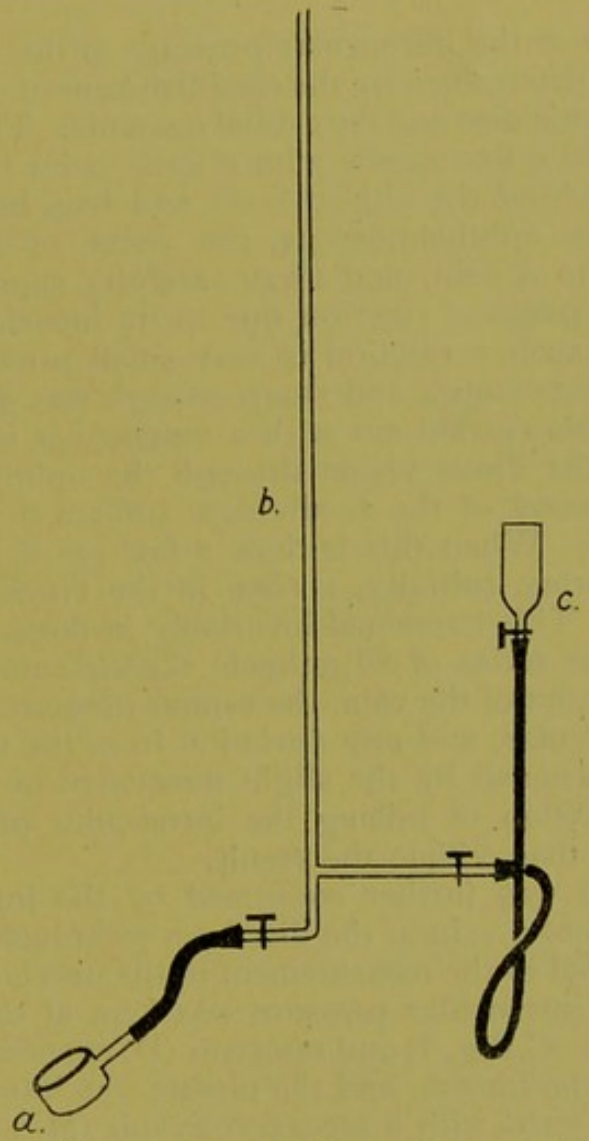


FIG. 6.—PRESSURE IN THE EXTRA-SCLERAL VEINS.

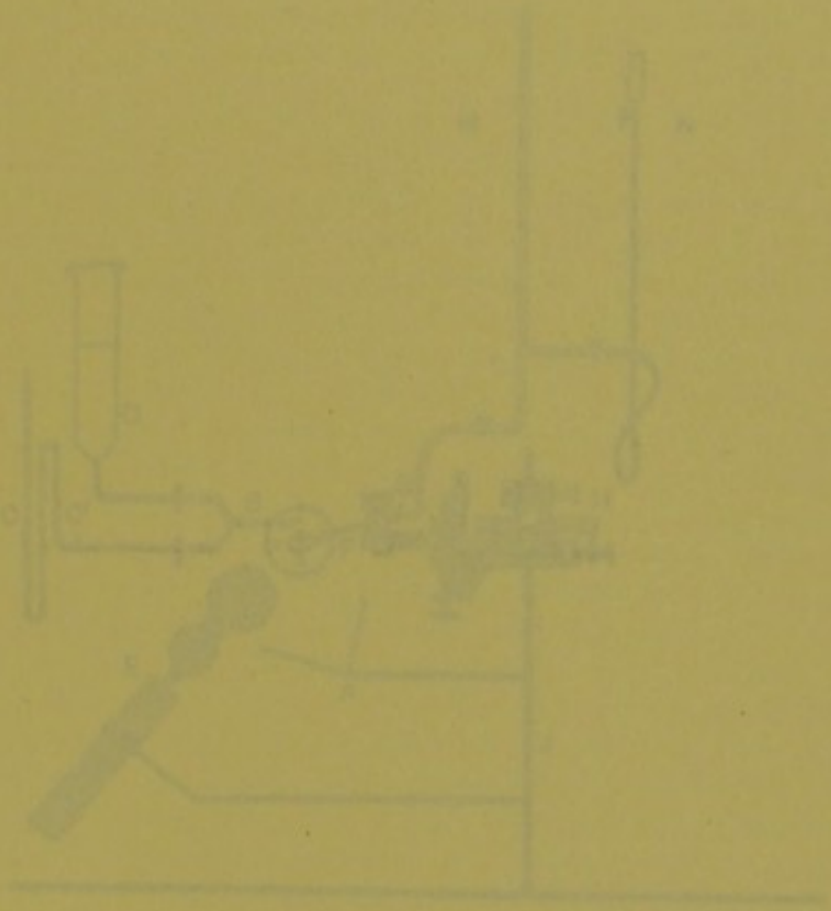
of the heart is thus automatically compensated for, and negative pressures are registered only when the veins are kept permanently open by their fascial investments as in the lower part of the neck.

(3) *The Pressure in the Intraocular Veins.*—The pressure in the intraocular veins was studied in the veins of the retina. Evidence has already been brought forward to point to the fact that the exit pressures in the uveal and retinal circulations are identical and vary together; and the vessels of the latter lend themselves to investigation more readily, since they are seen by

the ophthalmoscope at a sufficient magnification to permit easy observation, and they are less under the influence of a delicate vasomotor mechanism which reacts to any intraocular manipulation by an immediate response. On pricking the iris large pressure variations invariably follow which would completely vitiate any result obtained by experimental procedures involving this structure.

The relation of the intraocular pressure to the venous pressure in the eye was determined by the establishment of a fistula between a vein on the optic disc and the orbital contents. The outer canthus was slit up, and a fine needle with a knife point inserted through the sclerotic behind the ciliary body and lens into the vitreous. Guided by the ophthalmoscope, the point of the needle was approximated to a vein, and there carefully supported for some time until the pressure reaction due to its introduction had subsided. That such a reaction is very small provided the needle employed is fine enough and sharp enough was demonstrated by repeated controls carried out with a manometer inserted into the eye. Still under direct vision through the ophthalmoscope, the slightest movement of the needle now suffices to pierce the vein with the point. When this is done a fine jet of blood flows out slowly, and forms, initially, a cone in the vitreous in the track of the needle. This happened invariably in dogs, in cats, and in rabbits over the series of 25 animals experimented upon. Since the blood flows out of the vein, the venous pressure must be higher than the intraocular, and any deviation from the normal pressure conditions occasioned by the slight movement of the needle will act in the direction of raising the intraocular pressure, and so confirm rather than vitiate the result.

This relation was further confirmed by the introduction of a micro-pipette into a vein at the disc by a technique similar to that already described in the measurement of the pressure in the retinal arteries. The intraocular pressure was kept at the normal level by a manometer (C, Fig. 7) and reservoir (D) containing saline as in the previous experiments, and the pipette was introduced into the eye while connected with a second reservoir (M) consisting of an upright tube of 4 mm. bore adjusted to the same level as (D) by a levelling bulb (N). When the reaction subsequent to the insertion of the two instruments had died down, the pipette was made to enter the vein with the aid of the micro-manipulator. Again, in every case, blood flowed from the vein up the pipette, and the saline column in the reservoir in connection with it rose by an amount varying from 2 to 3 cm. It is not claimed that this measurement gives an accurate determination of the normal difference between the two levels, since the intraocular pressure, and with it the venous pressure, must have been upset to some degree by the necessary manipulations. In the case of the entrance



arteries this small error will be of no consequence, but it cannot be safely neglected in measurements so nearly alike and so intimately varying as the chamber pressure and the venous pressure. The only deduction that can justifiably be made is that the venous pressure is higher than the chamber pressure, and that the difference between them is not large—a deduction borne out by the fact of the occurrence of a spontaneous venous pulse, and

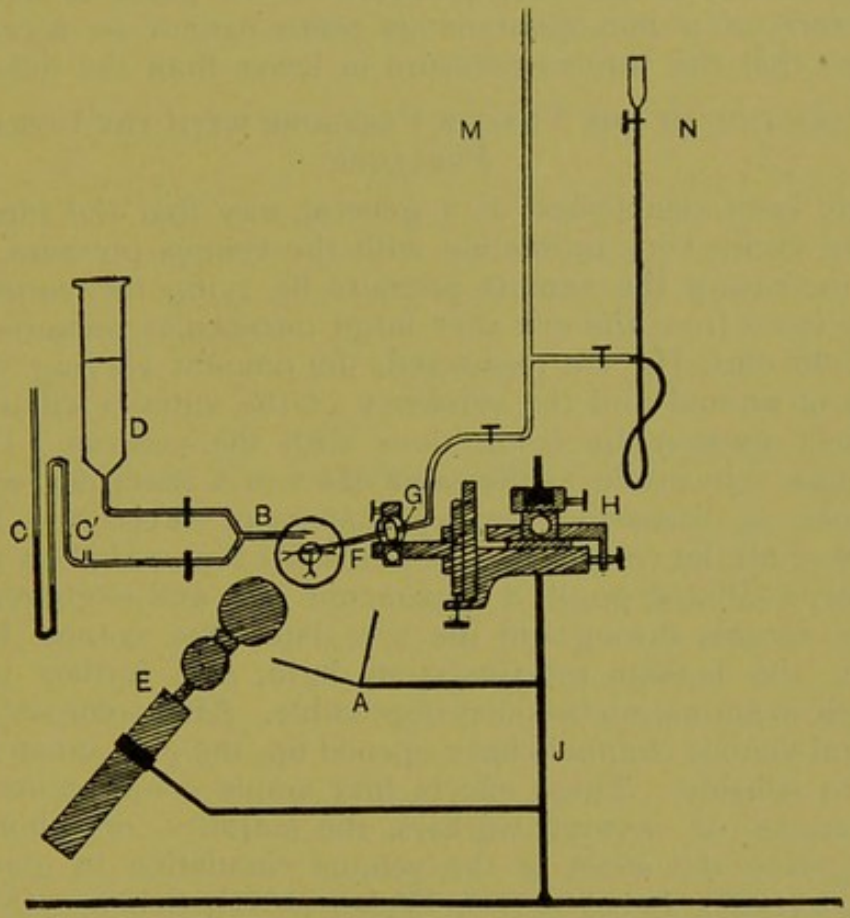


FIG. 7.—THE INTRAOCULAR VENOUS PRESSURE.

the constriction that occurs at the veins at the disc on the application of a small amount of pressure to the lids (T. Henderson, 1914).

As mentioned above, Bailliart (1918,b), and Magitot (1922) consider that those cases wherein no venous pulsation can be elicited on pressure should be interpreted as having a venous pressure lower than the intraocular. We have seen that such a phenomenon occurs also in animals; it is particularly well seen in some cases in cats. In these the establishment of a fistula and the insertion of a micro-pipette has given, in my experiments, the invariable demonstration of a higher pressure in the vein than in the eye. When the delicate nature of the venous walls is kept in mind, it is difficult to imagine how they could resist any such external pressure as Bailliart postulates without collapsing.

Even the large superficial veins of the arm, protected as they are by the skin, collapse under an external pressure of about 0.8 mm. Hg (Moritz and Tabora, 1910). To maintain the circulation, therefore, it would seem to be necessary that the venous pressure should be always higher than the intraocular; and my experimental findings point to the fact that this is constantly so. In any case they definitely show that Bailliart's contention is unjustified, and that the failure of increased pressure on the globe to induce the appearance of a non-spontaneous pulse cannot be accepted as evidence that the venous pressure is lower than the intraocular.

THE VARIATION OF THE VENOUS PRESSURE WITH THE INTRAOCULAR PRESSURE

It has been established in a general way that the intraocular pressure varies very intimately with the venous pressure.

On increasing the venous pressure by tying the vortex veins as they issue from the eye very large intraocular pressures up to 80 and 90 mm. Hg are registered, the amount varying with the species of animal and the efficiency of the anterior ciliary veins and their anastomotic connections with the vortices. Ligature of a single vein produces the same effect to a lesser degree, as we have seen in discussing the experiments of Weiss and Lullies; ligature of all the veins produces in a short time a shallow anterior chamber, a dilated pupil, a hyperaemic iris, and engorgement of all the vessels throughout the eye—later the cornea becomes opaque, the tension remains stony hard, and further ophthalmoscopic examination becomes impossible. After some time, when collateral venous channels have opened up, the glaucomatous state tends to subside. These effects find ample confirmation in the observations of several workers, the majority of whom were investigating the effect of the venous circulation in glaucoma: Adamük (1867), Leber (1873), Weber (1877), Schöler (1879), Alt (1884), v. Schultén (1884), Ulrich (1889), Koster (1895), van Genus (1899), Bartels (1905), and Magitot (1923). A similar rise occurs on ligating the veins at the back of the orbit (Hiroishi, 1924), or on obstructing them with irritant injections (Birch Hirschfeld, 1909). The somewhat equivocal results that have been obtained on ligating the jugular veins are readily understood when the very free anastomoses are taken into consideration; thus while Memorski (1865) and E. E. Henderson and Starling (1904) got no constant changes, Adamük (1867), Graser (1883), v. Schultén (1884), and Parsons (1903) produced only slight rises in pressure. When, however, the channels are all simultaneously impeded, the result is more marked, as on passing a ligature round the neck (Bonnefon, 1922), or on compressing the thorax (Mazzei, 1920) or the abdomen (Comberg and Stoewer, 1925), or on obstructing the vena cava (L. Hill, 1912).

A large amount of clinical evidence, moreover, is available on the production of glaucoma by the obstruction of the efferent veins by traumatic, thrombotic, or inflammatory processes. The literature of such cases with their pathological findings include these: Roser (1859), Birnbacher and Czermak (1886), Wagenmann (1892), Stirling (1893), Koster (1895), Römer (1895), Zirm (1895), Bartels (1905), Stähli (1911), Christel (1912), Ischreyt (1912), Rönne (1913), Magitot (1917), Thomsen (1918), Haussen (1918), Seefelder (1924), Guist (1925), Magitot and Bailliart (1925), and Larsen (1926).

Conversely, on decreasing the local venous pressure by venesection the intraocular pressure falls (Schneller, 1857; Bornacini, 1909; Leplat, 1923): the fall is not constant (Pergens, 1899), and its regular occurrence appears to be complicated by vasomotor reflexes. Clinically, phlebotomy has been used in one form or other (by scarification, leeches, etc.) since the time of the Hippocratic writings (*περὶ τόπων τῶν κατ' ἄνθρωπον*, § 13; *περὶ ἑλκων*, § 26,27). Further, in a previous paper (1926,a), I have shown that the intraocular pressure tends to follow the variations in both directions of the systemic venous pressure, sometimes even more closely than it does the arterial pressure.

Similarly when the intraocular pressure is raised, the venous pressure is found to rise coincidently with it. If a mercury manometer with a reservoir is connected with the eye of a cat, and the behaviour of the retinal vessels watched as the pressure is raised, these vessels show no compression, apart from an occasional slight disturbance just at their exit, until a pressure of from 60 to 70 mm. Hg is reached; when the intraocular pressure is raised above this level, ophthalmoscopic examination reveals that the veins, which in the lower stages of pressure increment had been engorged, have now been reduced to mere streaks, the contained blood taking up a granular appearance as the circulation ceases. This experiment finds its analogue in the procedure adopted by L. Hill (1912), who, on opening one of the vortex veins and allowing it to bleed, was able to stop the haemorrhage only when he had raised the intraocular pressure almost to the level of the carotid pressure; and its clinical demonstration is seen in the engorged ciliary veins often so apparent subconjunctivally in cases of glaucoma.

In order to test the relative values more exactly, the venous pressure was estimated in the intra-scleral veins by the capillary manometer already described, while the intraocular pressure was raised by means of a mercury manometer inserted into the eye. On raising the intraocular pressure to a considerable height, the pressure in the exit veins was observed to rise coincidently, but to remain at a level slightly below that obtaining in the eye: thus with an intraocular pressure of 40 mm. Hg the venous exit pressure was found to be 39 mm. At the same time ophthalmoscopic examination showed that the intraocular retinal veins were engorged. A needle was then inserted into the posterior part of the eye as in the previous series of experiments, and the same

result was obtained as formerly on the establishment of a fistula —a haemorrhage into the eye, demonstrating that the intraocular venous pressure was still higher than the chamber pressure. A further reading of the intra-scleral venous pressure was then made, the results of which confirmed the previous findings—that it was slightly less than the artificial pressure maintained in the eye. This would seem to have an important bearing on the physiology of the intraocular pressure, and the mechanism called into action to conserve normality in its variations.

The experimental results of this investigation suggest that the venous pressure in the eye is always higher than the intraocular pressure, and that, while there is a fall of pressure in the veins as they pass through the thickness of the scleral coat, normally the pressure at the exit is still in excess of that in the eye. The eye thus falls into line with the rest of the body, wherein the venous pressure is slightly higher than the tissue pressure, the tissue pressure in this case being represented by the intraocular pressure. Owing to the delicate and pliable nature of the venous walls it is unlikely that the pressure in these vessels can normally be greatly in excess of the chamber pressure, a consideration borne out by the readiness with which venous engorgement is noted pathologically. Conversely, and for the same reason, it is difficult to understand how they could withstand any degree of pressure from outside without collapsing: it is an essential postulate for the maintenance of a continued circulation that the arterial pressure should be higher than the capillary, the capillary higher than the venous, and the venous higher than the intraocular pressure. When the chamber pressure is raised the circulatory system is compressed. That part with the lowest lateral pressure will give way first, that is, the veins at their point of exit will tend to become obliterated. 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 rising with the intraocular. This process will repeat itself in a cumulative manner until the available force from the arteries is exhausted, that is, until the pressure in the ophthalmic artery has been reached, at which point the entire circulation will cease and the vessels will be obliterated.

The venous pressure in any part of the body behaves in an exactly similar manner in similar circumstances. Thus experimentally, by compressing the arm by a sphygmomanometer the pressure of the veins in the limb can be raised to 120 mm. Hg (Frank, 1913); and the same phenomenon is met with clinically in states of venous obstruction from any cause—mediastinal tumour (Eyster and Middleton, 1924), a gravid uterus (Runge, 1924), phlebo-scleritis (Hooker and Eyster, 1908), etc.

While this is going on the pressure in the exit veins just inside the eye has approximated the chamber pressure, the pressure

decrement 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 sclera will now fall below the intraocular pressure. Thus while it is not possible normally, under conditions of raised intraocular pressure, a hydrostatic outflow may be set up, draining off aqueous, acting as a safety valve, and tending to restore the normal pressure conditions of the eye. Such a flow may in some degree be aided through the activity of the ciliary muscle by the pump-action of the scleral spur of A. Thomson (1910).

IV. The Capillary Pressure

Inasmuch as all vital processes take place through the capillary walls the determination of the capillary pressure is of the greatest importance and interest from the physiological point of view: the arteries and veins are merely conducting tubes and the heart a pump, the capillaries are the essential part of the circulation. No one has yet devised a method to measure its value in the eye. Its determination would seem to present many difficulties, since any intraocular manipulation or external pressure applied to the eye at once affects the intraocular pressure, through it the venous pressure, and therefore the capillary pressure, the three tending to rise coincidently but not in parallel. The influence of the venous pressure generally on the capillary pressure (although the reaction is not invariable, Boas and Doonieff, 1924) is usually very readily felt (Bayliss and Starling, 1894; Danzer and Hooker, 1920; Liebesny, 1923); further, on raising the intraocular pressure any effect thereby produced on the capillary circulation is referable not to the capillaries themselves but to the feeding vessels, that is, ultimately to the ophthalmic artery. For this reason all the estimates that have hitherto been made are valueless.

Two such methods have been employed:

(1) *By the stoppage of the formation of aqueous by raising the intraocular pressure.*—This method postulates that the intraocular fluids are a simple transudate of the blood plasma, and that therefore, when the chamber pressure is raised to that in the capillaries, the transudation of fluid will stop. Niesnamoff (1896) thus determined that at 50 mm. Hg the outflow of fluid into the eye from a reservoir was the same for the dead and the living eye; this point he presumed to be the capillary pressure, since in neither case was there any formation of fluid. This observer, however, as far as one can gather, based his conclusions on a single experiment; Grönholm (1900) by the same method found that the outflow was not the same in the two cases at this pressure; and E. E. Henderson and Starling (1904), repeating the experiments, failed to find any agreement. The argument is full of fallacies. We have already

seen that a rise of intraocular pressure necessitates a coincident rise in capillary pressure; in addition, by stretching the globe in the act of raising the pressure, fresh channels of outflow are opened out at the higher pressure levels; and in any circumstances the conditions of the dead and the living eye are in no way comparable.

(2) *By raising the intraocular pressure and observing the capillary flow.*—Bleidung (1924) estimated the external pressure which had to be applied to the globe in order to induce a capillary pulse at the disc, and claimed that this represented the pressure in the small arterioles feeding the capillaries (77 to 91 mm. Hg in man). Deiter (1925) has claimed that the pressure at which the cessation of the capillary flow occurs as it is seen entoptoscopically at the macular region represents the capillary pressure (51 mm. Hg in man). Any such method as these, however, measures neither the pressure in the capillaries nor in the arterioles supplying them, but inasmuch as the whole eye is compressed and the entire circulation in it affected, it measures, with the large and unknown error already pointed out, a quantity depending on the pressure in the ophthalmic artery. Consequently, each measuring the same thing with the same error, Deiter's figures for the capillary pressure are the same as the value given by Bailliart (1923,b, p.50) for the systolic pressure in the retinal artery.

As a result of their investigations both observers have come to the most far-reaching conclusions. Thus Deiter (1925), who finds that the capillary pressure is always in the region of 33 mm. Hg above the chamber pressure, concludes, since this figure represents the partial osmotic pressure of the blood colloids, that the intraocular pressure is determined in all conditions—normally, in glaucoma, and after trephining—by the simple formula: I. O. P. *equals* capillary pressure *minus* osmotic pressure of blood proteins. Upon this foundation he has built up a theory of glaucoma. Since, however, the first two of these measurements are mutually interdependent as cause and effect, by thus manipulating variables without reference to any constant, and dealing in circles with conclusions without a premise, it would seem that with enough ingenuity he could have come to any conclusion he cared.

A direct method of measuring thus being denied us—in the meantime, at any rate—we must resort to an indirect method of estimation, and, by considering first what is known about the pressure conditions in the capillary circulation generally, and seeing how far the results thus obtained can be applied to the eye, base our estimation upon the arterial and venous pressures therein which are now definitely known quantities.

The Capillary Circulation.—The very many attempts that have been made to estimate the capillary pressure in the body have produced an assortment of results so discordant and bewildering as to represent this value as anything from 1 to 70 mm. Hg. Most of the methods which have been employed lend themselves to a considerable amount of criticism, and the various criteria which have been adopted by different observers as a standard of measurement have led to much confusion in the interpretation of the results they have obtained.

The first momentary stoppage of capillary flow seen entoptoscopically: due to venous flow being arrested. It occurs before capillary pressure reached, as is proved by micro-pipette observations (Landis, 1926)

[f]irst momentary stoppage – venous.

micro-pipette method ~~ditto~~ it. denies

[mo]mentary stoppage in venous flow – reversal of capillary flow

Landis 1926. p 588 xxx

6/B1 | 11/4

may have no influence upon it (Boas and Doonieff, 1923). The tone of the capillaries is an independent property, controlled in part by a special capillariomotor nervous mechanism, and in part by complex physico-chemical influences, some of them locally determined, some of them hormonal, acting on the contractile elements of the capillary wall over which they exercise a balanced control. A similar though lesser control persists apparently through to the veins, whose tonus is regulated in part by an independent venomotor nervous mechanism (Hooker, 1918; Bancroft, 1898; etc.), and in part directly by chemical agencies (Y. Henderson, 1916; Ebbecke, 1923). This active tonicity suggests that the peripheral resistance is not confined to the arteriolar region, but that no inconsiderable part of it is located in the capillary region of the circulation, and that therefore a large part of the fall of pressure in the arterial system occurs normally here, and that on occasion it may to some degree be transferred through to the venules. To the influence of this variable tonicity in deciding the point of pressure fall must be added the factor of the resistance offered by the passage through the capillaries of the blood corpuscles (Krogh, 1922), which appear to be normally much deformed as they traverse these vessels; and also the factor of the tortuosity of the path with its increasing multiplication of passages in this region, since the average diameter-ratio of the stem to the branch entails the consequence that the smaller subdivisions offer a higher resistance than the larger (Priestley Smith, 1917), a process which goes on progressively to the mid-capillary region.

These deductions have received striking confirmation in the recent work of Dale and Richards (1918) and Burn and Dale (1926), who, by dissociating the arteriomotor and capillariomotor effects, have brought forward a large amount of evidence to show that the peripheral resistance is not limited to the arterioles, and that the common assumption is unwarranted that their exists an abrupt fall in pressure in this part of the circulation. Such a conception—that the fall of pressure is evenly distributed without any sharp line of demarcation—would seem to have been recently substantiated by the work of Landis (1926), who, using a micro-injection technique, such as is followed in this paper, found that in the peripheral vessels of the frog's mesentery the fall of pressure does not cease abruptly in the arterioles, but while a large part of it occurs in the capillary bed, it continues evenly through to the venous capillaries before flattening.

Defining capillaries, therefore, as simple endothelial tubes through which fluid interchange can take place, there is probably no sharp dividing line—either anatomically or physiologically, in structure or in function—between them and the arterioles on the one hand and the venules on the other. With their continuously

		S.	D
		cm H₂O	
radiis Art.	0·25 mm diam.	39	23
Interlobular.	0·15 mm.	38	24
arteriole	40 - 50 μ	22	16
capillary	10 - 30 μ	14	
venous ent.	80 · 65 μ	10	
veni	0·3 mm.	7·5	

Cauterisis arteriole → 29 | cm. H₂O. S.
Capillary → 24
Diastolic level slow horizontal

changing conditions and wide range of variation, it seems unreasonable to speak of a capillary pressure at all, and if we do it must be in elastic terms as comprising a large part of the pressure gradient from the arteries to the veins.

Such a conception of a dynamically active capillary bed and an ever changing capillary pressure shows the inadequacy of estimating the capillary pressure by any schema based on calculations of the sectional area, or on the rate of flow, or any hard and fast mechanical considerations derived from the study of the flow of fluids through tubes, as has been elaborated by Priestley Smith (1918: capillary pressure, 40 mm. Hg in the eye). The assumption that such mechanical considerations, or that the calculations on which they are based hold for the same capillary for any length of time or for any two capillaries at the same time, can lead to no quantitatively correct results (see Dale, 1926).

It also effectively answers the argument stressed by T. Henderson (1910), Flack (1913), and others in discussing the "secretion" of the aqueous, that the capillary walls, being films of fluid protoplasm, would be unable to bear any such strain as a filtration theory demanded. Apart from the support afforded them by the Rouget cells, such an argument takes no cognizance of a world of physical forces. In the human skin where the normal pressure is undoubtedly relatively low, Lewis (1924) estimated their contractile power as being capable of expelling fluid against a pressure of 50 to 60 mm. Hg, and when contracted, of resisting the entry of fluid up to 90 to 100 mm. Hg.

The Capillary Circulation in the Eye.—It has been said on so many occasions that the capillary pressure of the eye is governed by the diastolic arterial pressure and must be less than it, between it and the intraocular pressure, that it may be worth while pointing out that the statement is quite wrong.

Thus during this year, Seidel (1926, p. 547), who finds the diastolic pressure in the anterior ciliary arteries to be 30 mm. Hg, insists that the capillary pressure in the eye lies between this and 25 mm. Hg—the intraocular pressure. And Serr (1926, p. 699): ". . . . der diastolische Druck 30-45 mm. Hg beträgt. Der intraokulare Capillardruck muss aber unbedingt niedriger sein als dieser extrabulbär gemessene Wert. . . ." Hence, they argue, the aqueous is a secretion.

On the contrary it may almost be said that the capillary pressure has nothing to do with the diastolic arterial pressure; certainly it need not be less than it. If we neglect the ocular capillary pulse, provided there were no friction, the capillary pressure would equal the arterial mean pressure, and its actual value is determined by the amount deducted from this mean pressure by friction. The capillary pressure throughout the body is governed by the aortic pressure; at the beginning of the aorta the diastolic pressure is nil, and in a case of regurgitation it is a negative quantity; yet the capillary pressure exists as a positive quantity. In the eye

we have already seen that it is no uncommon thing for the arteries to be completely obliterated at diastole when a spontaneous "pressure pulse" occurs, that is, the diastolic pressure is less than the intraocular; in the same eye the veins are full, their pressure must therefore be higher than the intraocular pressure; the circulation goes on indefinitely, and therefore the capillary pressure must be still higher than this, that is, than the diastolic pressure of the entering arteries. We will admit that in normal circumstances the capillary pressure is less than the diastolic, but it need not be, it often is not, and under no circumstances should its value be deduced from it.

We have seen that the mean pressure of the arteries entering the eye is about 75 mm. Hg, and that the pressure in the veins leaving the eye is from 1 to 2 mm. Hg above the intraocular pressure. There is therefore a fall of from 50 to 55 mm. Hg in the vascular system. We have seen further that a large part of this fall occurs in the capillaries. But in addition to the fact that the "tissue pressure" in the eye is 20 to 25 mm. Hg, instead of 1 to 2 mm. as obtains throughout the body generally, there are several indications that the capillary pressure in this organ will be higher proportionately than in any other organ in a state of rest. The ciliary arteries seem to be anatomically peculiar in that they break off almost at once into a rich net-work of wide capillaries (Fusita, 1919), which appear to be capable of such extreme distension in places as to allow of the passage of ten corpuscles at a time; in these it will be possible for the energy component represented by the lateral pressure to rise to a very considerable height, theoretically higher than that in the arterioles. Again the veins of the eye are physiologically constricted at their exits, and the whole circulation is confined under considerable tension in a feebly distensible and elastic case under whose influence the whole system preserves a pulsatile flow. This will tend to throw the point of the fall of pressure further towards the veins, and make the vascular system approximate in its behaviour to a series of rigid tubes.

It is very probable, therefore, that a variation of from 30 to 35 mm. Hg occurs in the capillary region of the eye, and that, while definite figures are apt to give a wrong idea of what is an indefinite and ever changing quantity, at the arterial end of the capillary bed the pressure may be in the region of 50 to 55 mm. Hg, and that in the venous capillaries it may be a few mm. Hg above the intraocular pressure.

If it be permitted to transpose the measurements obtained in the dog and apply them comparatively to the cat, we therefore arrive at the following scheme of the blood pressures in the eye (Table IX).

TABLE IX

		Pressures mm. Hg		
		Diastolic	Systolic	Mean
Cat... ...	Pressure measured in carotid ...	70	150	108
	Pressure in ophthalmic artery...	78	115	97
	Pressure in retinal arteries, *i.e.*, first arterial branchings in eye	64	88	76
	Estimated capillary pressure ...	—	—	55–28
Dog ...	Pressure of venous exits ...	—	—	21.5
Cat and Dog	Intraocular pressure	—	—	20
Dog ...	Pressure in episcleral veins ...	—	—	12.8
	(Facial vein: dog — Burton-Opitz, 1909)	—	—	5.1
	(Jugular ,, ,, ,, ,,)	—	—	0.5
	Sup. vena cava ,, ,, ,,)	—	—	−1.4 – −2.9

V. The Physiological Significance of the Vascular Pressures

From the physiological standpoint the main interest in these vascular pressures is their relation to the formation and absorption of the aqueous humour. The formation of the aqueous is associated mainly with the vessels of the ciliary body and iris, and from a theoretical point of view it would have been preferable to have obtained measurements of the arterial pressures here. In the cat, as has been noted, the circulus arteriosus iridis major, which supplies the ciliary processes and iris directly, instead of lying inaccessibly at the base of the iris as in man, lies in the iris itself, and with sufficient magnification is readily seen particularly on the nasal side. To introduce a pipette into this vessel, however, was found to be difficult or impossible on account of the mobility of the supporting structures, while the immediate and high rise in the intraocular pressure which invariably followed penetration of the iris—due presumably to nociceptive vasomotor reflexes from this richly innervated structure—seemed to render any such attempt useless. This vessel, however, is directly formed from the long posterior ciliary arteries. Since, other things being equal, arterial pressure falls proportionately to the number of branchings and the size of the lumen of the vessels, and since the long posterior ciliary arteries and the central artery of the retina are both direct branches of the ophthalmic, and are of the same order of size, it would seem probable that the pressure in this arterial circle would approximate that in the branches of the central artery of the retina. Moreover, the close relationship between the pressures in the two circulations—uveal and retinal—under physiological variations has already been pointed out. It is probable, therefore, that we can assume with a fair degree of certainty that the pressures measured in the branches of the central

artery of the retina are not far removed from those in the ciliary body.

It may thus be assumed that in the ciliary body the arterial mean pressure is about 75 mm. Hg, and that the venous pressure is about 21 mm. Hg when the intraocular pressure is about 20 mm. Hg. There is thus a pressure fall in the ciliary vascular system of from 50 to 55 mm. Hg, and a capillary pressure may be suggested varying from about 22 to 55 mm. Hg.

When it is remembered that the intraocular pressure is 20 to 25 mm. Hg, it would seem that the arterial and venous pressures in the eye bear a relation to the chamber pressure similar to that which the vascular pressures do to the tissue pressures throughout the body. If the aqueous is formed by a simple physical mechanism as are the tissue fluids generally (Starling, 1896; Bayliss, 1920) without the intervention of a special "secretory" force exercised by the cells of the ciliary endothelium, the hydrostatic pressure in the capillaries must be capable of exceeding the intraocular pressure by the difference between the osmotic pressures of the aqueous and the plasma. I have elsewhere shown (1926,d) that in their estimates of the osmotic pressure of the aqueous, previous observers were largely in error, and that it is less than that of the plasma by an amount depending on the electrostatic forces conditioned by the stresses called into being by the almost complete impermeability of the capillaries of the eye to colloidal micelles; the difference between the osmotic pressures of the two therefore varies with the protein content of the blood—in the rabbit it is about 20 mm. Hg, in man about 30 mm. Hg. The tissue fluids generally contain about one-half the quantity of blood proteins, and therefore (in man) a difference in hydrostatic pressure between aqueous and capillary of about 30 mm. Hg must exist in the eye, instead of about 15 mm. Hg between tissue fluid and capillary elsewhere in the body. We have already seen that the specialized conditions in the eye provide every reason to believe that this is the case. The capillaries in various parts of the body vary very considerably in their degree of permeability to colloids (Krogh, 1922, etc.), and it may be suggested that the great impermeability of those in the eye is a biological adaptation to keep the intraocular fluids optically homogeneous, and that the specialized circulatory conditions which obtain here are a further adaptation to compensate for the higher pressure differences which are thus rendered necessary.

E. E. Henderson and Starling (1906), in an investigation to test whether it was possible that the capillary pressure was capable of forming the aqueous by a process of filtration, compared the aortic and intraocular pressures over a large series of animals. The average difference was found to be 84.4 mm. Hg, and the conclusion arrived at by them was that the pressure fall rendered

such a view possible. The present investigation takes the matter a step further and amply corroborates their findings. There is every reason to believe that the capillary pressure in the eye rises to 50 or 55 mm. Hg. Around this level it will be constantly fluctuating, at one moment above it, at another below it; and in any one capillary the balancing hydrostatic and osmotic forces will render a flow of fluid possible outwards at one moment, inwards at another throughout its length, or in both directions contemporaneously in different parts of its length, the amount of fluid interchange being a function of the pressure head as the intensity factor and the length of the path over which flow takes place as the capacity factor. While such fluid interchange in both directions is possible throughout the eye as a whole the greater amount of dialysation outwards will take place, that is, the larger part of the aqueous will be formed, from the vessels in the ciliary body and iris. This we would expect from the direct vascular supply of this region from the uninterrupted long posterior ciliary arteries. The results of innumerable injection experiments amply confirm this deduction, as also do the experiments of Wagenmann (1890), who found that on ligating the short posterior ciliary arteries or the anterior arteries little or no change resulted, but that on obliterating the long posterior ciliaries hypotony and widespread degenerative changes took place throughout the eye.

Thus while they do not of themselves prove anything, the vascular pressures of the eye show nothing inconsistent with the hypothesis that the intraocular fluids are formed by dialysation from the blood. It is hoped in further researches to be published in the near future to offer evidence of another kind and of a more conclusive nature that this is the case.

VI. Summary and Conclusions

(1) The methods which have been adopted in the estimation of the vascular pressures of the eye are detailed and criticized. It is shown that no one has yet succeeded in measuring the pressure in the intraocular arteries, that the technique employed hitherto in measuring the venous pressure has been inadequate in that it has involved in every case a wide departure from the normal conditions, and that no method has been suggested which can claim to have measured the normal pressure in the capillaries.

(2) The mechanism of the arterial and venous pulses in the eye are discussed: the arterial pulse is shown to be dependent upon the excursion of the pulse pressure, and upon the difference between the lowest point of this cyclical variation and the intraocular pressure. The venous pulse is dependent primarily on the arterial pulse, and in addition to the factor of pressure relations, its occurrence or non-occurrence is influenced by other factors, being largely determined by the ease with which the blood finds an exit

from the eye; any method of estimating the venous pressure from its occurrence is therefore fallacious.

(3) Experimental technique is described which has established the first measurements which have been made of the arterial pressure in the eye; and which has provided measurements of the venous pressure for which are claimed a closer approximation to the normal conditions than that involved by the methods employed hitherto.

(4) The mean pressure in the ophthalmic artery is not greatly below the mean aortic pressure (about 100 mm. Hg in the cat.)

The pressure in the retinal arteries is about 25 per cent. below that of the ophthalmic artery (75 mm. Hg in the cat).

The pressure in the intraocular veins is in all circumstances greater than the intraocular pressure.

The pressure in the venous exits is normally slightly above the intraocular pressure (1.5 mm. Hg in the dog).

There is a rapid fall of pressure as soon as the veins leave the eye; the pressure in the episcleral veins in the dog is about 7.2 mm. Hg below the intraocular pressure.

(5) The venous pressure and the intraocular pressure vary together very intimately.

(6) Under conditions of raised intraocular pressure the pressure in the venous exits may fall below the chamber pressure.

(7) The nature of the capillary circulation is discussed, and the variability of its pressure pointed out. It is suggested that the capillary pressure in the eye varies from about a few mm. Hg above the intraocular pressure to a height of about 50 or 55 mm. Hg.

(8) It is shown that the vascular pressures and their relation to the intraocular pressure are compatible with the theory of the formation of the aqueous by a process of dialysis from the blood, and do not necessitate the postulate of any "secretory" energy.

(9) The circulatory conditions lead to the expectation that the dialysation of the intraocular fluids would occur from the blood stream mainly, but not entirely, through the vessels of the ciliary body and iris, and to the blood stream mainly, but not entirely, through the canal of Schlemm.

(10) Inasmuch as the venous pressure in the eye is normally higher than the intraocular pressure, a hydrostatic outflow of the aqueous is impossible. Osmotic re-absorption into the blood stream is possible throughout the eye generally, but with its favourable position down the venous pressure gradient, and with its endothelial wall resembling that of a capillary, it is probable that a great part of the process takes place in the canal of Schlemm. Further, under conditions of raised intraocular pressure, the equilibrium is so altered that a hydrostatic outflow may occur here temporarily, the canal of Schlemm under these conditions acting as a safety-valve mechanism to aid in the maintenance of the intraocular pressure at its normal level.

Abramowicz, J. (1927) Untersuchungen über den Blutdruck in den Augengefässen Klin. Wschr. Bd V. S. 125.

BIBLIOGRAPHY

Adamük, E. (1867).—De l'étiologie du Glaucome. *Ann. d'Ocul.*, T. LVIII, p. 8. Also *Cent. f. d. Med. Wissensch.*, No. 36, 1866; No. 28, 1867.

———— (1868).—Noch einige Bemerkungen über den intraokularen Druck. *Klin. Monatsbl. f. Augenheilk.*, Bd. VI, s. 386-393.

Alt, F. (1884).—"Zur Lehre von Glaukom." *Wien.*

Bailliart, P. (1909).—Contribution à l'étude de pouls rétinien. *La Clin. Ophtal.*, p. 178.

———— (1917, a).—Circulation artérielle rétinienne. *Ann. d'Ocul.*, T. CLIV, pp. 257-271.

———— (1917, b).—La pression artérielle dans les branches de l'artère centrale de la rétine. *Ann. d'Ocul.*, T. CLIV, pp. 648-666.

———— (1918, a).—Quelques variations de la tension artérielle intraoculaire. *Ann. d'Ocul.*, T. CLV, pp. 267-296.

———— (1918, b).—La circulation veineuse rétinienne. *Ann. d'Ocul.*, T. CLV, pp. 453-472.

———— (1919, a).—Determination of the blood pressure in the branches of the retinal artery by the Bailliart dynamometer. *Trans. Ophthal. Soc., U.K.*, Vol. XXXIX, pp. 329-335.

———— (1919, b).—Les oscillations du lever du tonomètre de Schiötz. *Ann. d'Ocul.*, T. CLVI, pp. 72-89.

———— (1919, c).—A propos d'un cas d'hypertension artérielle rétinienne. *Ann. d'Ocul.*, T. CLVI, pp. 297-304.

———— (1920).—L'état actuel de nos connaissances sur la pression artérielle rétinienne. *Ann. d'Ocul.*, T. CLVII, pp. 308-316.

———— (1921).—La vérification des tonomètres. *Ann. d'Ocul.*, T. CLVIII, pp. 654-659.

———— (1922, a).—La circulation rétinienne dans le glaucome. *Ann. d'Ocul.*, T. CLIX, pp. 432-441.

———— (1922, b).—La circulation rétinienne dans l'état d'hypertension intracranienne. *Ann. d'Ocul.*, T. CLIX, pp. 784-790.

———— (1923, a).—Présentation d'un nouveau tonomètre. *Soc. française d'Ophtal.*, June 13.

———— (1923, b).—La circulation rétinienne. Paris.

———— (1924).—La valeur clinique des chiffres tonométriques. *Ann. d'Ocul.*, T. CLXI, pp. 81-87.

———— (1925).—Hypertension artérielle et glaucome. *Rev. Méd. de l'est*, T. LIII, No. 22, pp. 818-822.

Bailliart, P. et Bollack, J. (1921).—De l'action comparé de certaines substances médicamenteuses sur la tension intraoculaire, et sur la pression artérielle. *Ann. d'Ocul.*, T. CLVIII, pp. 641-654.

Bailliart, P., et Magitot, A. (1925).—Le régime circulatoire du glaucome. *Ann. d'Ocul.*, T. CLXII, pp. 729-763.

Bajardi (1910).—Atlas stéréoscopique de chirurgie oculaire. Paris.

Ballantyne, A. J. (1913)—Pulsation of the retinal arteries. *Ophthalmoscope*, Vol. XI, pp. 271-283, 338-342, 460-465. Also *XVIIth Internat. Con. Med.*, London, Vol. IX, pt. ii, p. 208.

Bancroft, F. W. (1898).—The venomotor nerves of the hind limb. *Amer. Jl. of Physiol.*, Vol. I, p. 477. Compare **Thompson, W. H.** *Arch. f. Anat. u. Physiol.*, s. 102, 1893; **Knoll, P.** *Arch. f. d. ges. Physiol.*, Bd. LXVIII, s. 339, 1897; **Burton-Opitz, R.** *Quart. Jl. of Exper. Physiol.*, Vol. V, p. 329, 1912; **Gunn and Chavasse.** *Proc. Roy. Soc., B.*, Vol. LXXXVI, p. 192, 1913. **Edmunds, C. W.** *Jl. Pharm. and Exper. Therap.*, Vol. VI, p. 569, 1915; **Horiuchi, K.** *Arch. f. d. ges. Physiol.*, Bd. CCVI, s. 473, 1924; **McDowall. R. J. S.** *Jl. of Physiol.*, Vol. LIX, p. 41, 1924.

Barach, J. H., and Marks, W. L. (1913).—Effect of change of posture . . . on the arterial and venous pressures. *Arch. of Intern. Med.*, Vol. XI, p. 485. See also **Villaret, M., Saint Girons, F., and Grellity-Bosviel.** *Bull. et Memoirs de la Soc. Med. des hôpitaux de Paris*, T. XLV, p. 848, 1921.

Barber, M. A. (1911).—A technique for the inoculation of bacteria and other substances, and of micro-organisms into the cavity of the living cell. *Jl. of Infec. Dis.*, Vol. VIII, p. 348. See also *Jl. of Kans. Med. Soc.*, Vol. IV, p. 487, 1904; *The Phillipine Jl. of Sc., Sec. B., Trop. Med.*, Vol. IX, p. 307, 1914; *Zeitschr. wissenschr. Mikr.*, Bd. XXXII, s. 82, 1915.

Bartels, M. (1905).—Über Blutgefässe des Auges bei Glaukom, u.s.w. *Zeitschr. f. Augenheilk.*, Bd. XIV, s. 103-130, 258-294, 458-489.

v. Basch (1876).—Die volumetrische Bestimmung des Blutdruckes am Menschen. *Wien. med. Jahrb.*, s. 431.

Basler, A. (1914).—Untersuch. ü. den Druck in den kleinsten Blutgefässen der menschlichen Haut. *Arch. f. d. ges. Physiol.*, Bd. CLVII, s. 345-370. See also *ibid.*, Bd. CLXXIII, s. 389, 1919; Bd. CXC, s. 212, 1921.

Bauermann, M. (1925).—Über die Entstehung u. die klinische Bedeutung des Netzhautvenenpulses. *XLV. Zusamm. d. deutsch. ophthal. Gesell.*, Heidelberg.

———— (1926).—Verlgleichende Blutdruckmessungen am den Gefässen der Augen. Versamm. der Nordwestdeutsch. u. d. Niedersächsischen Augenärzte-Vereinigung, Mai, No. 2. Abstract *Klin. Monatsbl. f. Augenheilk.*, Bd. LXXVI, s. 874. Qr. 116, 118, 1927.

Bayliss, W. M. (1920).—The action of gum acacia on the circulation. *Jl. Pharm. and Exper. Therap.*, Vol. XV, pp. 29-74. Compare **Gildemeister und Hoffmann**. *Arch. f. d. ges. Physiol.*, Bd. CXCV, s. 162, 1922.

———— (1923).—The vasomotor system. London.

Bayliss, W. M., and Starling, E. H. (1894).—Observations on venous pressures, and their relation to capillary pressures. *Jl. of Physiol.*, Vol. XVI, pp. 159-202.

Bazett, H. C. (1924).—Factors in the causation of differential blood pressure. *Amer. Jl. of Physiol.*, Vol. LXX, pp. 550-585.

Becker, O. (1871).—Über Arterienpuls bei Aorteninsufficienz. *Klin. Monatsbl. f. Augenheilk.*, Bd. IX, s. 380-383.

———— (1872).—Über die sichtbaren Erscheinungen der Blutbewegung in der menschlichen Netzhaut. *Arch. f. Ophthal.*, Bd. XVIII, H. 1, s. 206-296.

———— (1873).—Über spontanen Arterienpuls in der Netzhaut, ein Symptom des M. Basedowii. *Wiener. med. Wochenschr.*, No. 24-25. See also *Klin. Monatsbl. f. Augenheilk.*, Bd. XVIII, s. 1-4, 1880.

Bellarminow. L. (1886).—Anwendung der graphischen Methode bei Untersuch. des intraokularen Druckes. *Arch. f. d. ges. Physiol.*, Bd. XXXIX, s. 449-472. See also *Ann. d'Ocul.*, T. XCVII, pp. 181-198, 1887.

Bergolomez (1911).—Über den Blutdruck in den kleinen Arterien u. Venen unter normalen u. gewissen pathologischen Verhältnissen. *Arch. f. d. ges. Physiol.*, Bd. CXLI, s. 118.

Berthold, H. (1870).—Zur Erklärung des an der V. centr. ret. bemerkten Pulsphänomens. *Klin. Monatsbl. f. Augenheilk.*, Bd. VIII, Auss. Beit. See also *Centralbl. f. d. Med. wissensch.*, 1869, No. 43.

Birch-Hirschfeld (1909).—In *Graefe-Saemisch Handb. f. d. ges. Ophthal.*, 2 Aufl., Bd. IX, s. 167-170.

Birnbacher und Czermak (1886).—Beiträge zur path. Anat. u. Path. des Glaukoms. *Arch. f. Ophthal.*, Bd. XXXII, H. 2, s. 1-148, H. 4. s. 26.

Black (1910).—Obstruction of the central artery of the retina. *Ophthal. Record*, Vol. XIX, p. 258.

Bleidung, C. (1923).—Experimentelles zur Tonometrie. *Arch. f. Augenheilk.*, Bd. XCII, s. 143-155.

———— (1924).—Die Beziehungen zwischen allgemeinem Blutdruck, Blutdruck in den intraocularen Gefässen, und Augendruck. *Arch. f. Augenheilk.*, Bd. XCIV, s. 198-257. See also *Münch. med. Wochenschr.*, Bd. LXXI, Nr. 9, s. 264-266.

———— (1925).—Die Bestimmung des Blutdruckes in der Arteria centralis retinae. *E. Abderhalden's Handb. d. biolog. Arbeitsmethoden*, Abt. V, Teil 6, H. 5, s. 803-838.

Boas, E. P., and Doonieff, G. (1924).—The mechanism of peripheral stasis, etc. *Arch. of Intern. Med.*, Vol. XXXIII, pp. 407-414.

Boas, E. P., and Frant, S. (1923).—The capillary blood pressure in arterial hypertension. *Arch. of Intern. Med.*, Vol. XXX., pp. 40-56.

Bonnefon (1920).—La régime circulatoire dans la choroide et la corps ciliare, etc. *Ann. d'Ocul.*, T. CLVII, pp. 504-507.

———— (1921).—De l'ophtalmomalacie expérimentale. *Ann. d'Ocul.*, T. CLVII, pp. 762-774.

Bonnefon (1922).—Nouvelles recherches expérimentales sur la physiologie de l'ophtalmotonus. *Ann. d'Ocul.*, T. CLIX, pp. 840-860.

Bornancini (1909).—Le sottrazioni sanguigne in oculistica. *Ann. di Ottal.*, Vol. XXXVIII, p. 187.

Bramwell, J. C., and Hill, A. V. (1925)—The formation of "breakers" in the transmission of the pulse waves. *Jl. of Physiol.*, Vol. LVII, *Proc. Physiol. Soc.*, p. lxxiii-lxxiv.

Briscoe, C. (1918).—Observations on venous and capillary pressures. *Heart*, Vol. VII, pp. 35-45.

Burdick, W., Clarke, N., Gerlichs, R., Priestley, J., and Richards, D. (1925).—Differences in blood pressure in the arm and leg in normal subjects. *Amer. Jl. of Physiol.*, Vol. LXII, p. 169.

Burn, J. H., and Dale, H. H. (1926).—The vasodilator action of histamine.—*Jl. of Physiol.*, Vol. LXI, pp. 185-215.

Burton-Opitz, R. (1903).—Venous pressures. *Amer. Jl. of Physiol.*, Vol. IX, pp. 198-213.

Carrier, E. B., and Rehberg, P. B. (1923).—Capillary pressure in man. *Skand. Arch. f. Physiol.*, Vol. XLIV, pp. 20-31.

Chambers, R. (1922).—New apparatus and methods for the dissection and injection of living tissues. *Jl. of Microscop. Soc.*, pp. 373-389. See also *Biol. Bull.*, 1918, Vol. XXXIV, p. 121; *Science*, 1921, N.S. Vol. LIV, pp. 411, 522; *Jl. of Infect. Dis.*, 1922, Vol. XXXI, p. 334. Compare **Taylor, C. V.**, *Science*, 1920, N.S. Vol. LI, p. 17; **Tchahotine, S.**, *Zeitschr. wissenschr. Mikr.*, 1912, Bd. XXIX, s. 188; *Compt. rend. d. l'Acad. des Sciences*, 1920, T. CLXXI, p. 1237; 1921, T. LXXXV, p. 137.

Christel, P. (1912).—Einseitiger angeborener Buphthalmus haemorrhagicus. *Arch. f. Augenheilk.*, Bd. LXXI, s. 247-258.

Coats, E. (1913).—Necrosis of cornea with ulceration after infarction of the posterior ciliary artery. *XVIIth Internat. Con. Med.*, London, Sec. IX, pt. ii, pp. 277-286.

Coccius (1853).—Über die Anwendung des Augenspiegels. Leipzig.

Collies (1901).—Beiträge zur Lehr vom primaren Keratoconus. *Inaug. Dissert.*, Rostock.

Comberg, W. (1924).—Zur Entstehung des Venenpulses. XLIV *Zusamm. d. deutsch. ophthal. Gesell.*, Heidelberg. *Klin. Monatsbl. f. Augenheilk.*, Bd. LXXII, s. 763. See also *Zeitschr. f. Augenheilk.*, Bd. LIV, s. 151-157.

Comberg, W., and Stoewer, E. (1925).—Die augendrucksteigerende Wirkung verschiedener Muskelaktionen, u.s.w. *Zeitschr. f. Augenheilk.*, Bd. LVIII, s. 92-105.

Dale, H. H., and Richards, A. N. (1918).—The vaso-dilator action of histamine. *Jl. of Physiol.*, Vol. LII, pp. 110-165. Compare **Dale, L. H., and Laidlaw, P. P.**, Histamine shock. *Jl. of Physiol.*, Vol. LII, p. 355, 1918-19.

Danzer, L. S., and Hooker, D. R. (1920).—Determination of the capillary blood pressure in man with the micro-capillary tonometer. *Amer. Jl. of Physiol.*, Vol. LII, pp. 136-167.

Deiter, W. (1925).—Über den Zusammenhang zwischen osmotischer Druck, Blutdruck, insbesondere Kapillardruck, u. Augendruck, nach neuen exp. u. klin. Untersuch. *Arch. f. Augenheilk.*, Bd. XCVI, s. 179-264.

———— (1925).—Über den Mechanismus von Gefässreaktionen im Auge. *Deutsch. med. Wochenschr.*, Bd. LI, Nr. 43, s. 1781-1783.

Dobrowolsky (1870).—Zur Lehre ü. die Blutcirkulation im Augenhintergrund des Hundes u. Menschen. *Centralbl. f. d. med. Wissensch.*, No. 20-21.

Donders (1855).—Über die sichtbaren Erscheinungen der Blutbewegung im Auge. *Arch. f. Ophthal.*, Bd. I, H. 2, s. 75-105.

Duke-Elder, W. S. (1926, a).—The reaction of the intraocular pressure to osmotic variation in the blood. *Brit. Jl. of Ophthal.*, Vol. X, pp. 1-29.

———————— (1926, b).—The venous pressures of the eye and their relation to the intraocular pressure. *Jl. of Physiol.*, Vol. LXI, pp. 409-419.

———————— (1926, c).—The arterial pressures of the eye. *Jl. of Physiol.*, Vol. XLII.

————————(1926, d).—The osmotic pressure of the aqueous and its physiological significance (to be published).

Duverger, C., et Barré, J. A. (1920).—Tension artérielle rétinienne. *Arch. d'Ophtal.*, T. XXXVII, pp. 71-88.

Ebbecke, U. (1923)—Gefässreaktion. *Ergebn. d. Physiol.*, Bd. XXII, s. 401.

Elliot, R. H. (1915).—The intraocular pressure and the tension of the eye. *Ophthalmoscope*, Vol. XIII, pp. 182-191, 237-241, 327-333.

——— (1921).—The retinal pulse. *Brit. Jl. of Ophthal.*, Vol. V, pp. 481-500.

Elschnig, A. (1892).—Über die Embolie d. A. cent. ret., *Arch. f. Augenheilk.*, Bd. XXIV, s. 65-67, u. 124.

——— (1917).—Beiträge zur Glaukomlehre. *Arch. f. Ophthal.*, Bd. XCII, s. 101.

Eppler (1884).—Über den Venenpuls in der Retina. *Mitt. aus. d. ophthal. Klinik. in Tübingen*, Bd. II, H. 1, s. 83-119.

Eyster, J. A. E., and Middleton, W. S. (1924).—Clinical studies on venous pressure. *Arch. Intern. Med.*, Vol. XXIV, p. 228.

Flack, M. (1913).—Discussion of intraocular pressure. *Proc. Roy. Soc. Med.*, London, Vol. VI, pt. iii, p. 63.

Fortin, E. P. (1925).—Vision direct dans son propre oeil des globules du sang et de leurs mouvements. *La Semana Médica*, Nos. 29 and 37. See also *Revista de la Soc. Argentina de Biologia*, Vol. I, Nos. 2 and 6.

——— (1926).—Capillaires et capillaroscopie de la rétine. *La Semana Médica*, No. 6, p. 1.

Frank, L. (1913).—Ueber den Ausgerich des arterillen u. venosen Druck u.s.w. *Zeitschr. f. exper. Path. u. Therap.*, Bd. XIII, s. 37.

Fuchs, A. (1896).—*Bericht ü. d. Zusamm. d. deutsch. ophthal. Gesell.*, Heidelberg.

Fusita (1919).—On the uveal capillaries. *Nippon Gank. Zasshi*, August ( ).

Galezowski (1916).—Le pouls choroïdien. *Soc. d'Ophtal. de Paris*, June.

Gaudissart (1921).—The ocular blood tension. *Amer. Jl. of Ophthal.*, Vol. IV, pp. 500-502.

v. Genus (1899).—Über Entstehung von Katarakt nach Unterbindung der Vv. vorticosae. *Arch. f. Ophthal.*, Bd. XLVII, s. 249-281.

Goldmann, E. (1914).—Über die Beeinflussung des Blutdrucks in den kapillaren, u.s.w. *Arch. f. d. ges. Physiol.*, Bd. CLIX, s. 51-92.

v. Graefe (1854).—Notiz ü. die Pulsphänomene auf der Netzhaut. *Arch. f. Ophthal.*, Bd. I, H. 1, s. 382-390.

——— (1855).—Bemerkungen ü. Glaukom, insbesondere ü. den bei dieser Krankheit vorkommenden Arterienpuls auf der Netzhaut. *Arch. f. Ophthal.*, Bd. I, H. 2, s. 299-307.

——— (1859).—Über Embolie der A. cent. ret. *Arch. f. Ophthal.*, Bd. V, H. 1, s. 136.

——— (1864).—Zur Casuistik der Tumoren. *Arch. f. Ophthal.*, Bd. X, H. 1, s. 176-221.

——— (1866, a).—Sichtbare Blutcirkulation infolge von Cirkulationsstörung der Netzhaut. *Arch. f. Ophthal.*, Bd. XII, H. 2, s. 141.

——— (1866,b).—Verhalten der Netzhautcirkulation bei Cholera. *Arch. f. Ophthal.*, Bd. XII, H. 1, s. 207-211.

Graser (1883).—*Inaug. Dissert.*, Erlangen.

Graves, B. (1922).—Venous pulsation. *Brit. Jl. of Ophthal.*, Vol. VI, pp. 237-238.

Greeves, A. (1913).—Discussion on intraocular pressure. *Proc. Roy. Soc. Med., Lond.*, Vol. VI, pt. iii, pp. 73-74.

Grönholm (1900).—Über die Einwirkung des Eserins auf den Flüssigkeitswechsel und die Cirkulation im Auge. *Arch. f. Ophthal.*, Bd. XLIX, H. 3, s. 620-711.

Guist (1925).—Entzündliche Orbitalprozesse und Glaukom. *Zeitschr. f. Augenheilk.*, Bd. LV, s. 308-317.

Gullstrand (1891).—Ett fall af keratoconus med tydling pulsation af hornhinnan. *Nord. Ophth. Tidskrift.*, Bd. IV.

Gunn, R. Marcus (1892).—Ophthalmoscopic evidence of increased arterial tension. *Trans. Ophthal. Soc., U.K.*, Vol. XII, pp. 124-125.

——— (1898).—On ophthalmoscopic evidence of general arterial disease. *Trans. Ophthal. Soc., U.K.*, Vol. XVIII, pp. 356-381.

v. Haab (1897).—Atlas u. Grundriss der Ophthalmoscopie. Auf. II.

Hill McQuinn. B.M.J. 1926 ① 919.

Halbern, R. (1909).—Über die mechanischen Vorgänge bei der Entstehung des Langbaues des myopischen Auges. *Arch. f. Ophthal.*, Bd. LXXI, s. 63-88, 283-312.

——— (1919).—Bemerkungen über den Binnendruck des bewegten Auges. *Arch. f. Augenheilk.*, Bd. LXXIII, s. 129-132.

Hamburger, C. (1914).—" Über die Ernährung des Auges." Leipzig.

——— (1922).—Zu den neueren Arbeiten über die Ernährung des Auges. *Klin. Monatsbl. f. Augenheilk.*, Bd. LXIX, s. 249-258, 393-407.

Haussen, R. (1918).—Beiträge zur Histologie des Glaukoms. *Klin. Monatsbl. f. Augenheilk.*, Bd. LXI, s. 509-525.

Heerfordt, C. H. (1911).—Über Glaukom. *Arch. f. Ophthal.*, Bd. LXXVIII, s. 413-493; 1912, Bd. LXXXIII, s. 149-188; 1914, LXXXVII, s. 494-513 u. 514-527; 1915, Bd. LXXXIX. s. 62-111 u. 484-501.

Helfreich, F. (1882).—Zur Lehre vom Venepuls der Retina und der intraocularen Circulation. *Arch. f. Ophthal.*, Bd. XXVIII, H. 3, s. 1-32.

——— (1882).—Über Arterienpuls der Netzhaut, *Festschr. z. Feier d. 300 jähr. Bestehens d. Univ. Würzburg.*

Henderson, E. E. (1903).—The ophthalmic arteries in the rabbit and dog. *Roy. Lond. Ophthal. Hosp. Reps.*, Vol. XV, pp. 260-274. See also **Ellenberger u. Baum**—Anatomie des Hundes, Berlin, 1891. **Krause.**—Die Anatomie des Kaninchens. Leipzig, 1868. **Virchow.**—Über dei Gefässe der Chorioidea des Kaninchens, in *Verhandl. d. phys-med. Ges. zur Würzburg, N.F.* Bd. XVI, 1881 (published also in separate work). **Lauber.**—*Anatomie*, p. 59, 1901.

Henderson, E. E., and Starling, E. H. ((1904).—The influence of changes in the intraocular circulation on the intraocular pressure. *Jl. of Physiol.*, Vol. XXXI, pp. 305-319.

——— (1905).—The factors which determine the production of intraocular fluid. *Proc. Roy. Soc.*, Sec. B, Vol. LXXVII, pp. 294-310.

Henderson, T. (1907).—Histology of iridectomy. *Ophthal. Rev.*, July.

——— (1907).—Pathology and treatment of glaucoma. *Brit. Med. Jl.*, Nov. 2.

——— (1908).—The venous connections of Schlemm's canal. *Trans. Ophthal. Soc. U.K.*, Vol. XXVIII.

——— (1910).—Glaucoma. Arnold, London, 1910.

——— (1913).—Discussion on intraocular pressure. *Proc. Roy. Soc. Med., Lond.*, Vol. VI, pt. iii, p. 66.

——— (1914).—Clinical proof of the venous level of the intraocular pressure and a method of estimating the arterial diastolic pressure in the eye and its clinical significance. *Trans. Ophthal. Soc., U.K.*, Vol. XXXIV, pp. 309-16.

Henderson, Y. (1916).—The veno-pressor mechanism. *Amer. Jl. of Physiol.* Vol. XLII, p. 589. See also **Henderson, Y., and Harvey, S.**—The veno-pressor mechanism. *Amer. Jl. of Physiol.*, Vol. XLVI, p. 533.

Henle (1876).—*Handb. d. syst. Anat.*, 2 Aufl., Bd. III, pt. i, s. 115.

Hess (1919).—Untersuch. ü. die Methoden der klinischen Perimetrie. *Arch. f. Augenheilk.*, Bd. LXXXIV, s. 1-10.

Hill, Leonard (1895).—The influence of the force of gravity on the circulation of the blood. *Jl. of Physiol.*, Vol. XVIII, pp. 15-53.

——— (1912).—A note on glaucoma. *Lancet*, Vol. I, p. 226.

——— (1913).—The physiology of the intraocular pressure. *Proc. Roy. Soc. Med.*, Vol. VI, pt. iii, pp. 31-44.

——— (1920).—Blood vessels and pressure: the blood pressure of the eye. *Lancet*, Vol. I, pp. 359-366.

——— (1920).—The capillary blood pressure. *Jl. of Physiol.*, Vol. LIV; *Proc. Phys. Soc.*, p. xxiv-v, xciii-v, xcliv. With **McQueen,** *Ibid.*, p. cxxiii-iv.

——— (1921).—The capillary blood pressure in man. *Brit. Jl. of Exper. Path. and Therap.*, Vol. II, pp. 1-7.

Hill, L., and Barnard, H. (1897).—The influence of the force of gravity on the circulation. *Jl. of Physiol.*, Vol. XXI, pp. 323-352. See also *Brit. Med. Jl.*, Vol. II, p. 904.

Hill, L., and Flack, M. (1912).—The relation between capillary pressure and secretion. *Proc. Roy. Soc. B*, Vol. LXXXV, pp. 439-459.

Hill, L., Flack, M., and Holtzman (1909).—The measurement of the systolic blood pressure in man. *Heart*, Vol. I, pp. 73-82.

Hill, L., and Rowland (1912).—The systolic blood pressure. *Heart*, Vol. III, p. 222.

v. Hippel und Grünhagen (1868).—Über den Einfluss der Nerven auf die Höhe des intraokularen Druckes. *Arch. f. Ophthal.*, Bd. XIV, H. 3, s. 234-250; 1869, Bd. XV, H. 1, s. 265-287.

Hiroishi, H. (1924).—Uber das Verhältnis zwischen Augendruck und Blutdruck in den episcleraren Venen und den Wirbelvenen. *Arch. f. Ophthal.*, Bd. CXIII, H. 2, s. 212-222.

Hoelzke (1883).—Exper. Untersuch. ü. den Druck in der Augenkammer. *Arch. f. Ophthal.*, Bd. XXIX, H. 2, s. 1.

Holloway, T. B. (1917).—Pulsation of the retinal arteries. *Ann. of Ophthal.*, Vol. XXVI, pp. 365-366.

Holtz (1889).—Über Venenpuls in Auge. *Berl. klin. Wochenschr.*, No. 50.

Hooker, D. R. (1911).—The effect of exercise on the venous blood pressure. *Amer. Jl. of Physiol.*, Vol. XXVIII, p. 235.

——— (1918).—The veno-pressor mechanism. *Amer. Jl. of Physiol.*, Vol. XLVI, p. 591.

——— (1920).—Functional activity of capillaries and venules. *Amer. Jl. of Physiol.*, Vol. LIV, p. 30.

Hooker, D. R. and Eyster, J. A. C. (1908).—An instrument for the determination of the venous pressure in man. *Johns Hopkins Hosp. Bull.*, Vol. XIX, p. 274. Compare **Middleton, W. S.** *Wisconsin Med. Jl.*, Vol. XXI, p. 189, 1922. **Ayerza, L.** *Semana Medica.*, Vol. XXXI, p. 956, 1924.

Howe, L. (1885).—On the pulsating variations of intraocular tension. *Jl. of Ophthal.*, Vol. II, pp. 139 and 155.

Ischreyt, G. (1912).—Von dem Eintritt entzündlichen Erscheinungen bei dem Glaucoma simplex. *Arch. f. Augenheilk.*, Bd. LXX, s. 319-334.

Jacobi (1876).—Studien über die Cirkulation im Auge. *Arch. f. Ophthal.*, Bd. XXII, H. 1, s. 111-134. See also *Centralbl. f. d. med. Wissenschr.*, H. 2, 1875.

v. Jäger, E. (1854).—Beobachtung der Cirkulation in den Netzhautgefässen. *Wiener. med. Wochenschr.*, No. 3-5.

——— (1876).—Ergebnisse der Untersuchung mit der Augenspiegel, u.s.w. *Vortrag. gehalten in d. math.-naturw. Klasse d. Wiener. Akad.*, Nov. 18, 1875.

Javal (1884).—Variation de courbure de la cornée en synchronisme avec les pulsations cardiques. *Compt. rend. Soc. de Biol.*, Oct. 4; *Progr. Méd.*, No. 43.

Knapp, A. (1874).—Ein Fall von Carcinom der äusseren Sehnervenscheide extirpt mit Erhaltung des Augapfels. *Arch. f. Augenheilk.*, Bd. IV, s. 209-238.

Koster, W. (1895).—Beiträge zur Lehre von Glaukom. *Arch. f. Ophthal.*, Bd. XLI, H. 2, s. 30-112, 113-158.

Krämer, R. (1920).—Die Bedingungen für das Entstehen arterieller Pulsation im Auge. *Arch. f. Ophthal.*, Bd. CIII, s. 14-24.

Krauss (1914).—Der Kapillardruck. *Sammlung klin. Vorträge inn. Med.*, Nr. 237-239, s. 315.

Krogh, A. (1922).—The Anatomy and physiology of the capillaries. New Haven.

Kugel (1863).—Über Kollateralkreisläufe zwischen Choroidea u. Retina. *Arch. f. Ophthal.*, Bd. IX, H. 3, s. 129-132.

Kuhnt, H. (1883).—Discussion after **E. Berger,** *XV Versam. ophthal. Ges.*, Heidelberg. Also **Just.** *Ibid.*

Kümmell, R. (1915).—Über Pulserscheinungen der Augengefässe. *Arch. f. Augenheilk.*, Bd. LXXVIII, s. 336-358.

——— (1923).—Über Pulsverhältnisse der Netzhautgefässe bei Exophthalmus pulsans. *Arch. f. Augenheilk.*, Bd. XCII, s. 127-142.

——— (1925).—Über den physiologischen Netzhautvenenpuls. *Arch. f. Augenheilk.*, Bd. XCV, s. 195-204.

Kylin, E. (1921).—Studien ü. das Verhalten des Kapillardruckes. *Acta med. Skand.*, Bd. LV, s. 368. See also *Deutsch. med. Wochenschr.*, 1920; *Zeitschr. f. inn. Med.*, 1920, Bd. XL; *Acta med. Skand.*, 1923, Bd. LVII, s. 566.

Kyrieleis, W. (1925).—Über seltene Pulsationserscheinungen an den Gefässen des menschlichen Augenhintergrundes. *Arch. f. Augenheilk.*, Bd. XCVII, s. 40-45.

Landerer, R. (1913).—Zur Frage der Kapillardruckes. *Zeitschr. f. klin. Med.*, Bd. LXXVIII, s. 91-101.

Lida E. et Ardoguné, E. (1926)
Pression du sang dans les capillaires
de la rétine.
C.R. de la Soc. de biol. T XCV p. 1160.

(1926) Der Blutdruck in der arteria
centralis retinae.
Semana méd. VI XXXIII. p. 1129.

Landis, E. M. (1926).—The capillary pressure in frog mesentery as determined by micro-injection methods. *Amer. Jl. of Physiol.*, Vol. LXXV, pp. 548-570.

Lang, W., and Barrett, J. W. (1888).—The frequency of cilio-retinal vessels and of pulsating veins. *Roy. Lond. Ophthal. Hosp. Reps.*, Vol. XII, pp. 59-60.

Laqueur (1877).—Über Atropin u. Physostigmin und ihre Wirkung auf den intraokularen Druck. *Arch. f. Ophthal.*, Bd. XXIII, H. 3, s. 155.

Larsen, Sven (1926).—Ueber Tenonitis u. die sie begleitende intraokuläre Drucksteigerung, u.s.w. *Acta Ophthal.*, Bd. III, H. 3, s. 207-227.

Lebensohn, J. E. (1925).—The determination of retinal blood pressure. *Illinois Med. Jl.*, Vol. XLVIII, No. 3, pp. 212-214.

Leber, Th. (1865).—Untersuch. über den Verlauf u. Zusammenhang der Gefässe im menschlichen Auge. *Arch. f. Ophthal.*, Bd. XI, H. I, s. 13-34.

———— (1865).—Denkschrift d. k. Akad. der Wiss. zu. Wien. *Math.-naturwiss. Cl.*, Bd. XXIV.

———— (1872).—Bemerkungen über die Cirkulationsverhältnisse des Opticus u. der Retina. *Arch. f. Ophthal.*, Bd. XVIII, H 2, s. 27-37.

———— (1873).—Studien über den Flüssigkeitwechsel im Auge. *Arch. f. Ophthal.*, Bd. XIX, H. 2, s. 141.

———— (1903).—Die Cirkulations u. Ernährungsverhältnisse des Auges. *Graefe-Saemisch Handb. d. ges. Augenheilk.*, Aufl. 2, Bd. II, Abt. 2, s. 1-78, 112-204.

Lederer (1912).—Der Binnendruck des exper. u. willkürlich bewegten Auges. *Arch f. Augenheilk.*, Bd. LXXII, s. 1-10.

Leplat, G. (1920):—La pression artérielle dans les vaisseaux de l'iris, etc. *Ann. d'Ocul.*, T. CLVII, pp. 693-701.

———— (1922).—De la circulation sanguine intraoculaire et de son importance clinique. *Scalpel.*, T. LXXV, No. 15, pp. 345-355.

———— (1923).—De l'influence des sowstractions sanguines locales sur la physiologie oculaire. *Ann. d'Ocul.*, T. CLX, pp. 348-356. See also *Bull. Soc. belge d'Ophtal*, November, 1922.

Levinsohn, G. (1908).—Beiträge zur. path. Anat. u. Path des Glaukoms. *Arch. f. Augenheilk.*, Bd. LXII, s. 131; *Berl. klin. Wochenschr.*, s. 1891; *Münch. med. Wochenschr.*, s. 1563.

———— (1910).—Über der Einfluss der aüsseren Augenmuskeln auf dem intraokularen Druck. *Arch. f. Ophthal.*. Bd. LXXVI, s. 129-145.

———— (1912).—Die Entstehung der Kurzsichtigkeit, Berlin.

———— (1913).—Zur Frage der intraokularen Drucksteigerung bei den Bewegungen des Auges. *Arch. f. Augenheilk.*, Bd. LXXIII, s. 151-154.

Lewis, T. (1924).—The force exacted by the minute vessels of the skin in contracting. *Heart*, Vol. XI, p. 109. See also *Jl. of Physiol.*, Vol. LVIII, p. i, 1923; *Proc. Physiol Soc.*, p. i, 1923. Compare **Dale, H. H.**—*Brit. Med. Jl.*, Vol. I, pp. 959-962, 1006-1010, 1923.

Liebesny, P. (1923).—Untersuch. ü. die Capillardruckmessung. *Arch. f. d. ges. Physiol.*, Bd. CXCVIII, s. 215-224.

Liebreich, R. (1858).—Histologisch.-ophthalmoskopische Notizen. *Arch. f. Ophthal.*, Bd. IV, H. 2, s. 294-295.

———— (1859).—Sichtbare Cirkulation in der Netzhaut bei path. Zuständen. *Arch. f. Ophthal.*, Bd. V, H. 2, s. 259.

Löhlein (1910).—Zur Frage der primären Sehnervengeschwülste. *Arch. f. Ophthal.*, Bd. LXXIII, s. 335-348.

Lullies, H. (1923).—Der Druck in den Venen des Scleralrandes. *Arch. f. d. ges. Physiol.*, Bd. CXIX, s. 471-480.

Lullies und Gulkowitsch (1924).—*Schrift. d. Königsberger Gelehrten-Ges. Naturw. Klin.*, Bd. I, H. 2, s. 105.

McBurney, M. (1914).—The absence of cicatrization in the iris after operation and injury. *Arch. of Ophthal.*, Vol. XLIII, pp. 12-15.

Mackenzie, S. (1875).—*Med. Times and Gaz.*, Vol. I.

MacLean (1919).—Experimental studies in intraocular pressure and tonometry. *Arch. of Ophthal.*, Vol. XLVIII, pp. 23-38.

Magitot, A. (1917).—Sur variations traumatiques de la tension oculaire. *Ann. d'Ocul.*, T. CLIV, pp. 667-694.

———— (1922).—How to know the blood pressure in the vessels of the retina. *Amer. Jl. of Ophthal.*, Vol. V, series 3, pp. 777-784.

Magitot, A. (1923).—Sur la tension oculaire et quelques-unes de ses modifications experimentales. *Ann. d'Ocul.*, T. CLX, pp. 1-15, 81-105.

Magitot, A., et Bailliart, P. (1919).—Modifications de la tension oculaire sous l'influence de pressions exercés sur le globe. *Ann. d'Ocul.*, T. CLVI, pp. 656-666.

——————— (1921).—Recherches sur l'action des vasomoteurs oculaires ; pression comparée dans les vaisseaux de l'iris et de la rétine. *Jl. de Physiol. et de Path. gén.*, T. XIX, pp. 532-541. See also *Ann. d'Ocul.*, T. CLVIII, pp. 81-95.

——————— (1922).—The retinal circulation. *Amer. Jl. of Ophthal.*, Vol. V, Series 3, pp. 824-828.

Manz (1874).—Über Veränderungen am Sehnerven bei akuter Entzündung des Gehirns. *Sitzungsber. d. ophthal. Ges.*, s. 447.

Mazzei, A (1920).—Rapposti tra la tensione oculare e le pressioni arteriosa, venosa, endotoracica. *Arch. di Ottal.*, Vol. XXVI, p. 163, Vol. XXVII, pp. 83-104.

Memorski (1865).—Über den Einfluss des intraokularen Druckes auf die Blutbewegung im Auge. *Arch. f. Ophthal.*, Bd. XI, H. 2, s. 84.

Merkel und Kallius (1910).—*Graefe-Saemisch Handb. d. ges. Augenheilk.*, Aufl. 2, Bd. I, H. 1, s. 146.

Michel (1881).—Das Verhalten des Auges bei Störungen im Cirkulationsgebeit der Carotis. *Beitr. z. Ophthal.*, Bd. I, s. 1-51. See also *Lehrb. d. Augenheilk*, 1890.

Möller, H. (1889).—*Lehrb. d. Augenheilk. f. Thierärzte*, Stuttgart.

Moore, R. Foster (1916).—The retinal circulation in arterio-sclerosis. *Trans. Ophthal. Soc. U.K.*, Vol. XXXVI, p. 319.

——————— (1917).—The intraocular tension, etc. *Roy. Lond. Ophthal. Hosp. Reps.*, Vol. XX, pp. 108-128

Moritz, F., und Tabora, V (1910).—Über eine Methode beim Menschen den Druck in oberfläschen Venen exakt zu bestimmen. *Deutsch. Arch. f. klin. Med.* Bd. XCVIII, s. 475-505.

Müller, O., und Blauel, K. (1907).—Zur Kritik des Riva-Rocci'schen u. Gärtner'schen Sphygmomanometers. *Deutsch. Arch. f. klin. Med.*, Bd. XCI, s. 517-553.

Niesnamoff (1896).—Über die quantitativen Verhältnisse der Filtration u. Sekretion des Kammerwassers. *Arch. f. Ophthal.*, Bd. XLII, H. 4, s. 1-35.

Oinuma, S. (1924).—Variation of capillary diameter and antidromic action in the frog. *Jl. of Physiol.*, Vol. LVIII, pp. 318-326.

Oliver (1916).—" Studies in Blood Pressure," London.

Onishi (1913).—(On the retinal pulse). *Nippon Gank., Zasshi*, Vol. XIII, May.

Osten-Sacken, V. d. (1890).—Der progressive periphere Puls den Netzhautvenen. *Inaug. Dissert.*, Dorpat, s. 97.

Parsons, J. H. (1903).—" The Ocular Circulation," London.

——————— (1904-8).—" The Pathology of the Eye," London, Vol. III, pp. 940-995 ; 1040-1070.

——————— (1912).—Theory and practice in the treatment of glaucoma. *Lancet*, Vol. I, pp. 15-17.

——————— (1913).—Discussion on the intraocular pressure. *Proc. Roy. Soc. Med.*, London, Vol. VI, pt. iii.

Parsons, J. H., and Snowball (1903).—On the relation between the intraocular tension and the general blood pressure. *Roy. Lond. Ophthal. Hosp. Reps.*, Vol. XV, pp. 275-285.

Pergens, E. (1899).—Die Blutentziehung u. die Revulsion in der Augenheilkunde. *Klin. Monatsbl. f. Augenheilk.*, Bd. XXXVII, s. 191-216.

Pflüger (1878).—Neuritis optica. *Arch. f. Ophthal.*, Bd. XXIV, H. 2, s. 169-189.

Poiseuille (1828).—Recherche sur la force du coeur aortique. Paris.

Quincke, H. (1868).—Beobachtungen u. Kapillar- und Venenpuls. *Berl. klin. Wochenschr.*, No. 34.

Rählmann (1885).—Über einige Beziehungen der Netzhautcirkulation zu allgemeinen Störungen des Blutkreislaufs. *Virchow's Arch.*, Bd. CII, s. 184-217, 221-257.

——————— (1890).—Über den sichtbaren Puls der Netzhautarterien. *Klin. Monatsbl. f. Augenheilk.*, Bd. XXVIII, s. 3-10.

Raynaud (1874).—Nouvelles recherches sur la nature et le traitement de l'asphyxie local des extrém. *Arch. gén. de Méd.*, 6 sér, T. XXIII.

v. Recklinghausen, H. (1906).—Unblutige Blutdruckmessung. *Arch. f. exper. Path. u. Pharm.*, Bd. LV, s. 376, 412, 463.

Iovan (1926) Observations sur la tension artérielle ~~rétinie~~ rétinienne à l'état normal et pathologique.
Bull. de la Soc. Roumaine d'ophtal.
p. 201.

samajloff. a. f. 1926 Sur la tension dans les veines choroïdiennes. Ann. d'Ocul. 1926, c7 XIII, p 689 - 695.

- (1927) - gr. a. f. O. Bd 119. S. 235: Zur Blutdruckmessung in den Augengefässen mittels der Pulsvenenmethode.

hiötz (1927) Der diastolische Druck in der arteria centralis Retinæ arch Ophthal Bd V S. 293.

Rieges und v. Forster (1881).—Auge u. Rückenmark. *Arch. f. Ophthal.*, Bd. XXVII, H. 3, s. 109.
Römer (1895).—Beiträge zur path. Anat. der Glaukoms. *Arch. f. Ophthal.*, Bd. XLII, s. 514.
Rönne (1913).—Zur pathologischen Anatomie des Glaucoma simplex. *Klin. Monatsbl. f. Augenheilk.*, Bd. LI, H. 2, s. 505-513.
Roser (1859).—Über Klappenwirkung beim sog. Glaukom. *Arch. f. physiol. Heilk.* N. F. III, s. 128-130.
Rubino (1911). La pressione del sangue nell' arteria retinica e suoi rapporti con la pressione nel circolo di Willis. *La Riforma medica*, p. 1345.
Runge, H. (1924).—Ueber den Venendruck in Schwangerschaft, u.s.w. *Arch. f. Gynäk.*, Bd. XXII, s. 142.
Salvati (1922, a).—La pression artérielle rétinienne en position assise et couchée. *Ann. d'Ocul.*, T. CLIX, pp. 69-71.
——— (1922, b).—La tension oculaire en position assise et couchée. *Ann. d'Ocul.*, T. CLIX, pp. 128-13 .
Scheerer, R. (1924.)—Die entoptische Sichtbarkeit der Blutbewegung im Auge. *Klin. Monatsbl. f. Augenheilk.* Bd. LXIII, s. 67-107. Über den Nachweis von Netzhautgefässtörungen auf entoptischen Weger. *XLIV Zusamm. d. deutsch. ophthal. Gesell.*, Heidelberg, 1923. Compare **Gescher.**—*Arch. f. Augenheilk*, 1925, Bd. XCVI, s. 430. **Fischer, F. P.**—*Arch. f. Augenheilk.*, 1925, Bd., XCVI, s. 97. **Fortin, E. P.**—*Revista de la Soc. Argentina de Biologia*, 1225, T. I, p. 2.
Schiötz (1905).—Ein neues Tonometer. *Arch. f. Augenheilk.*, Bd. LII, s. 401-423.
——— (1909).—Tonometrie. *Arch. f. Augenheilk.*, Bd LXII, s. 317-339.
Schmall, B. (1888).—Die Netzhautcirkulation, speziell der Arterienpuls in der Netzhaut bei Allgemeinleiden. *Arch. f. Ophthal.*. Bd. XXIV, H. 1, s. 37-107.
Schneller (1887).—Ein Mikrometer am Augenspiegel u. damit ausgeführte Untersuch. ü. den Einfluss bestimmter Eingriffe auf die Cirkulation in den Augenlebender Kaninchen. *Arch. f. Ophthal.*, Bd. III, H. 2, s. 121.
Schöler (1879).—Exp. Studien über Flüssigkeits Ausscheidung aus dem Auges. *Arch. f. Ophthal.*, Bd. XXV, H. 4, s. 63-111.
Schön (1881).—Der Venenpuls der Netzhaut. *Klin. Monatsbl. f. Augenheilk.*, Bd. XIX, s. 345.
v. Schulten, M. W. (1884).—Exp. Untersuch. über die Zirkulationsverhältnisse des Auges. *Arch. f. Ophthal.*, Bd. XXX, H. 3, s. 1-76, H. 4, s. 61-102.
Schwalbe (1870).—Untersuchungen über die Lymphbahnen des Auges und ihre Begrenzungen. *Arch. f. mik. Anat.* Bd. VI, s. 1-61, 261-263.
———— (1874).—*Graefe-Saemisch Handb. d. ges. Augenheilk.*, 1 Aufl., Bd. I, H. 4, s. 337-345.
———— (1887).—Anatomie der Sinnesorgane, s. 215.
Seefelder, R. (1924).—Über seröse Tenonitis und Glaukom. *Wiener. med. Wochenschr.*, Bd. LXIV, No. 40, s. 2054-2057.
Seidel, E. (1918).—Exper. Untersuch. über die Quelle u. den Verlauf der intraokularen Saftströmung. *Arch. f. Ophthal.*, Bd. XCV, s. 1-72.
———— (1922, a).—Über den manometrischen Nachweis des physiologischen Druckgefälles zwischen Vorderkammer u. Schlemmschen Kanal. *Arch. f. Ophthal.*, Bd. CVII, s. 101-104. See also *Arch. f. Ophthal.*, 1920, Bd. CII, s. 366-382, 415-420; 1921, Bd. CIV, s. 158-161, 357-402, 403-410; 1921, Bd. CVI, s. 176-186; 1922, Bd. CVII, s. 105-108, 507; Bd. CVIII, s. 420-424.
———— (1922, b).—Zur Manometrie u. Tonometrie des Auges. *Arch. f. Ophthal.*, Bd. CVII, 496-506.
———— (1923, a).—Micros. Beobachtungen ü. d. Mechanismus des Abfluss aus der Vorderkammer des lebenden Tieres bei physiol. Augendruck. *Arch f. Ophthal.*, Bd. CXI, s. 167-195; *Klin. Monatsbl. f. Augenheilk.*, 1922, Bd. LXIX, s. 773-786; *Deutsch. ophthal. Gesell.*, Jena. 1922, s. 280.
———— (1923, b).—Über die Messung des Blutdruckes in dem episcleralen Venengeflecht, u.s.w. *Arch. f. Ophthal.*, Bd. CXII, s. 252-260. Also *Ibid*, Bd. CXIII, s. 222-236.
———— (1924, a).—Über die Messung des Blutdruckes in den vorderen Ciliararterien des menschlichen Auges. *Arch. f. Ophthal.*, Bd. CXIV, s. 159-162; *Deutsch. ophthal. Gesell.*, Heidelberg; *Klin. Monatsbl. f. Augenheilk*, Bd. LXII, s. 760.

Seidel, E. (1924, b)—Über des Stromgefalle in Ciliargefässsystem, u.s.w. *Arch. f. Ophthal.*, Bd. CXIV, s. 163-168.

———— (1924, c).—Über . . . hydrostatische u. osmotische Triebkrafte beim physiologischen Flüssigkeitswechsel im Auge. *Arch. f. Ophthal.*, Bd. CXIV, s. 388-392. Also *Ibid.* Bd. CXIII, s. 222-236.

———— (1926).—Principelles zur Blutdruckmessung in den intraokularen Arterien. *Arch. f. Ophthal.*, Bd. CXVI, s. 537-552. Also *Deutsch. med. Wochenschr.*, No. 21, 1925.

Serr, H. (1926).—Über die Entstehung des Augendrucks besonders im Hinblick auf den intraokularen Capillardruck. *Arch. f. Ophthal.*, Bd. CXVI, s. 692-741. 1926
See also *Arch. f. Ophthal.*, Bd. CXIV, s. 393-440, 1924; *Ber. ü. d. 44 Zusamm. d. deutsch. ophthal. Gesell.*, Heidelberg, s. 113, 1924; *Ibid.* s. 22 u. 255, 1925.

Siegrist, A. (1900).—Die Gefahren der Ligatur der grossen Halssehlagadern für das Auge und das Leben des Menschen. *Arch. f. Ophthal.*, Bd. L, H. 3, s. 511-646.

Smith, Priestley (1891).—"Glaucoma," London.

————(1911).—Glaucoma Problems. *Ophthal. Rev.*, Vol. XXX, pp. 161-173; Vol. XXXI, pp. 1-8, 65-75, 129-138, 193-203, 287-296, 1912.

————(1913).—Discussion on intraocular pressure. *Proc. Roy. Soc. Med.*, London, Vol. VI, pt. iii, p. 51.

————(1917).—The blood pressure in the eye and its relation to the chamber pressure. *Brit. Jl. of Ophthal.*, Vol. I, pp. 4-26, 657-677; Vol. II, pp. 256-272, 487-490, 1918; Vol. VII, pp. 449-469, 1923.

Spalteholz, W. (1893).—Die Verteilung der Blutgefässe in der Haut. *Arch. f. Anat. u. Physiol.*, Vol, I.

de Speyr. Th. (1914).—Le pouls des artères rétiniennes. Phénomène physiologique. *Ann. d'Ocul.*, T. CLII, pp. 419-429.

Stähli, J. (1911).—Zur Anatomie des Glaucoma haemorrhagicum. *Arch. f. Augenheilk.*, Bd. LXVIII, s. 311-330.

Starling, E H. (1894).—The influence of mechanical factors on lymph production. *Jl. of Physiol.*, Vol. XVI, pp. 224-267.

———— (1896).—On the absorption of fluids from the connective tissue spaces. *Jl. of Physiol.*, Vol. XIX, pp. 312-326.

Stasińska, Jan. (1925).—Über das abnorme Verhältnis des Blutdruckes in der Aorta brachialis zum Blutdruck in den Netzhautgefässen bei Kranken ohne entzündliche Veränderung des Auges. *Klinika oczna.*, Bd. III, s. 49-58.

Stirling, A. W. (1893).—Conditions of vorticose veins in primary glaucoma. *Roy. Lond. Ophthal. Hosp. Reps.*, Vol. XIII, pp. 419-430.

Stocker (1887).—Über den Einfluss der Mydriatica u. Miotica auf den intraokularen Druck unter physiologischen Verhältnissen. *Arch. f. Ophthal.*, Bd. XXX, H. 4, s. 104-158.

Terrien, F. (1899).—Action de la sklérotomie postérieure dans glaucome. *Arch. d'Ophtal.*, T. XIX, pp. 691-695.

Thoma, R. (1889).—Über die Elasticität der Netzhautarterien. *Arch. f. Ophthal.*, Bd. XXXV, H. 2, s. 1-28.

Thomsen, H. (1918).—Anat. Untersuch. eines kürzlich entstandenen akuten inflammatorischen Glaukoms. *Klin. Monatsbl. f. Augenheilk.*, Bd. LX, s. 339-358.

Thomson, A. (1910).—The gross anatomy of the filtration angle of the human eye. *Ophthalmoscope*, Vol. VIII, pp. 608-614.

Thorner (1902).—Ein Fall von pulsierender Chorioidalvene. *Arch. f. Augenheilk.*, Bd. XLV, s. 36-39.

Tigerstedt (1919).—Lehr. der Physiologie des Menschen. 9 Aufl., s. 310.

van Trigt (1853).—Der Augenspiegel u. seine Anwendung. *Bearbeitet von Schauenburg*, 1859.

Türk (1899).—Untersuch. ü. die Entstehung des physiologischen Netzhautvenenpulses. *Arch. f. Ophthal.*, Bd. XLVIII, H. 3, s. 513-557.

Ulrich, R. (1880).—Über die Ernährung des Auges. *Arch. f. Ophthal.*, Bd. XXVI, H. 3, p. 66.

———— (1889).—Neue Untersuch. über die Lymphströmung in Auge. *Arch. f. Augenheilk.*, Bd. XX, s. 270-307.

Velter, E. (1920).—Mensuration de la tension artérielle rétinienne. *Arch. d'Ophtal.*, T. XXXVII, pp. 88-94.

Verway, A. (1925).—Bailliart's instruments used for estimating the elasticity of the small arteries. *South African Med. Rec.*, Vol. XXIII, pp. 427-429.
Vierordt, K. (1856).—Die Wahrnehmung des Blutlaufes in der Netzhaut des eigenen Auges. *Arch. f. physiol. Heilk.*, s. 255.
Vita, Arrigo (1925).—La pressione nell'arteria centrale della retina. *Ann. di Ottal. e clin. Oculist.*, T. LIII, No. 9, pp. 904-913.
Vossius, Axel (1921).—Persistierendes blutführendes Pupillarmembrangefäss. *Arch. f. Ophthal.*, Bd. CIV, s. 320-324.
Wadsworth and Putman (1878).—The intraocular circulation, etc. *Trans. Amer. Ophthal. Soc.*, Vol. II, p. 435.
Wagenmann, A. (1890).—Exp. Untersuch. ü. den Einfluss der Circulation in den Netzhaut u. Aderhautgefässen auf die Ernährung des Auges. *Arch. f. Ophthal.*, Bd. XXXVI, H. 4, s. 1-120.
——— (1892).—Anat. Untersuch. ü. einseitige Retinitis haem. mit sekundär Glaukom. *Arch. f. Ophthal.*, Bd. XXXVIII, H. 3, s. 213-260. Compare *Arch. f. Ophthal.*, Bd. XL, H. 3, s. 221-236, 1894.
——— (1897).—Beiträge zur Kenntnisse der Circulationsstörungen in den Netzhautgefässen. *Arch. f. Ophthal.*, Bd. XLIV, H. 2, s. 219-249.
——— (1898).—Über einem Falle von Keratoconus mit pulsatorischer Schwankung, u.s.w. *Arch. f. Ophthal.*, Bd. XLVI, s. 426-439.
——— (1900).—Multiple Blutungen der äusseren Haut u. Bindehaut, kombiniert mit Netzhautblutung nach Kompression des Körpers durch einen Fahrstuhl. *Arch. f. Ophthal.*, Bd. LI, H. 3, s. 550-562.
Waller (1856).—Observat. microscop. sur la circulation du sang dans les vaisseaux de l'oeil vue en transparence sur le vivant. *Compt. rend.*, T. XLIII, pp. 659-663.
Weber, Adolph (1868).—Versuch. ü. dem intraokularen Druck. *Klin. Monatsbl. f. Augenheilk.*, Bd. VI, s. 395.
———(1877).—Die Ursache des Glaukoms. *Arch. f. Ophthal.*, Bd. XXIII, H. 1, s. 1-91.
Weber, C. (1850).—Nonnullae disquisitiones quae ad facult. oc. rebus longing. et propinq. accommodand. spectant. *Inaug. Diss. Warburg.*
Wegefarth, P. (1914).—The drainage of the intraocular fluids. *Jl. Med. Res.*, Vol. XXXI, pp. 147-149. The establishment of drainage of the intraocular fluids and intracranial fluids with the venous system. *Ibid.*, pp. 149-166.
Wegner (1866).—Exp. Beiträge zur Lehre vom. Glaukom. *Arch. f. Ophthal.*, Bd. XII, H. 2, s. 1-22.
Wehrli. C. (1898).—Beiträge zur path. Anat. u. Path. des Glaukoms. *Arch. f. Augenheilk.*, Bd. XXXVII, s. 173-224.
Weiss, O. (1904).—Die Ernährung u. d. Zirkulation des Auges. *Nagel's Handb. d. Physiol.*, Bd. III, s. 438-468. Also *Arch. f. d. ges. Physiol.*, 1906, Bd. CXV, s. 602-611.
——— (1911).—Der intraokulare Flüssigkeitswechsel. *Zeitschr. f. Augenheilk.*, Bd. XXV, s. 1-14.
——— (1920).—Der Druck in den Wirbelvenen des Auges. *Zeitschr. f. Augenheilk.*, Bd. XLIII, s. 141-143.
——— (1923).—Der Flüssigkeitswechsel des Auges. *Arch. f. d. ges. Physiol.*, Bd. CXCIX, s. 462-470; *Deutsch. med. Wochenschr.*, No. 4, s. 134; *Med. Klin.* s. 97; *Klin. Monatsbl. f. Augenheilk.*, Bd. LXX, s. 257.
——— (1924).—Über den Druck in den Venen des Bulbus. *Arch. f. d. ges. Physiol.*, Bd. CCII, s. 642-644; *Schrift. d. Königsberg. Gelehrten-Ges.*, Bd. I, H. 2.
——— (1925).—Herkunft u. Schicksal der Augenflüssigkeiten. *Deutsch. med. Wochenschr.*, Nos. 1-2, 21-23, 63-65.
Weiss, O., und Lullies, H. (1924).—Über den intraokularen Flüssigkeitwechsel. *Arch. f. d. ges. Physiol.*, Bd. CCIV, s. 763-765.
Weizenblatt, S. (1926).—Fall von Anastomose zwischen Netzhaut- und Aderhautvene. *Ophthal. Gesell. in Wien*, Jan. Ref. *Zeitschr. f. Augenheilk.* Bd, LVIII, s. 454.
Wessely, K. (1908).—Exp. Untersuch. ü. den Augendruck, u.s.w. *Arch. f. Augenheilk.*, Bd. LX, s. 1-48, 97-160.
———(1912).—Beiträge zur Lehre von Augendruck., *Ophthal Gesell.*, Heidelberg.
——— (1915).—Weitere Beiträge zur Lehre vom Augendruck, die Kurve des Augenpulses. *Arch. f. Augenheilk.*, Bd. LXXVIII, s. 247-278.

Wessely, K. (1916).—Über der Einfluss der Augenbewegungen auf den Augendruck. *Arch. f. Augenheilk.*, Bd. LXXX1, s. 102-119.

White, H L. (1924).—Observations on venous pressure. *Amer. Jl. of Physiol.*, Vol. LXIX, pp. 10-20.

Whitnall, S. E. (1921).—" The Anatomy of the Human Orbit," London.

Wolff, J. (1917).—Aortic regurgitation with pulsation of all the smaller arteries. *Arch. of Ophthal.*, Vol. XLVI, p. 168.

Wordsworth (1863-65).—Note of a case in which pulsation was observed in the central artery of the retina of a healthy eye during a temporary faintness. *Roy. Lond. Ophthal. Hosp. Reps.*, Vol. IV, p. 1.

Zentn ayer, W. 1921).—The locomotor pulse. *Amer. Jl. of Ophthal.*, Vol. IV, p. 536.

Zirm (1895).—Ein Beiträge zur Anatomie des entzündlichen Glaukoms. *Arch. f. Ophthal.*, Vol. XLI, H. 4, s. 115.

BRITISH JOURNAL OF OPHTHALMOLOGY

(Monograph Supplement III.)

THE NATURE OF THE INTRA-OCULAR FLUIDS

By

W. STEWART DUKE-ELDER.

(Henry George Plimmer Research Fellow.)

Being the Sir Francis Laking Prize, 1926-1927.
From the Biochemical Department,
St. George's Hospital, London.

"*Nullius addictus jurare in verba magistri.*"
—Horace, Epis. 1.1.14.

LONDON:
GEO. PULMAN & SONS, LTD.,
24, THAYER STREET.
1927.

"Progress in Ophthalmology must depend chiefly upon the application of new discoveries in chemistry and physics."

SIR JOHN H. PARSONS.

(*Presidential Address, Ophthalmological Society U.K., 1926.*)

CONTENTS.

THE ARGUMENT.

PART I.—EXPERIMENTAL.

PART II.—THEORETICAL.

PART III.—BIBLIOGRAPHY.

THE ARGUMENT.

For more than half a century—ever since the beginning of scientific ophthalmology—the origin and nature of the intra-ocular fluids have been the subject of investigation, discussion and disagreement. A glance at the bibliography appended to this monograph will suffice to indicate the extent of the labour which has been expended upon the question; even to-day there is no consensus of opinion, and different authorities hold widely different views.

The theory which is most generally accepted at the present time is that the aqueous humour is secreted by the cells of the ciliary epithelium, that it circulates through the eye, and that it finds an exit therefrom largely by way of the canal of Schlemm. Alternatively it is held by some that this fluid is formed from the blood by a process of simple transudation. If we consider the pathological applications of the question we meet the same lack of agreement, the same unsubstantiated hypotheses, and the same innumerable discussions. Authority tells us that the most common cause of glaucoma is an obliteration or a diminution in the efficiency of the exit channels of the intra-ocular fluids at the angle of the anterior chamber, a damming back of the aqueous with a consequent increase of tension. If the condition of raised tension were due to the damming back of fluid at its exit, it appears only reasonable to expect that the aqueous, being unable to get out, would be present in excessive amount. The striking thing is that in the vast majority of cases exactly the opposite condition holds good; the aqueous is definitely diminished and in the more acute cases is present in negligible quantity, while the lens and iris are pushed forward almost to touch the cornea. It would seem, therefore, that Authority is certainly illogical, and it may be suspected that it is probably wrong.

An examination of the evidence in favour of the secretory theory shows that it is in no way conclusive. The strongest piece of direct evidence commonly put forward is anatomical in nature, depending on the histological structure of the ciliary epithelium and its resemblance to a gland—a form of evidence at best inconclusive and susceptible of varying interpretations. Some animals possess no ciliary body at all; others, possessing a ciliary body, show no structural glandular formation in it; and finally in those animals (*e.g.*, man) wherein the anatomical evidence is most complete, its resemblance to a true gland is questioned by many authorities. Moreover, it can be shown that even in these last

the formation of the intra-ocular fluid, although largely associated with the ciliary body, is by no means confined to it. The strongest piece of indirect evidence in favour of the intervention of secretory energy in the formation of the aqueous humour is that although physiological experiment has correlated the variations of intra-ocular pressure directly with variations of the blood pressure, clinical experience shows that, while there seems to be a certain association between them, the two do not vary in parallel. We have seen (1926, *a*), however, that this apparent divorce of opinion between the laboratory and the clinic might be due to neglect of a factor which, within the limits of physiological experiment, usually remains constant. When in addition to the hydrostatic pressure of the blood we take into consideration also its osmotic pressure, with the further influence of changes in the concentration of salts and hydrogen ions on the physical state of the vitreous and lens, there seems every reason to suppose that the energy necessary to maintain and vary the intra-ocular pressure can be adequately explained without postulating a special source in a separate secretory process.

The circulation of the aqueous has been demonstrated and measured only by unsound physiological experiments wherein the normal pressure conditions have been upset by opening the eye, or by making injections into the eye, or by employing other procedures which can be interpreted as calculated to initiate artificially an abnormal current. In a series of experiments on the influence of variations of the osmotic pressure of the blood on the intra-ocular pressure (1926, *a*) it was indicated that the pressure-equilibrium of the eye might be explained more consistently on the hypothesis that it was of a hydrostatic rather than of a hydrodynamic nature. These suggested the probability of a third hypothesis which has been more recently put forward, that the aqueous is formed by dialysation from the blood and is in equilibrium with it. A further series of experiments (1926, *b*) on the vascular pressures of the eye showed that they were of such a magnitude as is compatible with a dialysation hypothesis, while the fact that the pressure in the exit veins was under normal circumstances higher than the intra-ocular pressure indicated the impossibility of an hydrostatic outflow of the intra-ocular fluids.

A consideration of the work of previous observers makes it clear that confusion has arisen largely from a failure to appreciate the ease with which the normal equilibrium of the eye is disturbed, and the great majority of their deductions lay themselves open to the criticism of reasoning from the abnormal to the normal. In all physiological experiments the number of imperfectly controllable variables and the intrusion of accidental variables frequently lead to equivocal results, and rarely to a definite

pragmatic conclusion; while the attempt to eliminate the variables tends to introduce conditions so abnormal as to defeat its own ends. While the dynamic methods of experimental inquiry have therefore failed to give consistent results, we may perhaps approach more nearly what is actually occurring by making use of the more static methods of physico-chemistry. We can withdraw the aqueous from the complexity of the inter-related influences which affected it *in vivo*, and in the isolation of the test-tube, guarded from extraneous disturbances, determine with a much greater degree of precision what the normal really is. Similarly, after inducing abnormal conditions we can repeat the same process, and by comparison construct with a correspondingly smaller margin of error a coherent picture of the train of events as they have actually occurred. The process, like all metabolic processes, is ultimately a physico-chemical one. The legitimacy of this method of investigation is obvious; and its value is limited only by the exactitude of the methods of mensuration employed in determining the premises, and the correctness of the reasoning in deducing the conclusions.

The present monograph is therefore a study in the bio-chemistry of the intra-ocular fluids under normal conditions and as they appear under experimental variations from the normal. It is by no means a new study, and much work—often, it is true, fragmentary—has been done upon it by different authors at various times for varying purposes. This work I have freely drawn upon; where there have been gaps in our knowledge I have endeavoured to fill them, and to present the whole in a coherent form.

By unifying the whole a fairly authoritative statement of the physico-chemical nature of the intra-ocular fluids can be deduced. Considering the results in conjunction with those obtained by others, and viewing in their light other methods of inquiry and other hypotheses, I have come to the conclusion:

that—the nature of the mechanism of the formation and circulation of the aqueous humour as at present classically accepted and taught is wrong;
that—the aqueous is neither a secretion, nor in the accepted sense, a transudate from the blood;
that—it is a dialysate from the capillary plasma, the essential dialysing membrane being the capillary walls;
that—under normal conditions, while an interchange due to metabolic activity constantly occurs, and an internal thermal current exists, the aqueous humour does not circulate actively through the eye, but is in equilibrium with the capillary blood;
that—at the same time, constantly occurring changes of pressure, induced by muscular movements, etc., superimpose upon it secondarily a minimal and intermittent circulation.

PART I.

EXPERIMENTAL.

"History teaches that the commencement of every branch of science is nothing more than a series of observations and experiments which had no obvious connection with one another."

—J. VON LIEBIG (1846).

"In order that the facts obtained by observation and experiment may be capable of being used in furtherance of our exact and solid knowledge, they must be apprehended and analysed according to some conceptions which, applied for this purpose, give distinct and definite results, such as can be steadily taken hold of and reasoned from."

—W. WHEWELL.

THE CHEMICAL COMPOSITION OF THE NORMAL AQUEOUS HUMOUR.

The main difficulty which presents itself in the study of the bio-chemistry of the aqueous humour is the small quantity of intra-ocular fluid which is available from any one animal, and the minute concentration of some of the constituents. In order, therefore, to get a general comparison between the aqueous humour and the blood, large quantities of horse aqueous were obtained, and the pooled fluid was analysed concurrently with a typical sample of horse serum. By this procedure a qualitative comparison can be made, and although it cannot lay claim to quantitative accuracy, a relatively close approximation can be obtained. The principal constituents in each class of substance were then selected and micro-analyses made of these comparing each with the corresponding concentration in the arterial and venous plasma of the same animal.

I. THE GENERAL CHEMICAL COMPOSITION OF THE NORMAL AQUEOUS HUMOUR.

A considerable amount of work has already been done on the general chemistry of the aqueous humour. Partial analyses involving the determination of the quantities of water, organic materials, total salts, etc.,are to be found in the writings of Berzelius —ox (1832), Frerichs—ox (1848), Lohmeyer—ox (1854), Kletzinski —rabbit (1861), Michel and Wagner—ox (1886), Mörner—ox (1893), Pautz—ox (1894), Villasenor—man (1901), Castro—man (1901), Parisotti—rabbit (1908), Vladescu and Babes—ox (1914).

A more complete analysis of the intra-ocular fluids of the ox has been made by Cahn (1881), and of the horse by Mestrezat and Magitot (1921). In no case, however, has a systematic analysis been done and compared directly with the plasma.

Collection of Material.

The aqueous was taken from the eyes of horses immediately on their being slaughtered. In this animal each eye contains 1 to 2 c.c. of fluid: only the first c.c. was withdrawn, since on complete evacuation the last drawn fluid becomes contaminated with plasma exuded from the capillaries. The cornea was cleaned and dried, a nick was made through three-quarters of its substance with a sharp knife and the needle of a 1 c.c. syringe was inserted through it, care being taken to avoid the iris and to cause as little pressure disturbance as possible. The serum was a typical fresh sample obtained from the farm of the Medical Research Council.

The chemical analysis is given in Table I; in the first two columns are shown my own analyses, in the third column for the sake of completeness are given those constituents which I have not estimated, the authority being quoted in each case.

TABLE I.

	Aqueous.	Serum.	(In Aqueous.)
	Quantities in gms. per 100 c.c.		
Water	99.6921	93.3238	
Solids dried at 100° C.	1.0869	9.5362	
Total protein ...	0.0201	7.3692	
Albumen	0.0078	2.9557	
Globulin	0.0123	4.4135	
Fribrinogen ...	—	—	Traces (Hayano, 1921)
Immune bodies ...	—	—	Traces (see p. 21)
Ferments	—	—	Traces (see p. 24)
"Fats"	0.004	0.13	
Cholesterol ...	nil ?	—	
Non-protein N. ...	—	0.0239	
Total N.	0.0268	+	
Urea	0.028	0.027	
Amino acids ...	0.029	0.035	
Creatinine	0.002	0.002	
Organic acids ...	—	—	0.60 (Mestrezat and Magitot, 1921)
Lactic acid... ...	—	—	0.02 (Wittgenstein and Gaedertz, 1926)
"Sugar"	0.0983	0.0910	
Sodium	0.2787	0.3351	
Potassium	0.0189	0.0201	
Calcium	0.0062	0.0101	
Magnesium ...	0.0026	0.0028	
Chlorine	0.4371	0.3664	
Inorg. P. (P_2O_5) ...	0.0033	0.0030	
Inorg. S. (SO_4) ...	0.0061	0.0058	
Ammonia	—	—	0.003 (Mestrezat and
Bicarbonate ...	—	—	0.165 Magitot, 1921)
Oxygen	—	—	20 – 40 mm. (de Haan, 1922)
CO_2	—	—	7 – 15 mm. (de Haan, 1922)
Total CO_2	—	—	70 vols. % (Mawas and Vincent, 1925)

Methods of analysis. The proteins were estimated gravimetrically after precipitation: the total protein in the aqueous by acidifying 100 c.c. and coagulating by heat; the precipitate was washed with water and alcohol, dried at 100° C., and

Folin (1921) and Wu:

Nitrogen (Dogs) - mg. per 100 c.c.

Total N = 40
non. protein N = 25
Protein. N = 14
Amino. acid N = ±9
Urea. N = 12

Uric acid = 1.8
Creatinine = 1.3

+ hr. in aqueous plasmoma

normal human hr aqueous

= 0·019 - 0·034 %

acute plasmoma 0·213 - 0·457 %.

---

in hydrophthalmus also ↓ hr.

0·782 - 2·37 %.

- Ag $\overline{\text{I}}$ in such → 2·86 - 3·20 %

i.e. very high indeed.

---

weighed. 10 c.c. of serum, diluted to 100 c.c. with distilled water was treated similarly. The albumen was determined by precipitating the globulins by adding an equal volume of saturated ammonium sulphate to 100 c.c. of aqueous which had been allowed to stand in a desiccator, allowing this to stand for 24 hours, and filtering; the filtrate was acidified by N/10 sulphuric acid and filtered; the precipitate was redissolved in the original volume of distilled water, neutralized with dilute caustic soda, and reprecipitated with half-saturated ammonium sulphate, the albumen being precipitated again from the filtrate with acid. This process of fractionation was repeated five times. The final filtrate was acidified and boiled, the precipitate was washed with water, alcohol, and ether, dried at 100° C., and weighed. 10 c.c. of diluted serum was treated similarly. The globulin was taken as the difference between the total protein and albumen.

The total N of the aqueous was estimated by a micro-Kjeldahl, by titration; the non-protein-N of the serum, by treating similarly a protein-free filtrate (Folin and Wu). The urea was estimated by the urease method; the amino-acids by van Slyke's method; and the creatinine colorimetrically against a standard creatinine picrate solution.

The term "fats" is used without prejudice. The figures represent a gravimetric estimation of an ether extract of dried residue. The cholesterol was estimated after extraction by precipitation with digitonin.

"Sugar" is taken as reducing substance estimated as glucose by the Schaffer-Hartmann method.*

The total mineral ash was obtained by calcination. The material thus left was dissolved in HCl; barium chloride was added, and baryta, and the phosphates and sulphates removed; barium salts were removed by ammonia and ammonium carbonate; the filtrate evaporated to dryness, and the ammonium salts removed by heat; the residue was dissolved, treated again with ammonia and ammonium carbonate, filtered, acidified with hydrochloric acid, evaporated, and the sodium and potassium estimated. This residue was re-dissolved; the potassium estimated by precipitation with platinum chloride, and the amount of sodium calculated by difference. The calcium was precipitated as oxalate, and estimated as CaO; the magnesium precipitated as ammonium magnesium phosphate, and estimated as magnesium pyrophosphate. The chlorides were determined by Ruszynák's method; the inorganic phosphates gravimetrically as pyrophosphates; and the inorganic sulphates by conversion to benzidine sulphate and titration with sodium hydrate.

The results of the analysis show that the constituents of the aqueous when compared with those of serum may be divided into three groups of substances depending on the physical state of the molecules in solution.

1. *Colloid substances. Partition co-efficient: serum-aqueous* >1. —All the substances in colloidal aggregation are found in the aqueous humour in much less concentration than in the serum —proteins, "fats," immune bodies, and ferments.
2. *Diffusible substances.*—Since all the colloidal constituents of the serum appear only in traces in the aqueous humour the two solutions are of very dissimilar molecular aggregation. In comparing the distribution of the diffusible constituents it is therefore necessary to apply a correction factor to allow for the difference in solid displacement due to the unequal mass of solute. Thus 100 c.c. of aqueous contains 1.0869 gms. solids and 99.6921 gms. water, while the same quantity of serum contains 9.5362 gms. solid and 93.3238 gms. water.

*Throughout this monograph "sugar" is used in this sense as implying "reducing substance." Chemically it is a composite group including, besides glucose, fructose, aldehydes, ketones, glycuronic acid, uric acid, creatinine, and other substances.

A correction factor therefore of 100/99.6921 or 1.003 applied to the aqueous, and of 100/93.3238 or 1.07 applied to the serum gives comparative results expressed as concentrations dissolved in an equal quantity (100 gms.) of water.

(*a*) *Non-dissociated diffusible substances. Partition Co-efficient* = 1.

The total nitrogen of the aqueous is found to be 0.0268 gms. per cent. Deducting 0.0032 gms. per cent. to allow for 0.02 per cent. protein, the non-protein nitrogen becomes 0.0236 gms. per cent.—a close approximation to the non-protein nitrogen content of the serum (0.0239). The amino-acid content is probably too variable a quantity to permit of reliable deductions to be made from it when the method of collecting material is borne in mind. The creatinine appeared to be present in both in equal quantities as far as colorimetric determinations could be taken to indicate. The urea and the sugar when expressed as gms. per 100 gms. water also appeared in practically the same concentration.

TABLE II.

	Aqueous.		Serum.	
	Gms. per 100 c.c. sol.	Gms. per 100 gms. water.	Gms. per 100 c.c. sol.	Gms. per 100 gms. water.
Urea ...	0.028	0.028	0.027	0.0289
"Sugar" ...	0.0983	0.0986	0.0910	0.0974

The diffusible non-dissociated substances are therefore partitioned between the two in approximately equal amounts.

(*b*) *Dissociated diffusible substances.*

The dissociated diffusible substances are seen to be unequally distributed. In each case the cations have a partition coefficient >1, and the anions a partition co-efficient <1.

TABLE III.

	Aqueous		
	Per 100 c.c. sol.		
	Gms.	Millimols per litre.	Per 100 gms. water.
Cations			
Sodium ...	0.2787	121.2	0.2795
Potassium ...	0.0189	4.8	0.0190
Calcium ...	0.0062	1.5	0.0063
Magnesium ...	0.0026	1.1	0.0026
Anions			
Cl'	0.4371	123.1	0.4384
Po_4'''	0.0044	1.38	0.0044
So_4''	0.0061	1.8	0.0062

deduct

0.0037 [illegible] 0.0231 g. N.

Serum

	Per 100 c.c. sol.		
	Gms.	Millimols per litre.	Per 100 gms. water.
Cations			
Sodium ...	0.3351	145.6	0.3585
Potassium ...	0.0201	5.1	0.0215
Calcium ...	0.0101	2.5	0.0108
Magnesium ...	0.0928	1.2	0.0030
Anions			
Cl'	0.3664	103.2	0.3920
Po'''_4	0.0040	1.26	0.0043
So''_4	0.0058	1.7	0.0062

It is seen that in the serum there is a considerable excess of basic radicles in comparison with the aqueous, while with the acidic radicles the opposite relation holds good. The significance of this will be commented upon later. In addition to this general relationship, there is a further internal difference between the individual constituents of these two groups. The sodium and calcium show a relatively high predominance in the serum: this is accounted for by the fact that in blood a moiety of these is associated with protein as protein salts, and as such is rendered indiffusible. Rona and György (1913) found that 15 to 20 per cent. of the total quantity of sodium was thus indiffusible, and Rona and Takshashi (1913) that 30 to 40 per cent. of the total calcium was similarly in association with protein. In a similar manner, in the group of anions, the chloride in the aqueous shows a higher relative concentration than the phosphates and sulphates. This again suggests comparison with the work of previous observers, since on the dialysation of serum all the chlorides have been found to dialyse freely (Ascher and Rosenfeld, 1907; van Creveld, 1921), while the phosphates have been held back to some extent in loose combination with the proteins.

A general analysis thus shows that while all the constituents of the serum are present in the aqueous humour, the colloids are present in only small amount, the non-dissociated diffusible substances are equally partitioned, and of the ionized substances, the cations are in less and the anions in greater concentration in the aqueous than in the serum.

II. THE DETAILED CHEMISTRY OF THE AQUEOUS HUMOUR.

In the above analysis, owing to the methods which had to be resorted to in the collection of materials, any great degree of accuracy cannot be claimed. The more abundant and more easily manipulated constituents representative of each class of substance were therefore selected, and detailed examination made of these under more adequately controlled conditions.

1. COLLOID CONSTITUENTS.

(*a*) Proteins.

All observers from the time of Berzelius (1832) are agreed that the normal aqueous humour contains traces of protein : the only exception appears to be Rados (1922), whose failure to detect this substance was due to the inadequacy of the method he employed (precipitation by alcohol) for dilutions so great as are met with. Many varying analytical methods have been used, both physical and chemical : among the physical methods are those depending on the refractive index (many authors, *vide infra*), the viscosity (Scalinci, 1907, *a*), and the surface tension (Dieter, 1925, *a*) ; among the chemical methods, precipitation by Esbach's reagent (Wessely, 1908, etc.), nitric acid (Gilbert, 1924), trichloracetic acid (Mestrezat and Magitot, 1921 : Gala, 1924, etc.), and others. We may take it then that their presence is definitely established.

Apart from establishing their presence, however, no work has been done to determine their nature. Quantitatively they are present in the aqueous humour in much less concentration than they are found in the blood, a fact which can be explained by postulating a filtration or dialysation through a membrane relatively impermeable to their large-sized molecules. If this is the case we would expect to find them, although in total quantity less, yet relatively among themselves, in the same proportion as they occur in the plasma, and at the same time of unchanged and identical chemical nature. If this is not the case and an adequate explanation cannot be found to account for their alteration, it would seem necessary to postulate some secretory activity in their passage from the blood to the eye.

The Fractional Determination of the Proteins.

Qualitative determination.

The intimate nature of the proteins of blood plasma is unknown. It is still uncertain how many different individual proteins are present, how these are inter-related to each other, how far they are associated, or how far they are distinct. By artificial methods of precipitation certain fractions can be distinguished—albumen

sulfhydrylic acid - adler Landis
a. of Opth. (54) 265. 1925 -
& the methylmeth Francescheth & Wieland.
a. f. Augenheilk (99) 1. 1928
micro - Kjeldahl DZ 1927.

Ikebata. 1927

$\frac{alb}{glb} = aq \equiv$ blood.

and globulin; the globulin can be separated into euglobulin and pseudoglobulin; and, in very much smaller quantities and in more varying amount, fibrinogen also occurs. All these are present in the normal aqueous.

A large quantity of horse aqueous (100 c.c.) was concentrated in a desiccator: an equal volume of saturated ammonium sulphate was added: and the resultant precipitate demonstrated the presence of globulin.

The filtrate was saturated with ammonium sulphate: a further precipitate demonstrated the presence of albumen.

The globulin fraction was dissolved in dilute NaCl, and dialysed in a collodion tube against distilled water for forty-eight hours: a faint white haze demonstrated the presence of euglobulin.

The additional globulin fraction—pseudoglobulin—was demonstrated by further precipitation by half saturation with ammonium sulphate.

Fibrinogen is present in the plasma in amounts so minute that its recognition in the aqueous is difficult. It occurs here in quantities so small, if at all, as to render this fluid non-coagulable. The early observers, relying on the non-coagulability of the normal aqueous (see Terrien and Dantrelle, 1913), decided against its presence (Jesner, 1880); but that it is present in traces has been established by Hayano (1921).

Quantitative Determination: The Protein Quotient.

The relative quantities of the two most abundant protein groups found in the plasma of an individual animal are relatively constant under normal conditions (Howe, 1925): and although the ratio—globulin/albumen—varies considerably among different individuals of the same species (Hartley, 1914, *a*), it preserves among these, within a wide margin, a characteristic value. This ratio—the protein quotient—was determined in three species of animals wherein it differs widely.

In the *horse*, from which a large supply of aqueous was available, a quantitative determination was carried out by gravimetric analysis as previously indicated. The results were:—

TABLE IV.

	Aqueous.	Serum.
Total protein	0.0201	7.3692
Globulin	0.0123	2.9570
Albumen	0.0078	4.4125
Quotient—Glob./Alb.	38.8/61.2	39.9/60.1

The quantities of pseudoglobulin and euglobulin were unfortunately found to be too small to allow of reliable quantitative estimation.

Similar figures were determined for the *cow* and the *rabbit*, the estimations of the total protein being done by a micro-Kjeldahl estimation; that of the albumen by a similar method after precipitation of the globulin with half saturated ammonium sulphate, and subsequent removal of the ammonium salt by dialysis; while the globulin was calculated as the difference between the two.

Cow. TABLE V.

	Aqueous.	Serum.
Total proteins	0.017	7.53
Globulin	0.009	3.73
Albumen	0.008	3.80
Quotient—Glob./Alb. ...	50/50 approx.	50/50 approx.

Rabbit.

	Aqueous.	Serum.
Total proteins	0.04	5.57
Globulin	0.009	1.16
Albumen	0.031	4.41
Quotient—Glob./Alb. ...	20/80 approx.	20/80 approx.

It is thus seen that the proteins are present in approximately equal quantities in the aqueous and the serum, as far as the method of analysis of quantities so minute can be relied upon.

The Specific Identity of the Proteins.

The work of Dale (1912) and Dale and Hartley (1916) has shown that all the proteins of serum are capable of acting individually as anaphylactic antigens, a reaction which is characteristic of different species of blood serum. It is not clear of what properties, physical or chemical, this antigenic independence is an expression; but the reaction provides a test for the specific identity of these substances with a degree of sensitiveness that is almost inconceivably small. Thus Wells (1908) succeeded in sensitizing guinea-pigs with 1/20,000 milligrams of egg-albumen.

I am indebted to Dr. Hartley for being able to apply this test in the comparison of the proteins of the aqueous humour and the serum. Horse aqueous was collected as already described with minute precautions against any possible contamination with blood. Proteins from horse serum were used which were obtainable in a degree of exceptional purity (Hartley, 1914, *b*). With these last, young virgin female guinea-pigs were sensitized. After an interval exceeding twelve days the uterus was excised and the sensitiveness of its plain muscle tested by the method described by Dale and Hartley (1916). The uterus was suspended in a bath of Ringer, and the contractions of the muscle on the addition of protein were registered by a kymograph. The reaction of one horn was tested with the pure serum protein, and the reaction of the other horn, which can be regarded with some certainty as being equivalent in its specific sensitiveness and physiological condition to the first, was tested with a solution of protein from the aqueous humour. The investigation is still in progress and is being extended, but a typical result shows that a true anaphylactic reaction is obtained with the aqueous protein, and it is interesting that with the lens protein it is not obtained. It follows that the proteins in the aqueous humour are specifically identical with those in the blood.

Immunity mother → foetus
Kmpa. ~~[illegible]~~ 816 (69) 1922

It is seen therefore that although largely held back and occurring in much less quantity, *all the proteins of the plasma are found in the aqueous humour, that they are found here in the same relative proportion as they occur in the blood, and that they are specifically identical.* They thus appear to remain unchanged in their transit from the blood-vessels to the eye.

(*b*) Immune Bodies.

Closely associated with the question of the protein content of the aqueous humour is the occurrence in it of the various substances associated with the chemical aspects of immunity. It has frequently been stated that the presence or absence of these substances in the aqueous provides an argument for the existence of a special "permeability" of the epithelial cells, involving a selective mechanism other than a purely physical one. More recent work, however, employing more refined methods of investigation and interpreted in the light of the fuller knowledge of the nature and behaviour of these substances which we now possess has provided results which show that this is not the case.

It seems to have been established that antigens are invariably colloidal in nature, and it has never been conclusively shown that anything except proteins exhibit true antigenic activity (Wells, 1916, 1925).* Although their immunological specificity undoubtedly depends largely on their chemical individuality (Obermayer and Pick, 1906; Schmidt and Bennet, 1919, etc.), probably the essential factor in determining their characteristic biological activity is the large dimensions of their molecules with their attendant colloidal properties (Bordet, 1909). Further, they must be non-diffusible colloids of molecular size such that they are not able to enter the tissue cells by diffusion; were the molecules small enough to be so taken in, they would be destroyed and the formation of extra-cellular antibodies would cease to become a necessity for their destruction, and *ipso facto* they would cease to be antigens. They are thus all colloidal: a protein in colloidal solution is antigenic—its cleavage products are not (Wells, 1913); a re-combination of these cleavage products regains the antigenic nature (Gay and Robertson, 1912), while in aggregates greater than colloidal dimensions (as by coagulation) the antigenic properties are again lost (Wells, 1908).

Antibodies on the other hand, which are dependent for their existence on the presence of antigens, are of unknown nature, and have never been isolated. We do not even know whether they

*Although the evidence points to the fact that only protein bodies can act as antigens, it is possible that some toxic glucosides may be proved to have this property; moreover, it is to be remembered that the protein nature of the bacterial toxins, which are certainly antigens, has not yet been established. (See Pryde, *Recent Advances in Physiology*: Churchill, 1926.)

are specific molecular aggregates or merely physical forces dependent on altered conditions of surface energy. They are recognized by what they do, not by what they are; and according to what they do they are known by an imposing array of terminological labels: precipitins, agglutins, anti-toxins, complement-fixation antibodies, opsonins, cytolysins, haemolysins, bacteriolysins, anaphylactins. Whatever they are, and there is considerable evidence to show that they are essentially the same in nature, differing merely in the method whereby their specific action is demonstrated, they are certainly colloidal or associated with colloids, and are probably of a protein nature, related to, or associated with, globulin (Dean, 1923; Ruppel, 1923; and Homer, 1920). Certainly they behave as colloids as is seen by the fact that they are retained by porcelain filters and dialysing membranes (Eisler, 1923), by their behaviour in an electric field (Field and Teague, 1907; Bechold, 1907), or by the type of their reaction curves (Crawford and Foster, 1918).

Further, complement-fixation and complement-deviation reactions are typical colloid chemical reactions depending on the physical state of the colloids (Coultar, 1921; Hecht, 1923; Pandit, 1923; Abderhalden, 1922), and artificially constructed colloidal emulsions may be made to serve as antigen or as complement (Liebermann, 1921). Complement itself is a large colloidal complex consisting of more than one protein constituent, associated probably with substances of a "lipoidal" nature, of such a size that it is partially retained by a Berkefeld filter (Schmidt, 1912), and allowed through only when the absorptive power of the filter is satisfied (Muir and Browning, 1909).

It is therefore to be expected that these bodies will be found merely in traces in the aqueous humour, their concentration here bearing a relation somewhat similar to, or even smaller than, that of the proteins relative to the concentration of these substances in the blood. Further, it is to be expected that the various types of immune bodies will be found in proportion to the size of their molecules. The earlier writers held the view that the aqueous contained few or no bacteriolytic substances. When one recognizes the difficulty of their investigations with the technique which was available to them, and the minuteness of the concentration of these substances, their finding is not to be wondered at. We have seen that with a concentration of 8.0 per cent. in the blood only 0.02 per cent. of protein gets through the capillaries into the eye, that is, the ratio is 1:400. The majority of these immune substances are probably of more complex molecular structure than the more simple plasma proteins; and Poleff (1914) found the concentration of antibodies in the aqueous of the horse to be 1:250 to 1:800 of that in the blood of the same animal. The relative quantities are therefore strictly comparable.

While some failed to detect the presence of bacterial properties in the normal aqueous (Possek, 1906; Zur Nedden, 1908; Zade, 1910, etc.), the majority of the early writers found some evidence of their presence, although this was usually very slight—Nuttall (1888), Buchner (1890), Marthen (1893), Bach (1894), Perles (1895), Lobanow (1899), Rymowicz (1903), Gatti (1902), Koske (1905), Pignatari ((1909), Knapp (1909).

Antibodies have been identified by Römer (1902), Rymowicz (1903), A. Leber (1906), Salus (1910-11), Burgers (1910), Morax and Loiseau (1911), Kuffler (1913), Poleff (1914), Pastega (1914), Lagana (1915), Cronstedt (1923-24), Landis and Robertson (1925).

Agglutinins have been identified by Römer (1902), Lindahl (1910), Salus (1910-11), Kuffler (1912-13), Pastega (1914).

Bacteriolysins by A. Leber (1906), Axenfeld (1905), Grüter (1911), Salus (1910-11), Kuffler (1913), Pastega (1914), Cronstedt (1923).

Haemolysins, although their presence in the normal aqueous was denied by Römer (1902-03), Wessely (1903), Possek (1906), and Burgers (1911), have been conclusively demonstrated by Majischita (1909), Salus (1910-11), Kuffler (1913), and Pastega (1914).

Precipitins alone seem to have eluded all search in the normal aqueous, and when they have been looked for no evidence has been obtained of their presence—Dungern (1903), Zade (1910), Kuffler (1913), and Pastega (1914). We do not know what a precipitin is, and the only property associated with it which we can conjecture is its great molecular complexity. Since a precipitation reaction is presumably largely of the nature of a precipitation of colloids by other colloids to form a still more complex colloid suspension (Krogh, 1916; Nicolle, 1920; Hirsch, 1922), it would seem advisable to await further knowledge before attaching any great importance to its presence or absence.*

Complement was found to be present only in very small quantities or to be absent by Levaditi (1901), Falloise (1905), and Levaditi and Inman (1907), but was identified by Sweet (1903), Majischita (1909), Pastega (1914), while Bruynoghe and Stagnet (1924) have demonstrated certain of its elements. The presence of a Wassermann reaction, the activity of whose "antigen" may probably be taken as depending on the dispersion of a complex mixture of tissue lipoids in emulsion, has been denied by Blatt (1921), but Gilbert and Plant (1920-21) have found it on occasions, Gala and Fabian (1926) frequently, and Okazaki (1920) claims to be able to demonstrate it invariably when it is present markedly in the blood.

The evidence of the behaviour of these substances seems to suggest that their distribution is unaffected by any selective agency

*For review of physico-chemical theories see Epstein and Paul, *Kolloid Zeitschr.*, Bd. XXIX, S. 310, 1921.

except their own molecular size. Not only do they appear to be able to enter the eye in minute quantity, but they are also able to get out. It seems to be the general rule that the toxin molecule is smaller than that of the antitoxin. Thus agglutinogens can pass through collodion and other dialysing membranes which are impermeable to agglutinins, and the presence of bacteria in a collodion sac implanted in an animal leads to the general production of agglutinins in the blood of the animal (Wells, 1925). Correspondingly, several authors on infecting the anterior chamber have caused a generalized infection—Pfeiler and Kapfberger (1913), Kümmell (1910), Krusius (1910), Schönberg (1914). The experience of the first of these is typical: on inoculating the aqueous with rabies, the infection became generalized rapidly in 39 out of 40 rabbits, in 12 out of 12 sheep, and in 7 out of 8 dogs.

A review of the evidence, therefore, seems to suggest that while these large-molecular complex aggregates concerned in immunity reactions are found in the blood in great dilutions, only traceable owing to the delicacy of the biological reactions to which they are susceptible, *they are present in the normal aqueous of highly immunized animals in much the same proportion as we would expect on purely physical grounds,* in amounts corresponding closely with the concentration of proteins found there. According to Kolmer (1924) a similar state of affairs obtains in the serous cavities of men and animals (pericardium, peritoneum, etc.) where complement, opsinins, agglutinins, and bacteriolysins may normally be considered to be absent.

(*c*) Ferments.

Ferments resemble immune bodies in that little is known of them, in that they are recognized from what they do rather than what they are, and in that they appear to be essentially associated with colloids. Their presence in the normal aqueous humour is therefore demonstrable only in traces. As would be expected, those which do occur depend upon the substrate available. Leber (1891) found a diastatic ferment present, Hayano (1921) identified maltase, amylase and fibrin ferment. In addition, and more important, the presence of proteolytic ferments seems to have been definitely established: Goldschmidt (1914), Hayano (1921), and Jacinski (1925).

(*d*) Fats.

Being non-diffusible, "fats" are present in the aqueous humour only in traces. My analysis gave as total ether extract 0.004 gms. per 100 c.c., while cholesterol was present, if at all, in quantities so small as not to be determinable. Berzelius (1832) similarly found "traces" of an extract of alcohol, and Jess (1925) failed to isolate cholesterol from the normal aqueous.

Zeitschr. 1926.
a tryptic ferment; a fibrin ferment; and an
autolytic ferment.

Ikeda. T. 1927.
+ diastase. + lactolytic ferment. + lipase

DIFFUSIBLE SUBSTANCES.

From the foregoing analysis it is seen that all the diffusible substances in the blood are found in the aqueous. Typical examples of these substances were chosen—sugar as being representative of the non-dissociated substances, and chloride as being representative of the ionized constituents, these two being the most easily manipulated and the most abundant—and their concentration in the aqueous humour and the blood determined under more exact and adequately controlled conditions.

The two fluids under comparison—aqueous humour and blood—were in each case taken from the same animal. Rabbits were used in the investigation. The aqueous was withdrawn under sterile conditions by means of a syringe dried with alcohol and ether. The needle used had a broad lance point which was introduced through the cornea obliquely near the limbus. Two per cent. cocaine was instilled into the conjunctival sac as an anaesthetic; it has been repeatedly demonstrated that this substance does not alter the properties of the intra-ocular fluids to any appreciable extent. Before the needle was introduced, the cornea was dried with blotting paper to obviate any possible contamination with lacrymal secretion which is of widely different composition. Blood from the ear was taken, also with aseptic precautions, the central artery or the marginal vein being used as the case required. Plasma in preference to serum was employed, since it is the former which comes into equilibrium with the aqueous *in vivo*. The distribution of sugar and salts between plasma and corpuscles is unequal. Thus in the latter the sugar appears to be present in very small quantity only (Irving and Kay, 1926; Ege, 1920, etc.), or may be absent altogether (van Creveld and Brinkman, 1921; Falta and Richter, 1919, etc.). For comparative purposes, therefore, plasma and not whole blood must be used. The use of anti-coagulants was dispensed with, since by altering the "impermeability" of the corpuscles these substances fundamentally alter the distribution of some of the constituents, *e.g.*, the sugar (Peters, 1925). They thus completely obscure the actual state of the blood *in vivo*, and make estimations carried out *in vitro* in their presence useless for comparative purposes. Blood was therefore drawn by suction (*v*) through a paraffined needle and paraffined tube (*p*) directly into a centrifuge tube (*q*), also coated in paraffin (see Fig. 1). It was collected there under a layer of paraffin and immediately centrifuged. The centrifuging was done rapidly, since the blood sugar in shed blood is rapidly destroyed, the degradation being largely associated with the corpuscles (Irving, 1926). After centrifuging, the middle layer of plasma was pipetted off for analysis without its ever having been in contact

with air. In order to obtain results providing further accuracy of comparison, estimations were carried out on both arterial and

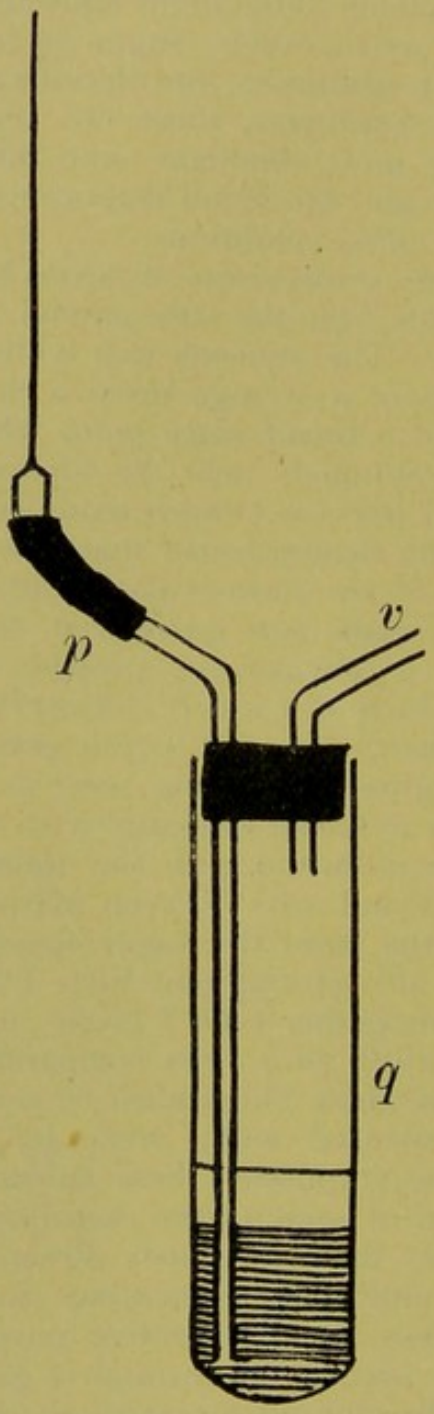


FIG. 1.
For collection of plasma.

venous blood, since the concentration both of sugar and of chloride is materially different in the two.

As in the general analysis, the results are expressed as gms. per 100 c.c. of solution and as gms. per 100 gms. of water.

...pine, & eserine, pilocarpine do not influence sugar of
...bbit. normal. aq. sugar: 0·10; 0·13, 0·13, 0·13.
sun. c̄ eserine, pilocarpine, salispine.

...gar in human eyes: ask (1927). (Bang's method)
In various path. conditions: cataract, glaucoma, iridocyclitis
tumours, seclusio pupillae,
all ages: aq. & blood = 1 : 1·2.
average = (human): Blood: 0·10, {venous. Plasma = 0·12; aq = 0·10
also in 1, 2, & 3rd aqueous (plasmoid): sugar increases.
Blood - 0·10; Plasma - 0·12, aq I 0·09. aq II 0·10; aq III 0·11
(mean value of 16).

...q = dialysate.
...aq: bound sugar.
average sugar human aqueous: 0·10%.

...ebata 1927 Sugar aq & blood

Bufano 1927. Sugar in pathological human eyes & blood = 1·41 : 1. (this work cannot be argued from.) ask's results more reliable.

		Ox.	Horse
Tron (1926)			1·10
	aq.	0·12	1·07.
...gar	vit.	1·14	
	ser.		

...udlin & others (1927)
glucose in dogs: 77 mmg. per 100 cc..

100 c.c. of rabbit's plasma was found to contain 8.6832 gms. of solids at 100° C., *i.e.*, 100 c.c. plasma contain 93.6168 gms. of water (density = 1.023). A correction factor of 100/93.6168 or 1.07 therefore gives the true concentration in watery solution. Similarly in the aqueous 100 c.c. were found to contain 1.0899 gms. of solids at 100° C., while its density is 1.007. A correction factor of 100/99.6101 or 1.003 is therefore correspondingly necessary.

(*a*) The Sugar.

Claude Bernard (1859) was the first to identify "traces" of sugar in the aqueous humour of the ox.

Subsequent observers obtained varying results:

Leber (1875)—0.045 per cent.

Chabbas (1877)—"traces."

Deutschmann (1877-87)—0.05 per cent.

Jesner (1880)—0.16 per cent.

Kuhn (1887)—0.03—0.04 per cent.

Pautz (1894) determined its chemical individuality by preparing from it glucosazone.

Ask (1914), using more modern and reliable methods of analysis, first investigated the question in man, and found the concentration in the aqueous equal to, or slightly above that in the blood—aqueous 0.12—0.15, blood 0.1—0.13 per cent. He concluded that the sugar of the aqueous would approximately equal that of plasma. His findings have been substantiated by subsequent work.

Osborne (1919)—ox: 0.07—0.12 per cent., equal to blood.

Holi (1920)—man: 0.081—0.091 per cent., equal to blood; ox—0.06; cat—0.08—0.15; sheep and pig—0.09; rabbit—0.14—0.116 when the serum was 0.110.

Mestrezat and Magitot (1921): horse—0.094 per cent.; man—0.090; dog—0.133.

de Haan and van Creveld (1921, *a*): rabbit—0.045 per cent., less than blood.

Hayano (1921): cattle—0.06 per cent.

Hamburger (1922) gives 0.125 per cent. in man (Jacoby, 1920).

Jess (1922): ox—0.075 per cent.

Dieter (1925, *b*): man—0.004 per cent. greater than the blood.

The quantity of sugar found in the aqueous humour therefore seems to approximate closely to that found in the blood. The results of the analysis given below were obtained by the technique of Hagedorn-Jensen (1923), a method which by common consent is regarded as being one of the most reliable for the estimation of small quantities of this substance. To obtain a reliable comparison all the precautions already outlined were carried out, both

arterial and venous plasma from the same animal being used protected throughout from air, and unaffected by anti-coagulants.

TABLE VI.

		No. of rabbit.	Gms. per 100 c.c. sol.	Gms. per 100 gms. water.
Aqueous		1	0.141	× 1.003 − 0.141
		2	0.138	0.138
		3	0.175	0.175
Arterial plasma ...		1	0.136	× 1.070 − 0.145
		2	0.139	0.148
		3	0.170	0.182
Venous plasma ...		1	0.120	× 1.070 − 0.128
		2	0.111	0.118
		3	0.143	0.153
Average	Aqueous		0.151	× 1.003 − 0.151
	Arterial plasma		0.148	× 1.070 − 0.158
	Venous plasma		0.125	× 1.070 − 0.133

It is seen that the sugar concentration of the aqueous humour lies between that of arterial and venous plasma. Since the sugar content of the venous plasma is considerably less than that of the arterial, this relation suggests that the concentration in the aqueous corresponds with that of the capillary plasma. Although falling between the two, its concentration appears to be more closely related to the arterial than to the venous plasma; a finding which may be compared with that of Foster (1923), Verzàr and Keller (1923), and Ege and Henriques (1925), who showed that the sugar content of "finger blood," and therefore presumably of capillary blood, was very nearly identical with that of arterial and widely different from that of venous blood. These findings may be compared with those of previous observers—Osborne (1919), who found the concentrations in the aqueous humour and the blood to be the same, Ask (1914), who found them the same, or the aqueous 0.01 to 0.02 per cent. greater, Dieter (1925), 0.004 per cent. greater, and de Haan and van Creveld (1921), who found the aqueous 0.045 per cent. less than the mean between arterial and venous blood, a figure which they accepted as being representative of capillary blood. These last observers accept the hypothesis of the dialysation of the aqueous, and conclude from their results that the glucose of the blood is partially retained in combination with the proteins of the plasma.* Until a more exact

*A controversy still exists as to the existence of this so-called "bound sugar" in blood—the "sucre virtuel" of Lépine (1909). For the later literature in favour of its existence see Kleiner (1918), Ege (1920), de Haan and van Creveld (1921). For the point of view of "free sugar" the early literature is found in Rona and Michaelis (1909); for later work see Hess and McGuigan (1914), McGuigan and Ross (1917), H. J. Hamburger (1919), etc.

knowledge of the sugar content of capillary blood is available it would seem dangerous to draw any conclusions of this nature from the above figures. The figures obtained in the present investigation, however, show that *the sugar content of the aqueous humour lies between that of arterial and venous blood,* and suggest that it corresponds, within the limits of exactitude of biological experimentation, with that of capillary blood.

The general analysis on page 14 provides no reason to suppose that all the undissociated constituents of the plasma are not partitioned in a similar manner. Andresen (1921) found the urea in the aqueous sometimes above and sometimes below that in the plasma; and Rados (1922, *b*) found, as is to be expected, the amino-acid content variable, but in concentration comparable to that in the blood; Pagani (1926) gives the value of 22 to 40 in gms. per 100 c.c. The concentration of lactic acid appears to be somewhat higher in the aqueous of some animals (dog) though not in others (cat, rabbit), according to the micro-analysis of Wittgenstein and Gaedertz (1926); but even in these its quantity was found to vary intimately with that in the blood. Mendel and Goldscheider (1926) found 20 to 24 in gms. per cent. in the aqueous, and 15 to 18 in the blood.

(*b*) The Salts.

A large amount of work has already been done on the salt content of the aqueous humour most of which has concerned itself with the estimation of the chlorides.

The following estimations have been given (they are expressed as percentages of NaCl.).

In the ox—Berzelius (1831)—1.15, Lohmeyer (1854)—0.689, Cahn (1881)—0.7811, Vladescu and Babes (1914)—0.612—0.731, Wessely (1921)—0.68, Rados (1922)—0.703, Jess (1922)—0.77.

In the horse—Mestrezat and Magitot (1921)—0.711, Rados (1922) —0.586—0.7618: the latter found in the serum—0.58.

In the rabbit—Wessely (1908)—0.7, Löwenstein (1915)—0.9—1.0, van Creveld (1921)—0.634—0.665, Ascher (1921)—0.605—0.633, Gala (1924)—0.62.

In the cat—Gala (1924)—0.76.

In the dog—Mestrezat and Magitot (1921)—0.734, Rados (1922) —0.586, Gala (1924)—0.78.

In man—Kletzinsky (1861)—0.48—0.53, Mestrezat and Magitot (1921)—0.737, Rados (1922)—0.879, Ascher (1922)—0.7, Gala (1924)—0.7.

In the present investigation the salt was estimated in the rabbit by Ruszynák's modification of Koranyi's method (1921), and compared with the chloride content of both arterial and venous

plasma, using all the precautions to get the biologically "normal" fluid already outlined. Particular attention was paid to avoid contamination with the tears, since the chloride content of the lacrymal fluid is probably higher than that of the aqueous humour.*

TABLE VII.

Chloride expressed as NaCl.

		No. of rabbit.	Gms. per 100 c.c. sol.	Gms. per 100 gms. water.
Aqueous	... ...	1	0.668	× 1.003 − 0.670
		2	0.597	0.599
		3	0.641	0.643
Arterial plasma	...	1	0.603	× 1.070 − 0.645
		2	0.543	0.581
		3	0.590	0.631
Venous plasma	...	1	0.578	× 1.070 − 0.618
		2	0.501	0.536
		3	0.573	0.613
Average	... ...	Aqueous	0.635	× 1.003 − 0.637
		Arterial plasma	0.579	× 1.070 − 0.619
		Venous plasma	0.551	× 1.070 − 0.589

It is thus seen that the chloride content of arterial blood is substantially higher than that of venous blood. This is due to the ionic interchange which follows the addition of carbon dioxide to unreduced blood. The chlorides are unequally partitioned between the plasma and corpuscles and the ratio of distribution at any one time is a function of the reaction, that is, of the amount of carbon dioxide which the blood is carrying (Rona and György, 1913; H. J. Hamburger, 1918). When carbon dioxide is added to arterial blood, there occur reactions between this gas and both the sodium proteinate compounds of the plasma and the haemoglobin or phosphoric acid salts of the corpuscles. In addition to this, the change from the arterial to the venous condition involves a diminution of the chloride content and an increase of the bicarbonate content of the plasma, with a corresponding increase in the chloride content of the corpuscles, while the actual metallic cation content of both remains unaltered. In any comparison therefore between the chlorides of the aqueous and the blood, it is essential that "true" plasma be used, and that its state in both the arterial and venous conditions be kept in mind. The aqueous comes into relation with the capillary plasma, and although from the work of Fraser, Graham and Hilton (1924) it would seem dangerous to reason with

*The chloride content of tears is given thus—Arlt (1868)—1.257; Lerch (quoted Hammersten, 1922)—1.3 per cent. Rötth (1922), however, finds 0.948 per cent., and Wada (1921), 0.8418 per cent.

von E. 1926, 1927. salts. (ox)

	K	Ca	Mg.	Na	Cl.	
q.	0·190	0·062	0·00105	0·339	0·437	} o/oo
th.	0·191	0·069	0·00096	0·338	0·441	
um.	0·285	0·103	0·0015	0·331	0·336.	

~~Jacob~~ Jacobs & Wittgenstein (1927)
Na + Cl in aqueous blood = Donnan equilibrium.
Na = 314 mg. % aq.
= 328 mg. % serum

um. 1928

	P.	S.	
A.	0·028	0·012	} o/oo
V.	0·010	0·014	
S.	0·047	0·027	

Baumann (Heidelberger Ber. 1928)
dialysed serum analysed dialysate and aqueous
found Na. K. Ca. Cl in dialysate & serum
almost = equal proportions.

Kaneko. Be. Heidel. p 53.
normalung = dm ag = 0.0029.

any great attempt at accuracy from the one state to the other, it would appear, as in the case of the sugar distribution, that the capillary plasma is in this respect more nearly related to the arterial than to the venous condition (Lundsgaard, 1922; Verzàr and Keller, 1923).

From the present investigation it is seen that the chloride content in the aqueous is substantially greater than in the plasma in any state of reduction; this will be found to have an important bearing upon considerations of the nature of its origin. From the general analysis carried out on horse aqueous it was seen that the other acidic radicles are partitioned in a similar manner when the degree to which they are associated in a non-diffusible form with the plasma proteins is kept in mind. Expressed comparatively as millimols per litre these were found to be

Chloride in aqueous (Cl')	123.1	; in serum	103.2
Phosphorous in aqueous (Po'''_4)	1.38	; in serum	1.26
Sulphur in aqueous (So''_4)	1.8	; in serum	1.7

Previous analyses to a large extent confirmatory of the concentration of these substances in the aqueous are :

Sulphates (SO_3)—Cahn (1881) 0.026 per cent. in the ox.

Mestrezat and Magitot (1921) 0.031 in the horse.

(SO_4)—Heubner and Meyer-Bisch (1926) 0.006 in the rabbit.

Phosphates ($N_3\ PO_4$)—Cahn (1881) 0.0199 per cent. in the ox.

(P_2O_5)—Mestrezat and Magitot (1921) 0.0073 in the horse.

An opposite relation was seen to hold good in the case of the basic radicles : they were all found in less concentration in the aqueous, and, relatively among themselves, approximately in the ratio of their diffusibilities.

Expressed as millimols per litre the comparative concentrations were found to be :

Sodium in aqueous	121.2	; in serum	145.6
Potassium in aqueous	4.8	; in serum	5.1
Calcium in aqueous	1.5	; in serum	2.5
Magnesium in aqueous	1.1	; in serum	1.2

Previous estimations of these substances in the aqueous are :

Cahn (1881) – ox		Mestrezat and Magitot (1921) – horse		Lehermann (1925) – rabbit	
Na_2O 0.470	p.c.				
K_2O 0.032	,,	Alkaline ash 0.140	p.c.	Na 0.2940	p.c.
CaO 0.033	,,	CaO 0.0105	,,	K 0.0187	,,
MgO 0.0013	,,	MgO 0.0030	,,	Ca 0.0101	,,

It would appear, therefore, that of the ionized constituents of the plasma, the cations are found in less concentration and the

anions in greater concentration in the aqueous, the individual differences between them being attributable to the known extent to which the various ions are associated with the indiffusible proteins.

THE REACTION OF THE AQUEOUS HUMOUR.

As will be seen later the hydrogen ion concentration of the aqueous humour relative to the plasma is a question of considerable importance.*

The aqueous is considerably to the alkaline side of neutrality. Its pH is 7.5 to 7.7, *i.e.*, higher than that of the blood, a fact which corresponds to the excess of negative radicles found in it. It is alkaline to litmus (Mays, 1885) and it gives no change with phenolphthalein (Dor, 1901). It has been found to be alkaline even in the acidosis of diabetes (Deutschmann, 1887; Leber, 1875), although Hertel (1921) has found a pH value as low as 7.02.

Hertel (1921) using the indicator method was the first to measure the degree of alkalinity of the aqueous. He found a pH of 7.3 to 7.5 in man and 7.6 to 7.7 in the dog. Nordenson (1921) obtained an average value of 7.5; Scalinci (1924, *a*), 7.5; while arterial blood was 7.4; Meesmann (1924-25), 7.7 in man, the rabbit, and the dog, while the blood was 7.5; Baurmann (1924-25), 7.43 to 7.52, arterial blood being 7.52 and venous 7.35; Schall (1925), 7.5; and Gala (1925), 7.40 to 7.52. Mawas and Vincent (1925) using the electrical method obtained a value of 7.55.

Its value is very constant and varies intimately with the blood (Meesmann, 1925). It varies with age; in the foetus it is slightly higher than after birth (Nordenson, 1921), and in the later years of life it tends progressively to become more acid: Schall (1925) gives average figures 7.5 at 45 years, 7.3 above 45, and even down to 6.9 in advanced age.

---

*In the present connection a brief explanation may be advisable.

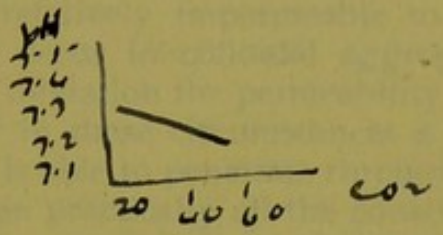
In pure neutral distilled water a small degree of dissociation occurs into free hydrogen and hydroxyl ions until equilibrium is established when the number of both of these is equal. The total number of free hydrogen ions present at 21° C. is 1/10,000,000 of a gm. per litre, *i.e.*, 10^{-7} gms. per litre. As an expedient of convenience Sörensen suggested using merely the negative logarithm to the base 10 omitting the negative sign, and employing the symbol P_H, usually modified for ease of printing into pH. This, the hydrogen ion exponent for neutral reaction, is therefore 7; solutions with a greater number of hydrogen ions are acid, and the pH, since it is a negative exponent, therefore falls; solutions with a less number of hydrogen ions are alkaline and the pH rises, *i.e.*, a pH above 7 is alkaline, below 7 is acid. Blood (pH = 7.4) is slightly alkaline. The pH of venous blood is slightly more acid, being 0.01 to 0.04 less. The extreme normal limits of blood may be taken as 7.28 to 7.41 (Cullen and Robinson, 1923), by hard physical work it may be reduced to 7.05, by forced breathing it may be raised to 7.85. The value of the pH as a rule varies slightly with the method employed in its determination. It is usually somewhat lower by the electrometric than the colorimetric method, although when both are carried out under adequately controlled conditions the difference appears to be negligible (Conway, Verney, and Bayliss, 1923).

Rubrik 1926. pH (electrometric)
non acid urine blood

Rabbits. blood 7.35 - 7.5 urine 7.15 - 7.3.

Human ~~7.35~~ 7.15 - 7.23 at 40 mm Hg. CO_2 tension

Taking into consideration CO_2 tension.
The above variation between the limits of blood



Sobit denies this

Lehmann and Hellsmann
pH - after hunger I. 7.77 : 7.72
II 7.68 ; 7.63 ; 7.53
III 7.46.

Bartelmann (1927) - improved methods.
Human aq = 7.2 - 7.35 - mean = 7.268
Blood = 7.31.
age no difference: and after hunger no difference in this

Kronfeld (1926-7) improved methods (van Slyke's method)
pH between 7.1 - 7.3: non acid than blood.
Total CO_2 = 10 - 30% higher than blood.
Heart = dialysate.

III. THE CHEMICAL CONSTITUTION OF THE ABNORMAL AQUEOUS HUMOUR.

If the aqueous is a secretion it is difficult to place a limit to the number and extent of the variations to which it may be liable qualitatively or quantitatively. If it is a dialysate there are only two possibilities which offer themselves: an alteration in the permeability of the dialysing membrane (the capillary walls) and an alteration in the composition of the blood. All the variations of which I am aware can be embraced under one or other of these heads.

(A) ALTERATIONS IN THE PERMEABILITY OF THE CAPILLARY WALLS.

Normally the capillaries are relatively impermeable to those constituents of the blood which occur in colloidal aggregation. It is well known that in a state of dilatation the permeability of the capillaries is increased, and that in these circumstances a larger proportion of colloidal molecules is able to penetrate through their walls until a stage is reached when practically all the constituents of the plasma are allowed to pass through indiscriminately (see Krogh, 1921). This occurs in the eye as elsewhere, and along with the increased protein content of the aqueous humour formed under those conditions very definite changes in the ionic distribution between it and plasma take place. This aqueous I have proposed to call the *Plasmoid Aqueous*.

The introduction of a new term requires an explanation. The aqueous humour, formed under these conditions which has been most extensively studied is the fluid re-formed after paracentesis of the anterior chamber. This re-formed aqueous has variously been called "albuminous" or "secondary" or "re-constituted" aqueous, "l'aqueuse de seconde formation," "de remplacement," "Kammerwasser nach Vorderkammerpunktion," etc. It will, however, be shown that in addition to albumen it contains all the colloidal constituents of the plasma in abnormal amount—globulin, immune bodies, etc.—and that definite changes involve its other constituents. Further, a fluid of the same chemical constitution is formed not only after paracentesis but under all conditions where capillary dilatation occurs, as on radiation of the eye or on the application of heat, irritant subconjunctival injections, mechanical and chemical irritation of the cornea, the production of venous congestion by subluxation of the eyeball or constriction of the neck. Moreover, its formation is prevented by any agency which prevents the capillaries dilating, as stimulation of the sympathetic, the injection of adrenaline, or ligature of the carotid. It would seem, therefore, that none of these names meets the requirements of the case. Inasmuch as it differs from the normal aqueous only in resembling the plasma more closely, I have called it the "plasmoid" aqueous.

I. Dilatation by Lowering the Intra-Ocular Pressure.

(a) *By Paracentesis of the Anterior Chamber.*

When the eye is punctured and the intra-ocular fluids are withdrawn, the capillaries, deprived of the supporting pressure of the aqueous, undergo immediate dilatation. The aqueous re-formed under these conditions was examined in rabbits. It was withdrawn with the same technique as has already been described, and the

re-formed fluid was withdrawn twenty minutes after the first paracentesis.

The chemical compositions of the normal and the plasmoid aqueous were compared in respect of their colloid content, their sugar content, and their chloride content.

1. *Colloid Content.*

The colloids, which are largely composed of proteins, were estimated refractometrically. This appeared to be the most appropriate method for the purpose, since the power to refract light is a function of the size of the molecules, the property with which we are largely concerned, and is additive, being independent of their chemical nature. A Dipping refractometer (Zeiss) was used provided with an auxiliary prism to enable one drop of fluid to be dealt with: the instrument reads to an accuracy corresponding to ± 3.7 units of the fifth decimal place of nD. The increase of refractive index found in the plasmoid aqueous (see Table VIII) shows an increase of colloids. Considering the total colloid as protein the approximate corresponding percentages of this substance are also given. The figures do not pretend to any great accuracy, but are only approximate. They were calculated by the technique suggested by Robertson (1915), making use of a large quantity (100 c.c.) of horse aqueous for the purpose. The refractive index of the normal aqueous was first obtained; the refractive index of a protein-free filtrate of this fluid was then determined, and the difference between the two correlated with a gravimetric estimation of the total proteins in the original fluid.

Normal horse aqueous. Refractive Index	1.335130
Protein-free horse aqueous „ „	1.335091
Refractive index of protein „ „	0.000039
Per cent. of protein (chemical estimation)	0.02

The aqueous of the rabbit was found to have on the average a higher refractive index than that of the horse:

Normal rabbit aqueous. Refractive Index	1.335168
Protein-free aqueous ... „ „	1.335091
Hence refractive index of protein	0.000077
Hence approximate percentage of protein	0.04

TABLE VIII.

No. of rabbit.	Quantity of aqueous removed in c.c.	nD Normal	nD Plasmoid	Difference Plasmoid–Normal.	Approximate protein per cent.
1	0.10	1.335244	1.337088	0.001844	1.0
2	0.20	1.335130	1.338428	0.003298	1.8
3	0.25	1.335168	1.339036	0.003868	2.0
4	0.32	1.335244	1.339834	0.004590	2.5

kin H. (1927) Glucose dog - 77 mg. in 100 cc. aq.

ok 1927. + Sugar in human plasmoid. aqueous.
Blood. 0·10. Plasma 0·12. Aq. I : 0·09. Aq II 0·10. Aq III · 0·11
No sugar.
(Banjo method).

That this increased refractive index was due in large measure to increase of protein—both of globulin and albumen—was seen in the recognition of increased quantities of these substances by special tests. The Noguchi globulin test gave a granular flocculent precipitate; Pandy's reaction gave a typical blue-white cloud. Both of these reactions are absent in the normal aqueous. Similarly the Nonne-Apelt test gave a positive reaction for globulin, and on filtering and acidifying the presence of increased albumen was confirmed.

Concurrent sugar and salt estimations showed the following results:

1. *"Sugar."*

Estimation by the Hagedorn-Jensen method. Results expressed as glucose per 100 c.c.

TABLE IX.

No. of rabbit.	Normal aqueous.	Plasmoid aqueous.	Difference. Plasmoid-Normal.
1	0.143	0.148	0.005
2	0.155	0.173	0.018
3	0.173	0.175	0.002
4	0.165	0.172	0.007

This increase of sugar is probably largely to be explained by an increase in the blood sugar during the experiments. An effort was made to accustom the rabbits to experimental procedures before performing any of the above experiments upon them, but, even so, the necessary manipulations induced an increased sugar content in the blood due to emotional excitement, the liberation of adrenaline, and general sympathetic disturbance. Thus, in one experiment the blood sugar at the start was 0.154 and at the end 0.177 per cent. It may be taken, therefore, that the glucose content is practically unchanged.

2. *Salt.*

Estimation by Ruszynák's method. Results expressed as NaCl per 100 c.c.

TABLE X.

No. of rabbit.	Normal aqueous.	Plasmoid aqueous.	Difference. Normal-Plasmoid.
1	0.641	0.600	0.041
2	0.597	0.561	0.036
3	0.680	0.536	0.144
4	0.500	0.421	0.079

It is thus seen that after paracentesis the colloid content of the plasmoid aqueous is increased and that it is increased in proportion to the extent to which the anterior chamber has been evacuated, *i.e.*, to the degree of capillary dilatation induced. Coincidentally with this, the anions (chloride) show a diminishing concentration, while the non-ionized diffusible substances (sugar) remain unchanged.

These findings receive corroboration from the work of many investigators and may be further amplified from their researches.

That the protein content of the secondary aqueous formed after paracentesis is increased was shown by Adamük (1868), Deutschmann (1879), Grünhagen and Jesner (1880), Ehrlich (1882), Nicati (1890), Bauer (1896), Raehlmann (1906), Scalinci (1907), Wessely (1908), Herzfeld (1917), Kumajai (1920), Siehe (1921), Bellavia (1923).

Recent and more detailed papers are :—

Referring to the cat : Seidel (1918), Löwenstein (1920), Gala (1924, *a*).

Referring to the dog : Löwenstein (1920), Rados (1922), Lehmann and Meesmann (1924), Gala (1924, *a*). Yudkin (1926)

Referring to the horse : Rados (1922).

Referring to the rabbit : Hagen (1920, *a* ; 1921), van Creveld (1921), Gebb (1922), Wessely (1921, 1923), Gala (1924, *a*), Lehmann and Meesmann (1924).

While in the lower animals all are agreed that there is an increased protein in the plasmoid aqueous, in man the issue has not always been so clear. Hamburger (1910) first pointed out that in him the increase of protein was less than in animals, and Römer (1920), Hagen (1920, *a* and *b* ; 1921, *a* and *b*), Gebb (1922), and Rados (1922) claimed that there was often no increase at all ; while zur Nedden (1920) claimed that on similarly puncturing the vitreous, the human aqueous showed no increase of protein. Löwenstein (1920) also found the increase so small as to be negligible. While there is undoubtedly less protein in the plasmoid aqueous of man than in that of most animals, a circumstance the significance of which will be dealt with later, there is as certainly more protein in it than in the normal fluid. The negative results detailed above are partly due to the fact that practically all of these observers made use of the refractometric method of estimation, which is inaccurate as a means of estimating small percentages of this substance in dilute solutions. Further, the time chosen for the withdrawal of the plasmoid aqueous was not often appropriate (Römer, ten days ; Rados, up to twenty-four hours, etc.) : the optimum time at which the maximum increase occurs after the first paracentesis is 30 minutes according to

Franceschetti & Wieland
(nephelometer)
A. f. Augenh. (94) 1, 1928, +
up to minimum of 0·110.

Ascher. K.W. (1922)
after puncture in human eye. plasmoid
aqueous has + protein (refractivity) and
less salt.

+ protein in human plasmoid aqueous
27 hrs: vesicles in ciliary Epithelium
fibrinous Exudate in A.C.
hyperaemia of whole uveal tract.
Samojloff. Gr (122) 139. 1929 (? Bib.).

Wessely (1908), or 45 minutes according to Mestrezat and Magitot (1922).

In contradistinction to these experimenters, the following have shown that an increase does occur in man, and the variety of the methods used seems to indicate that it may be taken as occurring in fact :

		Per cent.
Wessely (1922) ; using Esbach's method found an increase		of 0.07 to 0.16
Gilbert (1924)	„ nitric acid	0.102
Hagen (1920)	„ refractometric	0.2
Löwenstein (1915)	„ refractometric	0.05
Mestrezat and Magitot (1921),	trichloracetic acid ...	0.17
Gala (1924)	trichloracetic acid ...	0.048
Deiter (1925)	surface tension ...	0.066

Mestrezat and Magitot (1922) give the following figures :

25 minutes after puncture	0.05	per cent.
30	0.08	„
40 to 45	0.283	„
180	0.025	„

Any difference between the two—man and animals—is therefore quantitative and not qualitative.

Along with the increase of protein there is an increase of all the colloidal constituents of the plasma, and sometimes, in excessive degrees of dilatation, an entrance of the cellular elements of the blood into the eye.

Fibrin is present in readily detectable quantities (Adamük, 1868; Grünhagen and Jesner, 1880; Erhlich, 1882; Nicati, 1890). While the normal aqueous therefore does not coagulate, the plasmoid aqueous does (Bauer, 1896-9; Scalinci, 1907; Magitot, 1917; Wessely and Fassin, 1923).

Cholesterol is also detectable (Morax and Loiseau, 1911; Mawas, 1912). So also is bile (Rados, 1922).

Immune bodies of all kinds are readily found (many observers), even including precipitins which have not been detected in the normal aqueous (Dungern, 1903, Pastega, 1915, etc.). Further, serological reactions which usually are not readily found in the normal aqueous are present in the plasmoid type of fluid—the Wassermann reaction (Gilbert, 1920; Okazaki, 1920; Gilbert and Plant, 1921), the gold sol reaction (Magitot, 1922; Gilbert, 1924) and Pandy's reaction (Gilbert and Plant, 1920-1921; Gilbert, 1924).

Difficultly diffusible drugs, which get into the normal aqueous only in traces occasionally, such as the organic compounds of

arsenic, find their way readily into the plasmoid aqueous (Neame and Webster, 1923). Yudkin (1926)

The lowering of the concentration of anions, as seen by the diminished salt content, with the increase in protein has been demonstrated by ~~Ascher (1922)~~, Rados (1922), Gala (1924), and Lehmann and Meesmann (1924).

Ascher (1922)

There is a similar change to the plasmoid type of aqueous on lowering the intra-ocular tension by any method whatever. An increase of protein has been demonstrated in the following circumstances :—

(*b*) *Lowering tension by vitreous puncture.*—(Löwenstein, 1911-12-15; Rados, 1922). Yudkin, 1926.

(*c*) *By external pressure* applied to the globe of the eye. (Bellavia, 1923; Knapp, 1912; Musy, 1914), or by *massage*. (Löwenstein and Kubik, 1915.)

(*d*) On the intra-venous injection of *hypertonic salts* (Nakanura and Mukai, 1922; Mazzola, 1924), or intraperitoneal milk injections (Tristaino, 1923).

(*e*) In the lowered tension occurring in *detachment of the retina* : Gilbert (1924), Magitot and d'Autrevaux (1925).

II. Dilatation of the Capillaries by Radiant Energy—Heat, Etc.

(*a*) *Ultra-violet light.*—A rabbit was exposed for 10 minutes before a water-cooled mercury vapour lamp in such a way that its left eye was protected.

Table XI.

	Left eye normal.	Right eye radiated.
Refractive index ...	1.335168	1.340898 (3 p.c. protein)
Sugar	0.154	1.172
Chloride	0.693	0.520

(*b*) *Infra-red Rays.*—A rabbit was exposed for 10 minutes before a carbon arc, the ultra-violet being filtered off, and the left eye being protected.

Table XII.

	Left eye normal.	Right eye radiated.
Refractive index ...	1.335247	1.341990 (3.5 p.c. protein)
Sugar	0.125	0.131
Chloride	0.661	0.501

Leberman (1925) gets a rise in salt (Na + NaCl) after paracentesis in rabbit along with + protein.

	Pr %	Na	NaCl	K.	Ca.
		mg. per 1 cc. aq.			
Thus. normal	0·02	2·75	6·98	0·175	0·08
aq. I	3·05	3·12	7·89	0·2	0·1
aq. II	3·00	3·12	7·89	0·2	0·105

He quotes Ascher as confirming this.

He finds a similar rise of salts in plasmoid aqueous after subconj.al salt injection.
Quotes Hertel (1910) as confirming this. & Wessely.

Tron (1928), however, gets
+ colloids
+ kations (Na)
− anions (Cl)
} in aq II in rabbit.

Russk. oftalm. VIII. 45, 1928.

Zbl. (19) 214

It is probable that both these agencies act in the same way, the radiant energy being absorbed by the pigment of the iris and converted into heat which causes capillary dilatation. Particularly after radiation of ultra-violet rays is the coagulability of the aqueous very apparent (see Duke-Elder, 1926, *c*); when the needle is withdrawn from the eye a solid spear-head of clot frequently remains fixed to the inner surface of the cornea and projecting backwards into the anterior chamber.

(*c*) *Heat—Hot Fomentations and Diathermy.* Wessely (1903), Juselius (1910), Sattler (1912), Löwenstein and Kubik (1915), have demonstrated an increase of protein.

III. Capillary Dilatation by Local Irritation.

The capillaries may be dilated by reflex action when the eye itself is subjected to local irritation. In these circumstances the increased protein in the aqueous has been observed by the following :

(*a*) *Mechanical Irritation* of the cornea, etc. Grünhagen (1886), Bach (1894), Tornabene (1904), Mastrobuono (1909).

(*b*) *Subconjunctival Injections—of Salt* : Wessely (1908), Hertel (1910), McIlroy (1910), Löwenstein (1911), Kochmann and Römer (1914), Löwenstein and Kubik (1915), Kumagai (1920), Alajmo (1923), Samajloff (1925).

—of dionin : Löwenstein and Kubik (1915), Biagio (1923), Sankowski (1927)

(*c*) *Chemical Irritation, e.g.*, silver nitrate (Wessely, 1908).

IV. Capillary Dilatation by Nerve Stimulation.

(*a*) *Lesion of the Cervical Sympathetic.* Lodato (1901), Tornabene (1904), Scalinci (1907) have demonstrated an increase of proteins.

(*b*) *Trigeminal Stimulation.* Nicati (1890).

V. Dilatation by Interference with the Blood Supply.

(*a*) *Local Bleeding.* Leplat (1923).

(*b*) *Luxation of the Eye.* Hamburger (1914).

(*c*) *Congestive Hyperaemia.—Bier's Congestion.* Wessely (1908), Löwenstein and Kubik (1915).

—Constriction of the Neck. Leber (1903), Leboucq (1913), Wessely (1909).

VI. Increase of Permeability by Damage to the Capillaries.

An increased permeability with increased exudation of protein and the formation of a typical plasmoid aqueous is also induced by damaging the capillary walls.

(*a*) *In inflammation.*—An increase of proteins in iritis and cyclitis has been demonstrated by Raehlmann (1906), Schirmer (1910), Löwenstein (1920), Römer (1920-24), Hagen (1921), Gala (1924), Gilbert (1924), Magitot and d'Autrevaux (1925). A similar increase on sympathetic disturbance in the other eye was shown by Parisotti (1908); and a decrease in salts was found by Gala (1924) and Magitot and d'Autrevaux (1925). Yudkin (1926) + hr. in iritis.

(*b*) *On Poisoning.*—By the local injection of sodium fluoride, Scalinci (1907).

(*c*) *On Death.* Kletzinsky (1861), Deutschmann (1879), Freytag (1909), Angelucci (1915), van der Hoeve (1912) have shown that an increase of proteins occurs.*

The increase of proteins in the plasmoid aqueous after paracentesis has frequently been attributed to the increased difference of pressure suddenly produced between the capillaries and the chambers of the eye. That this is not the essential cause is seen in the formation of a plasmoid aqueous under conditions where capillary dilatation or increase of the permeability of their walls is brought about by factors which do not alter the pressure conditions appreciably. Further, when a maximum pressure disturbance is produced, as by paracentesis, and the capillary dilatation at the same time is prevented, a typical plasmoid aqueous does not form.

To show that the changed chemical constitution is due essentially to the dilatation of the capillary wall, a paracentesis was done after 1 c.c. of adrenaline and cocaine had been injected behind the eyeball. This has the effect of maintaining the capillaries in a state of relative constriction. That an increase of protein in the aqueous re-formed in these circumstances is not so marked as is the case normally has already been shown by Wessely (1909), Hagen (1920), and Belavia (1923). It is seen that the secondary aqueous thus formed resembles in its entire constitution the normal rather than the plasmoid type.

---

*For the action of drugs—*vide* page 101.

this increase makes itself evident 10 hrs. after death (Yudkin, 1926).

dkin (1926).

TABLE XIII.

	Normal aqueous.	Aqueous re-formed after adrenaline injection and paracentesis.
Refractive Index ...	1.335130	1.335244
Sugar	0.152	0.175
Chloride	0.638	0.63

A similar occurrence—the formation of a normal rather than a plasmoid type of aqueous—is met with apparently after paracentesis if the capillaries are prevented from dilating by any other agency. This one would infer from the observations of Wessely (1921), who found that the fluid re-formed secondarily after puncture with simultaneous stimulation of the sympathetic contained no great excess of protein, and of Wessely (1908, 1921) and Magitot and d'Autrevaux (1922), who found a similar occurrence on puncture after ligation of the carotid. *The composition of the aqueous is therefore a function of the state of capillary dilatation rather than of the pressure difference between the blood stream and the chambers of the eye.* This consideration will be seen later to have an important bearing on the localization of the effective dialysing membrane in the capillary walls.

(B) ALTERATIONS IN THE CONSTITUTION OF THE BLOOD.

1. *By the Addition of Colloids.*

Owing to the relative impermeability of the interposed membrane to substances in colloidal aggregation, these do not find their way into the eye when they are injected into the blood. I have verified this experimentally after the injection of large quantities of gum arabic in cats: the refractive index of one eye before the injection was found to be the same as that of the other after it. Similarly, on inducing artificial albuminuria in dogs, Vollaro (1907) found that the albumen in the aqueous did not exceed the proportion obtained in normal dogs. The membrane, however, like all biological membranes, is not wholly impermeable, as is evident by the presence of a small quantity of protein in the normal aqueous. Sugita (1922) claims to have obtained an increased quantity of cholesterol in the eye after feeding rabbits with lanolin; and in the case of those substances which are susceptible to tests of high delicacy, such as immune bodies, a slightly increased quantity can be detected in the aqueous when their concentration in the blood is greatly increased (Poleff, 1914). Difficultly diffusible drugs, moreover, when they are injected into the blood stream are found in traces in the normal aqueous. Thus Neame and Bury (1922) found no arsenic in the normal aqueous of rabbits after the intra-venous injection of N.A.B., but, repeating this work, Neame and Webster (1923) demonstrated its presence in minute quantities. It has already been noted that when the permeability of the capillaries is increased by dilatation or by diminishing the physiological integrity of their walls by any agency, all these substances pass with much greater freedom into the eye.

It has been stated (Collins, 1925, p. 149) that the difficulty which arsenical compounds find in entering the eye indicates a secretory activity, or differential permeability of the ciliary epithelium. Although some of their estimations yielded negative results, Neame and Webster found in others that the normal aqueous did contain traces of arsenic. This was present in the proportion of other non-diffusible substances—0.2 mgm. per cent. (1/500,000). In muscle they found even smaller quantities—0.12 mgm. per cent. (1/833,333), yet it has never been suggested that the tissue-fluid of muscle is specially secreted. In the plasmoid aqueous they found a concentration of 1/40,000. The entrance of arsenical compounds into the eye is, therefore, comparable with the behaviour of difficulty diffusible materials, *e.g.*, the proteins, and is in every way consonant with a physical transit by diffusion.

It therefore appears that *when the concentration of colloidal substances in the plasma is varied, their passage into the eye follows laws which seem to be determined merely by the relative impermeability of the interposed membrane to large-sized molecules.*

(neosalvarsan)
(arsenic - S-> appears - only traces.
Stühmer - Arch. f. Dermatol. u. Syph. 70. 589. 1914
Löhlein - Münch. med. Woch. 1911, No. 16.

Kramer, Yudkin, & Morton 1927
Injected arsenic into dogs.
traces in normal appears.
Large quantities after paracentesis.

. Accardi. (1926)
Bismuth - small quantity entering in
primary appears: much more in placenta.

Ehrlich & Wiltgenstein (1927-8)

ected substances into blood - studied influence of sol.

Anions a. acid dyes. (Uranin, Eosin, Orange G, Chrysolin, Erioglaucin. Fuschin. S. Azocarmin. & others). → aq.

visible.

b. other anions & organic { - salicylate acid → aq.
hydroferrocyanic acid

β inorganic Cl, Br } - aq.

i.e. all anional diffusible substances go blood → aqueous.

2. Diffusible cations. a. basic dyes (Methyl red. methylene green. Safranin O, Brilliant bright blue, methylene blue. Fuchsin, Pyronin G.)

do not → aqueous.

attach themselves to substance of blood &c.

b. other cations Na (as NaCl) K (as KCl) Ca (as CaCl2) } not → aq.

i.e. under phys. condition. cations injected into the blood stream do not → aqueous.

(cf. Wiltgenstein & Krebs. in C.S.F.)

i.e. permeability = function of the electric charge and is a purely physical affair.
- not secretory.

P.T.O

2. *By the Addition of Diffusible Substances.*

Those substances which when injected into the blood are to a greater or less extent absorbed by the proteins in the plasma necessarily partition themselves between this fluid and the aqueous somewhat in the same way as do the proteins themselves. The best known of these is fluorescine, which, being highly absorbable (Trümpy, 1922), largely associates itself in an indiffusible state with the plasma colloids. Thus Wessely (1905) found that after its intra-venous injection fluorescine was present in the blood in a concentration of 1/13,000 and in the aqueous of 1/1,000,000; Löhlein (1910) found it also in corresponding proportions after its intra-venous or subcutaneous injection. It occurs in the aqueous in the proportion which physical laws demand, a fact strikingly proved by de Haan and van Creveld (1921), who showed that this dye appeared in the aqueous in exactly the same concentration relative to the plasma as they obtained by dialysing blood through a collodion membrane.

Substances on the other hand which remain in a diffusible condition partition themselves equally according to the laws of diffusion between the aqueous and the blood. Even substances in extremely minute concentration in the plasma can be detected in the aqueous when tests of sufficient delicacy are available for their identification, as witness adrenaline (Rossi, 1923).

Sugar.—It has already been shown that the concentration of sugar in the capillary plasma and the aqueous is strictly comparable. On the intra-venous injection of sugar I have shown in another connection (1926, *a*) that the concentration of this substance rises *pari passu* in the aqueous. A similar variation is seen in any condition wherein the sugar content of the blood is raised: the aqueous changes correspondingly, though slightly less quickly, while it returns to its normal condition somewhat more slowly than the blood. This is seen:

In diabetes—Goldschmidt (1860), Stöber (1862), Knapp and Carius (1863), Fischer (1863), Ossowidzki (1869), Schmidt (1873), Leber (1875), Deutschmann (1877), Calderaro (1915), Ask (1914), Holi (1920), Dieter (1925).

On the oral administration of sugar—Ask (1914), Hertel (1914), Holi (1920).

On the injection of adrenaline—Calderaro (1915), Holi (1920), de Haan and van Creveld (1921).

On extirpation of the pancreas—Vollaro and Calderaro (1915).

Conversely it is decreased on the injection of insulin—Ohkuni (1924).

The sugar, therefore, in the aqueous varies intimately with the blood.

Salts.

Sodium chloride.—Similarly the salt content of the aqueous varies with that of the plasma. This I have already demonstrated on intra-venous injection (1926, *a*; where a fuller discussion will be found). Other corroboratory findings are given by Scalinci (1907), Grignolo (1913), and Hertel (1914). A similar rise occurs after subconjunctival injections—Demons (1906), Wessely (1908), Verderame (1913), and Kochmann and Römer (1914). Gala (1924) found that in patients with nephritis with chloride retention in the blood, the chloride of the aqueous was increased, and that it was similarly subnormal in pathological conditions when the blood chlorides were below the normal level.

In a similar manner foreign salts, when introduced into the blood, are found in the aqueous.

Bromides.—Ascher (1922) on administering bromides recovered them from the aqueous.

Iodides.—After the administration of iodides by the mouth Leber (1903) recovered iodine in ten minutes from the aqueous, and Schläfke (1879) in six minutes. After subcutaneous injection it has been recovered by Deutschmann (1883) and Hilbert (1884) in three minutes, and by Leplat (1887) in ten minutes. Confirmatory findings were obtained by Ottolenghi (1886), Ovio (1900), and Vinci (1901). After subconjunctival injection iodine has been recovered by Hilbert (1884) and Addario (1899) in five to six minutes; Guglianetti (1919) identified iodine in the eye after its application to the skin of rabbits. Further, Löhlein (1910) found that its concentration in the aqueous after systemic administration varied relatively to the blood as its diffusion constant would lead us to expect.

Potassium ferrocyanide provides a suitable example of such a substance in that it is non-toxic to animal tissues and is capable of easy recognition and quantitative estimation by the Berlin blue reaction. Its passage into the aqueous has been studied by Memorski (1865), Knies (1869), Weiss (1877), Ulrich (1880), Weber (1881), Wessely (1903), Wegefarth (1914). Löhlein (1910) found that its concentration in the aqueous and the blood described parallel curves, and that at all times its distribution between them was according to the physical laws of diffusion.

It is thus seen that, as far as they have been investigated, diffusible substances seem to enter the eye by simple diffusion, and their behaviour shows no evidence of the existence of any selective mechanism.

anderby Swithgenstein (1926)

2. 3 Colloids - dye trypan blue. ~~Congo red~~, not → Br
congo red: (non diffusible) → slightly.
Water blue - not at all.

i.d. colloids - no.

IV. THE PHYSICAL PROPERTIES OF THE AQUEOUS HUMOUR.

THE NORMAL AQUEOUS HUMOUR.

1. Specific Gravity.

I find the specific gravity of the aqueous humour of the horse at 15° C. to be 1.0077; of the rabbit, 1.0073.

Other estimations from the literature are (see especially Steindorf, 1908):

Horse—1.0059-1.059 (Steindorf, 1908); 1.0074 (Mestrezat and Magitot, 1921).
Ox—1.0038-1.0077.
Rabbit—1.007-1.008.
Pig—1.0058-1.0084.
Sheep—1.009.
Dog—1.008-1.009.
Cat—1.0088.
Man—1.004 (Chenevix, see Berzelius, 1832, p. 442).
1.004 (Kletzinsky, 1861).
1.012 (Villasinor, 1901); 1.0075 (Castro, 1901).
1.002-1.009 (Steindorf, 1908).

2. Refractive Index.

I find the aqueous humour to have a refractive index with the Dipping refractometer at 17° C.:

in the horse—1,335130 ± 0.000037;
in the rabbit—1.335130 − 1.335244 ± 0.000037.

This corresponds almost exactly with the refractivity of a protein-free filtrate of plasma.

The following readings are given in the literature:

Using the Abbé or the Pulfrich refractometer:
Horse—1.33378-1.3364 (Fleischer, 1872; Becker, 1882; Klingberg, 1889; Freytag, 1907; Cirincione, 1913; Rados, 1922).
Ox—1.33347-1.3366 (Fleischer, 1872; Mönnich, 1883; Matthiessen, 1891; Freytag, 1907; Cirincione, 1913; Osborne, 1919; van der Hoeve, 1912; Rados, 1922).
Sheep—1.33347-1.3365 (Fleischer, 1872; Klingberg, 1889; Meyer, 1897; Freytag, 1907; Cirincione, 1913).
Dog—1.3337-1.3379 (Valentin, 1879; Meyer, 1897; Freytag, 1907; Cirincione, 1913; Löwenstein, 1920; Rados, 1922).
Pig—1.33347-1.3369 (Fleischer, 1872; Klingberg, 1889; Freytag, 1907; Cirincione, 1913).
Cat—1.3335-1.3364 (Klingberg, 1889; Valentin, 1879; Cirincione, 1913; Seidel, 1918; Löwenstein, 1920; Adler, 1925).
Rabbit—1.3340-1.3358 (Löwenstein, 1915; Hagen, 1920, *a*; van Creveld, 1921; Rados, 1922; Gebb, 1922; Alajmo, 1922; Wessely, 1923).

Monkey—1.33428-1.3363 (Valentin, 1879; Cirincione, 1913).

Man—1.33366-1.337 (Helmholtz, 1856; Hirschberg, 1874; Freytag, 1907; Hallauer, 1913; Schiötz, 1913; Löwenstein, 1920; Hagen, 1920, *b*; Rados, 1922; Gebb, 1922).

Using the interferometer:

Ox—1.33520-1.33532 (Vladescu and Babes, 1914).

3. Surface Tension.

Three methods have been employed in the estimation of the surface tension of the aqueous humour. Bardier and Cluzet (1902), experimenting on dogs, found the surface tension of the aqueous slightly in excess of that of water. They used, however, a stalagmometer—a dynamic method not always suitable when colloids are present since the elasticity of such solutions complicates the results. van Creveld (1924), using the static method of Brinkman and Dam (1923), wherein the force necessary to rupture a film of fluid held within a platinum ring is measured by a torsion balance, found that the aqueous had a surface tension greater than plasma and less than water. His figures were: aqueous 60.4, plasma 57.0, water 76.8, dymes/cm. at 37° C. Dieter (1925, *a*) using a capillary viscometer obtained a similar result: that the surface tension of the aqueous was 72.4 to 73.0 dymes/cm. at 180° C., being slightly less than that of water and greater than blood in the proportion which one would expect from the difference in colloid content.

4. Viscosity.

The viscosity of the aqueous is, as we should expect, greater than that of water and considerably less than that of blood. Cavazzani (1905-9-10) was the first to determine its value. In comparison with water (=1.0) he obtained the result of 1.029 to 1.030. Scalinci (1907), measuring the time of flow through an Ostwald viscometer, obtained comparative results in the dog: aqueous—1 minute 51 2/5th seconds, distilled water—1 minute 46 2/5th seconds, serum—2 minutes 56 1/5th seconds. Results confirmatory to these were got by Mastrobuono (1909), Troncoso (1910), Löwenstein (1911), and Guglianetti (1920-24). Dieter (1925, *a*) in the human aqueous found a value varying from 1.024 to 1.040.

5. Conductivity.

I have found that in the rabbit at 18° C. the conductivity of the aqueous, as determined by the Kohlrausch method and expressed as $\lambda \times 10^4$ varies from 129.3 to 136.3.

Other determinations in the literature are (expressed in the same notation) :

Ox—150 at 25° C. (Hertel, 1909; Vladescu and Babes, 1914).
177 at 35° C. (Botazzi and Sturgio, 1906).
178.24 at 37° C. and 96.8 at 10° C. (van der Hoeve, 1912).

Rabbit—132.15 at 18° C. and 154.37 at 25° C. (Hertel, 1909).
131 at 18° C. (van der Hoeve, 1912).
148 at 25° C. (Knape, 1910).
193.51 at 36°C. (Vladescu and Babes, 1914).

Dog—173 at 38.5° C. (Scalinci, 1907).

In comparing these it is to be noted that the conductivity value varies with the temperature, a constant occurrence with all solutions (Johnstone, 1909), the relation involving the varying fluidity of water (Washburn, 1911). The temperature co-efficient for the aqueous is 0.023 (Hertel, 1908), for the serum 0.022 (Bugarsky and Tangl, 1898).

In comparison with the serum these results all agree in the fact that the conductivity of the aqueous is the greater. The difference between the two is due to the excess of colloids in the serum impeding by their viscosity the migration of the ions. Bugarsky and Tangl (1898) found that conductivity decreased by 2.5 per cent. per one per cent. of protein added, *i.e.*,

$$\lambda_c = \lambda \times \frac{100}{100 - 2.5 \times \text{per cent. protein}}$$

where λ_c and λ are the corrected and the determined conductivities respectively. Applying this correction formula to the serum, the two are reduced to a common denominator, and on this comparative basis they are found to agree closely :—

				λ aqueous.	λ_c serum.
Scalinci (1907)	...	...	...	170—175	174
Hertel (1909)	...	...	...	132	129
Knape (1910)	...	...	...	148	147

6. Osmotic Pressure.

Two methods have been employed in the determination of the osmotic pressure of the aqueous humour : a physical method depending on the lowering of the freezing point, and a biological one based on the plasmolysis of the red blood corpuscles. Each of these has failed to give consistent results.

Those employing the cryoscopic method have been handicapped by technical difficulties. The minuteness of the quantity of fluid available compelled them to experiment with the collected aqueous of many animals and to compare this pooled fluid with a "typical" sample of serum. An exact comparison cannot be said to result

from this procedure; and the comparison is rendered still more questionable when it is remembered that in the estimation a temperature difference of 0.001° C.—a quantity difficult to assess with any approach to accuracy—registers to the quite appreciable variable of 9 mm. Hg.

The early observers consistently arrived at the conclusion that the aqueous was hypertonic to blood serum, the average ratio being 11 :10—Dreser (1892) and Kunst (1895) experimenting on the ox, Richon-Duvigneaud and Onfray (1904) experimenting on the rabbit, Botazzi and Sturgio (1906) experimenting on the ox, and Scalinci (1907) on the dog. Later, van der Hoeve (1912) finding variations in either sense, pronounced them isotonic, a conclusion corroborated by Osborne (1919), both of these experimenting on the ox. Dieter (1925, *b*) experimenting on the rabbit and using a micro-apparatus in order to compare the two fluids of the same animal, found in three experiments that the aqueous was isotonic in one and hypotonic to the serum in two.

The method has therefore given results which have severally represented the aqueous as being hypotonic, isotonic, or hypertonic to the serum. In so far, therefore, as the depression of the freezing point can be taken to indicate the osmotic pressure of a physiological fluid,* these results point to the fact that the two—aqueous and serum—are in this respect nearly related.

Using the method of plasmolysis,† the earlier observers were again united in considering the aqueous hypertonic to serum—H. J. Hamburger (1893), in the horse; Kunst (1895), Manca and Deganello (1898) in the ox, a conclusion supported by Manca (1898), using the haematocrit. Later investigators, however, using the same method, failed to get the same consistent results. Römer (1907) in the ox, considered that the friability of the red cells varied in itself up to 50 per cent., and he arrived at the same conclusion as did Nuel (1905) and Rissling (1908), using various animals, that any differences found were within the limits of the experimental errors involved in the method, and that the aqueous was isotonic with the blood serum "more or less." The method cannot pretend to any great accuracy, and in addition to the source of error depending on the variable behaviour of the red cells, there are others depending on the treatment of the serum.

From a consideration of these results it would seem apparent that, whatever their exact relationship, the osmotic pressures of

*For discussion see Washburn (1911).

†For a resumé of the principles concerned see H. J. Hamburger (1904, Bd. I, S. 439).

the aqueous and the blood are not far removed in magnitude. In comparing values so nearly alike, and in dealing with solutions so widely different in their molecular aggregation, it would seem preferable to employ as far as possible a direct method of measurement, which, if the aqueous humour is a dialysate, would allow a comparison between it and the blood of the same animal to be made under conditions as constant and as near to the normal as experimental manipulations permit. Totally impermeable membranes not being available, the total osmotic pressure was divided into two fractions—that due to the colloids, and that due to the crystalloids. The osmotic pressure of the former was measured directly by employing a micro-osmometer capable of dealing with the small quantities of fluid available, provided with a membrane impermeable to colloids. Through this membrane the crystalloids permeated freely and any variation in their distribution through osmotic interchange was determined by estimating their concentration before the experiment commenced and after equilibrium had been established. These estimations were confined to the aqueous, since, being a comparatively simple and dilute solution, the results obtained therein are more readily interpreted than corresponding results obtained in blood. Any change in the total concentration of the dissociated salts was determined by electrical conductivity measurements; the aqueous is to all intents and purposes a physiological salt solution and practically protein-free, and it may be taken that the measure of its conductivity under constant conditions provides an index of any variation in its salt content. The power of conducting a current depends on the actual number of ions engaged in the carriage of the charges and also on the rate at which they move. The rate has considerably different values for different ions, and is in relation not only to the atomic or molecular weight of the ions in question, but to the extent to which they are hydrated. The value, however, is constant for each ion under similar conditions. A comparison, therefore, of two solutions containing the same ions under constant conditions gives an exact indication of their relative concentration.

Any change in the concentration of the undissociated crystalloids, which are represented largely by glucose, was determined by the chemical estimation of this substance. The difference in the osmotic pressure due to the non-diffusible substances was therefore read off directly on a manometer as mm. Hg; since the membrane offered no permanent resistance to the passage of diffusible substances and they would therefore pass freely from the one side to the other until osmotic equilibrium had been established, a determination of any change in their distribution would be an index of the difference, if any, in the component of the osmotic pressure due to their influence. A summation of these

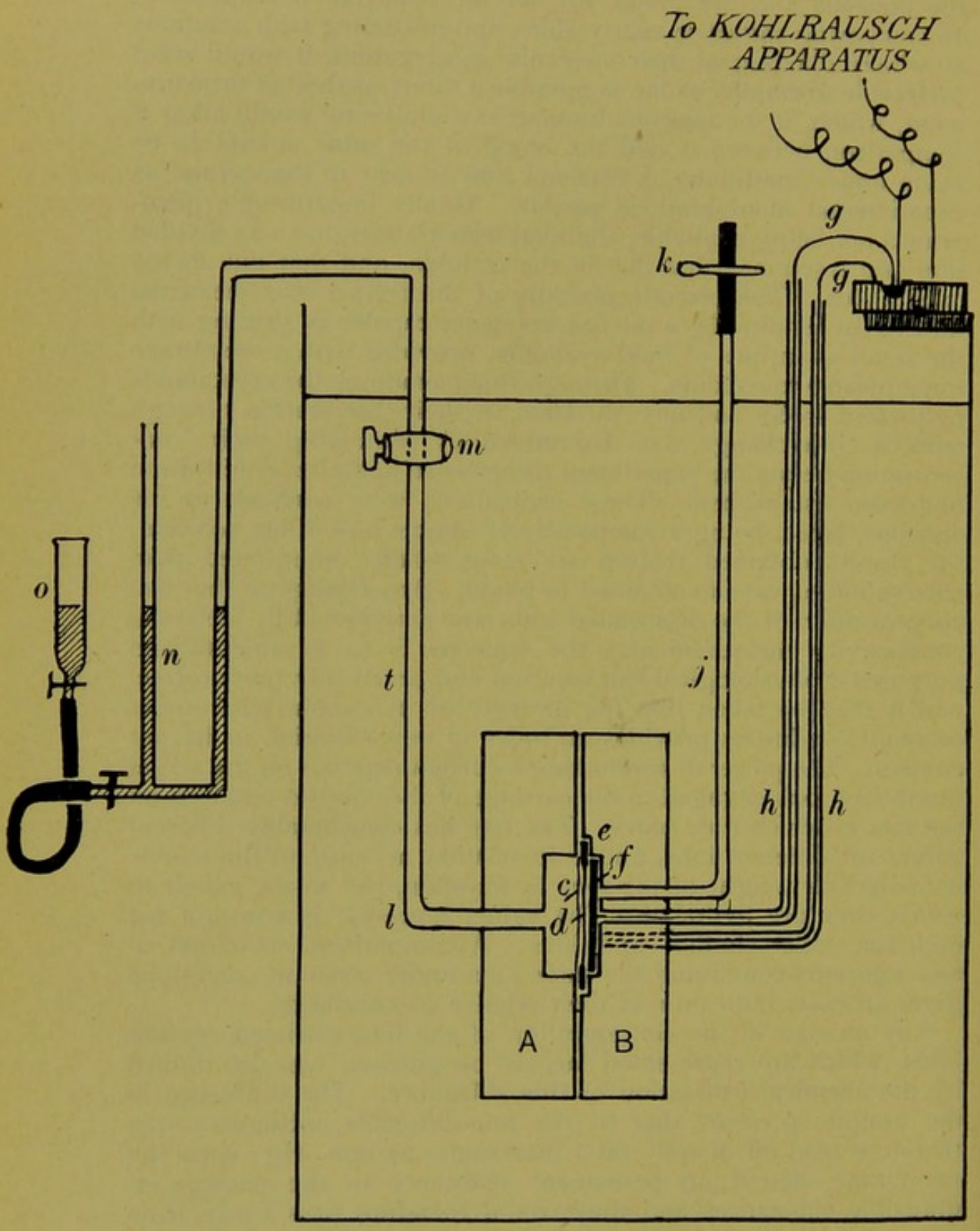
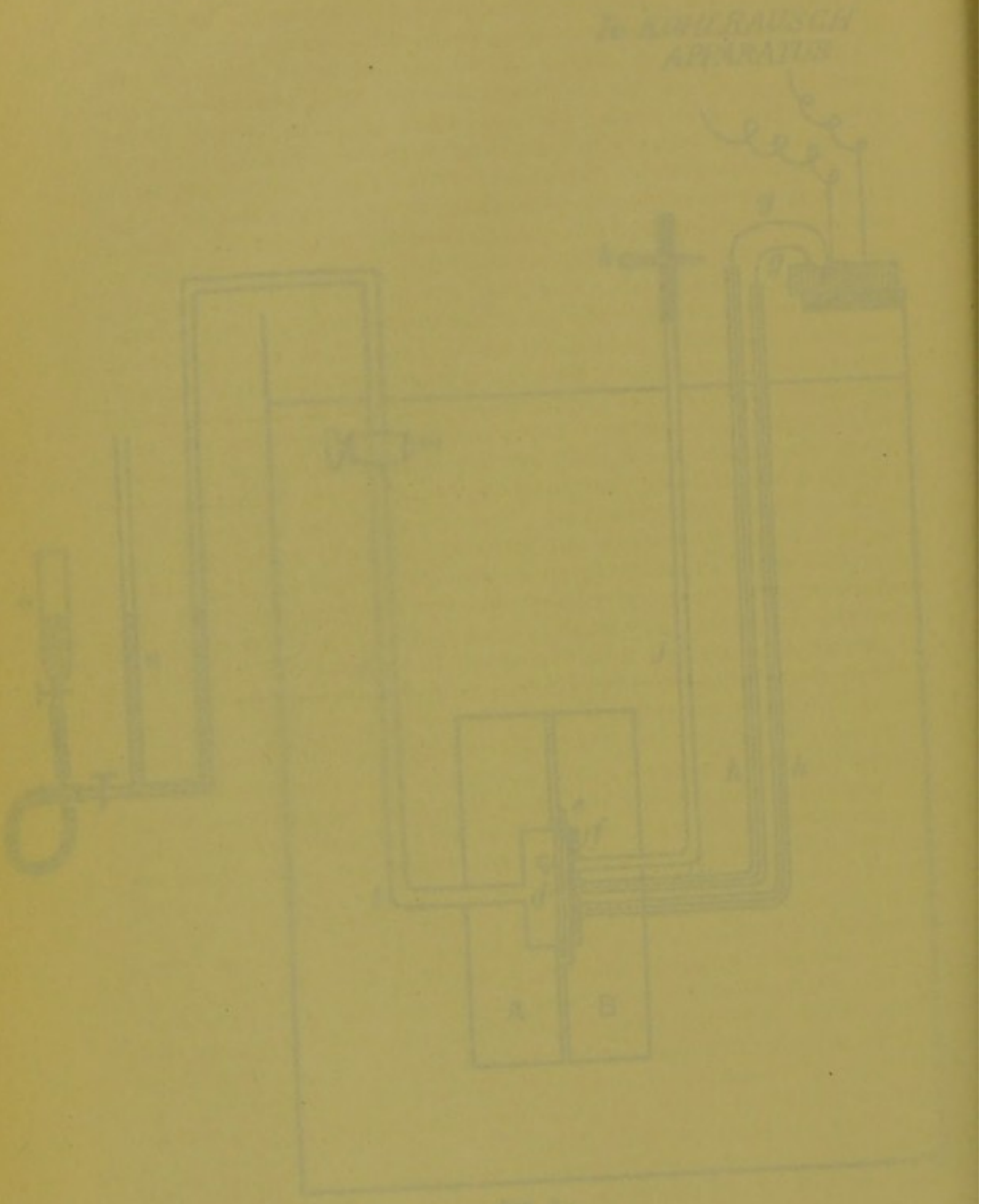


FIG. 2.

Micro-osmometer and conductivity apparatus.



two fractions was taken as providing a relative determination of the total osmotic pressure of the two fluids.

A micro-osmometer was designed as illustrated (Fig. 2), and throughout all the experiments it was used immersed in a thermostat kept at 18° C. It was made of glass, two plates of which (A and B), with the opposing surfaces accurately ground, were clamped together. (In the figure the clamp is not shown in position.) In each plate a rectangular cell was cut : that in (A)—the "blood cell"—was made of such capacity as to contain 0.5 c.c. of blood ($1 \times 1 \times 0.5$ cm.); that in (B)—the "aqueous cell"—to contain 0.2 c.c. of aqueous ($1 \times 1 \times 0.2$ cm.). This was the size of cell with which it was found most convenient to work, as the total quantity of aqueous obtainable from the eye of the average rabbit is from 0.25 to 0.3 c.c., and such a size, while leaving the cell shallow enough to allow osmotic equilibrium to establish itself fairly rapidly, at the same time permitted the spacing of two rectangular electrodes of sufficient area at a sufficient distance apart to ensure reliable conductivity measurements. Between the two a membrane of cellophane* (c) was interposed, supported by a stout copper gauze (d), the joint being made water-tight by surrounding the gauze peripherally on both sides by a thin rubber washer which fitted accurately into a shallow ledge (e) cut from the plate (B). The washer projected slightly from the sides of the aqueous cell so that the electrodes in no place came into contact with the gauze, which was further insulated by coating it with bitelite, thus preventing any interference with the measurements of the conductivity. The platinum electrodes (f and f) were cemented on to the parallel sides of the aqueous cell, and led off by platinum wires (g.g) cemented into holes running through the thickness of the plate (B). These were carried above the level of the surface of the water in the thermostat by glass capillaries (h.h.) ground and cemented into the plate of the osmometer. Connection was then made with the wires by mercury contacts (i.i.) with a Kohlrausch bridge. From each cell, fitting securely by ground joints into holes running through the thickness of the glass plates, two tubes ran upwards above the water surface : one (j)—the tube from the aqueous cell—terminated in a small rubber tube which could be opened or closed by a clamp (k); the other (l)—the tube from the blood cell—could be closed by a stop-cock (m), beyond which connection was made to a mercury manometer (n) and levelling bulb (o).

The majority of the experiments were done on rabbits. The aqueous was taken from both eyes and mixed. It was withdrawn

*See Verney (1926), who has tested the permeability of cellophane to crystalloids and its impermeability to the serum proteins. In view of the nature of the results detailed above the permeability of each piece of cellophane used was again verified.

under sterile conditions by means of a syringe, as already indicated in the technique used for the collection of materials for chemical analysis. Blood was taken also with similar precautions, from the ear, the central artery or the marginal vein being used as the case required. Plasma in preference to serum was employed: the osmotic pressures of the two are different, if only by a small amount, and it is the former which comes into equilibrium with the aqueous *in vivo*. It was also considered essential that the blood should be protected rigorously from air, since the osmotic pressure varies with the carbon dioxide content. Blood in the venous state has a considerably higher osmotic pressure than in the arterial state, since as a result of the ionic interchange consequent on the addition of carbon dioxide to the plasma, the increase of its bicarbonate content undergoes a greater change in molarity than the concomitant decrease of its chloride content. The serum was therefore kept constantly under a layer of sterile liquid paraffin. Carbon dioxide is soluble in liquid paraffin, but its presence prevents any large escape of this gas by restricting surface diffusion to within negligible dimensions, the passage from a watery medium to the oil being rendered slow by the high viscosity of the oil. It was also considered essential that the plasma should be kept free from the disturbing influence of anti-coagulants until the corpuscles had been separated off, since these substances are known to alter the distribution of its constituents; and that throughout all the manipulations it should be kept sterile, since with the activity of micro-organisms a progressive fall in the osmotic pressure of its protein constituents takes place.

Blood was therefore drawn off and centrifuged immediately using the same technique as has been already described (see page 26), and the middle layer of plasma was pipetted off when ready for introduction into the blood cell of the osmometer.

Before use the osmometer was sterilized, the rubber washers and cellophane by autoclaving, the glass cells by keeping them in a solution of perchloride of mercury, and drying them with alcohol and ether. The inside of the instrument was then coated with sterile paraffin wax, care being taken to leave the surfaces of the electrodes clear. To compare the conductivity of the aqueous before and after the experiment under constant conditions, it was necessary to obtain the first measurement after the fluid and the cell containing it had assumed the constant working temperature, and before it had had opportunity to come into association with the diffusible constituents of the plasma. After 0.2 c.c. of the aqueous had been put aside for the determination of its glucose content and its refractometric value, a sterile vulcanite plug (s) was inserted into the open mouth of the aqueous cell, clamped into place and

sealed with paraffin wax. The cell was then filled with aqueous from the syringe, and the tube (j), after its lower end had been dipped in sterile liquid paraffin, was pushed home into position, so that the aqueous rose a little way up its lumen, its exposed surface being protected from the air by a layer of liquid paraffin : the tube was then sealed in position with paraffin wax. The half-cell was then immersed in the thermostat, and allowed to remain for half an hour until temperature equilibrium had been reached, when the conductivity was measured. Thereafter it was taken out of the thermostat, the clamp (k) shutting the outlet of the tube was closed, and, the cell being turned with its inner side uppermost, the plug (s) was taken off, the cellophane membrane and its supporting gauze put into place, the washer being sealed with paraffin wax, and the blood cell (A), also paraffin-coated, was clamped into position. Into this the plasma was deposited directly from the centrifuge tube, and a small quantity of heparin added as a precaution, in addition to the paraffin, against subsequent clotting. With the stop-cock open, the tube (l) was then pushed home until the plasma surface rose to the mark (t), when it was sealed into place with paraffin wax, and the osmometer immersed again in the thermostat. The clamp (k) was then opened, and the top of the tube (l) was connected with the manometer, the level of which was so adjusted by the levelling bulb as to exert a pressure upon the meniscus of plasma approximating that which experience had shown to be the final pressure reading; the stop-cock was then closed. At the end of 24 hours the pressure in the air enclosed between the meniscus and the stop-cock was measured by manipulating the levelling-bulb of the manometer until the level of the plasma had reached its original mark as determined by observation through a horizontal microscope. The apparatus was then allowed to stand for two hours to ensure the attainment of equilibrium when, if this was the case, the reading on the mercury manometer, corrected for the difference in level of a column of plasma between the meniscus and the cell and for the capillarity of the tube (which averaged 1.3 cm. plasma), gave the osmotic pressure of the non-diffusible constituents. The conductivity was then again measured, the osmometer dismantled, and the aqueous was withdrawn for the estimation of its refractive index and its glucose content.

The glucose was estimated as previously by the micro-method of Hagedorn-Jensen : and the refractive index was taken in the thermostat under constant temperature conditions with the Dipping refractometer.

TABLE XIV.

Experiments on Rabbits.

1. *Colloid Osmotic Pressure.*

	No. of rabbit.	Manometer reading mm. Hg.	Diff. in. levels c.c. plasma.	Capillarity of tube c.c. plasma.	Corrected colloid o.p. mm. Hg.	Mean value.	Variation.
With arterial plasma	1	20.8	+3.2	−1.2	22.3	21.6	+0.164
	2	19.2	+3.0		20.5		−1.160
	3	20.5	+3.5		22.2		
With venous plasma	4	21.5	+3.8	−1.2	23.5	22.1	+1.400
	5	18.8	+3.0		20.1		−1.000
	6	21.0	+3.5		22.1		

2. *Electrical Conductivity of Aqueous* $\lambda_{18^\circ C} \times 10^5$.

	No. of rabbit.	Conductivity before exp.	Conductivity after exp.	Difference.	Mean difference.	Variation.
With arterial plasma	1	1293	1293	− 0	−3.3	+ 3.3
	2	1313	1306	− 7		− 3.7
	3	1342	1339	− 3		
With venous plasma	4	1363	1385	+22	+17.4	+10.6
	5	1300	1328	+28		−16.4
	6	1353	1355	+ 2		

3. *Glucose Content of Aqueous.*

	No. of rabbit.	Before exp.	After exp.	Difference.	Mean difference.
With arterial plasma ...	1	0.141	0.141	—	+0.012
	2	0.138	0.168	+0.030	
	3	0.154	0.159	+0.005	
With venous plasma ...	4	0.170	0.102	−0.068	−0.053
	5	0.155	0.104	−0.051	
	6	0.164	0.122	−0.042	

4. *Refractive Index of Aqueous.*

	No. of rabbit	Before exp.	After exp.
With arterial plasma ...	1	1.335168	1.335168
	2	1.335244	1.335244
	3	1.335206	1.335206
With venous plasma ...	4	1.335130	1.335130
	5	1.335206	1.335206
	6	1.335168	1.335168

The results compare favourably with the work of many investigators on the dialysation of serum proteins (see Seidel, 1924; Serr, 1924; Dieter, 1925, *b*). The point of equilibrium is rapidly established, the curve of pressure, a typical one of which is

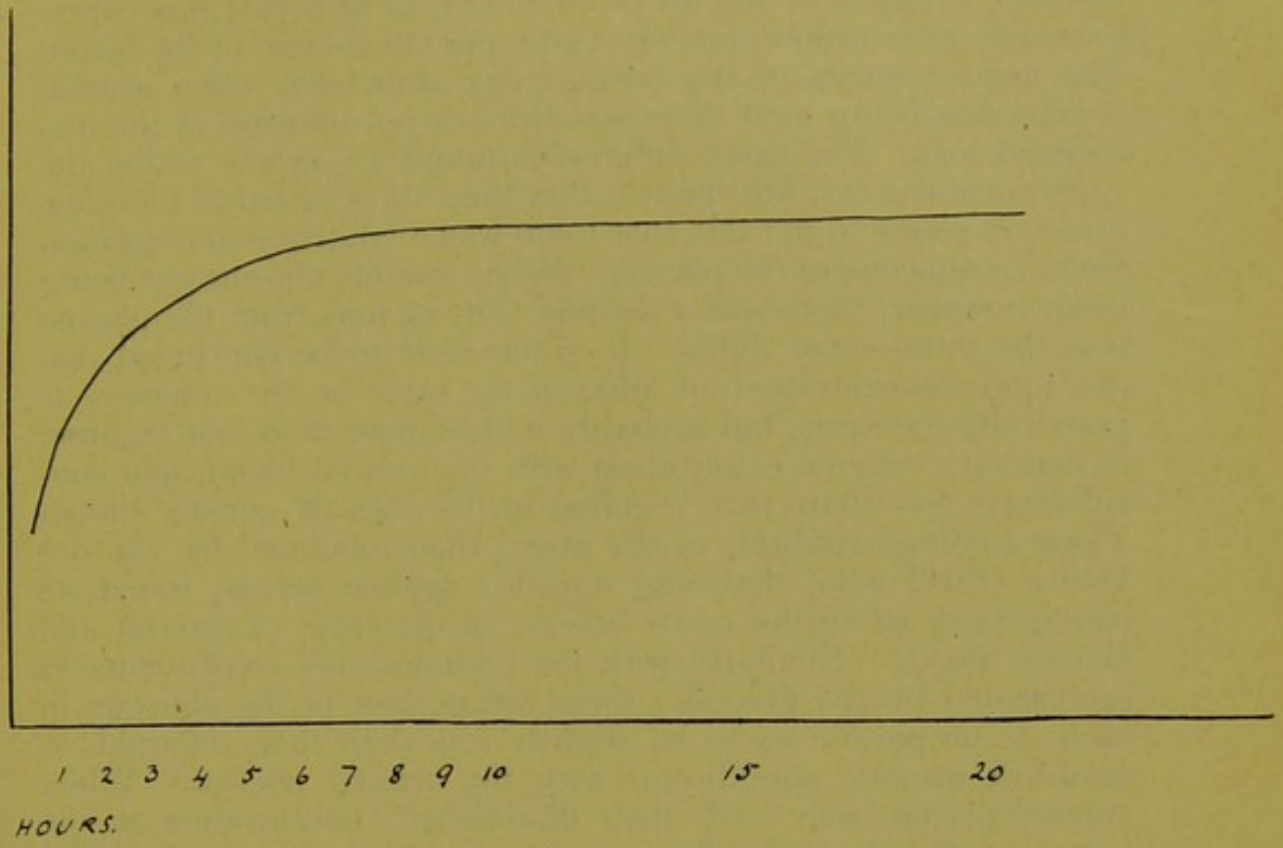


FIG. 3.

Curve showing the attainment of equilibrium in determination of colloid osmotic pressure of plasma of rabbit when equilibrated with the aqueous humour.

reproduced in Fig. 3, arising rapidly during the first four hours, practically reaching its maximum about the eighth hour, and having in every case established equilibrium within twenty hours.

Similar readings were determined in other animals wherein the quantity of plasma protein differs.

TABLE XV.

Animal.	Corrected osmotic pressure. mm. Hg.	Approximate protein per cent. in blood.
Rabbit	20.27	5-6
Cat	31.33	7-8
Dog	29.80	7-8
Man (Dieter (1925, *b*) using Krogh's modification(1921) of Sörensen's apparatus)...	31.70	7-8

From these results it is seen that, owing to the excess of non-diffusible substances in it, the plasma exerts an osmotic pressure of about 20 mm. Hg greater than the aqueous in the rabbit.

Further, in different species of animals it is seen that this excess pressure varies proportionately as the protein content of the blood. The measurements of the conductivity show that when arterial plasma was being used there was little or no diffusion of the dissociated ions. The small differences found are nearly within the experimental error, but the fact that they all occurred in the same direction seems to indicate that there was a tendency to migration from the aqueous to the plasma. When venous plasma was being used, however, there was a definite shift of ions from the plasma into the intra-ocular fluids. It is therefore to be concluded that the total concentration of dissociated salts in the aqueous is practically the same, but probably a little more than that required to maintain osmotic equilibrium with the arterial blood, and considerably less than that required in the case of venous blood. These findings confirm, in the main, those obtained by van der Hoeve (1912) who, dialysing aqueous against serum, found its conductivity to be the mean between a dialysate of arterial and venous blood. Similarly with the undissociated constituents as represented by the glucose: these are present in the aqueous in such a proportion as to be slightly less than that required to establish osmotic equilibrium with the arterial plasma. When venous plasma was used, their diminished concentration in the aqueous cell indicated a diffusion into the blood, that is, the initial osmotic concentration of this substance in the aqueous was greater than that in the venous plasma. The osmotic concentration of the diffusible constituents of the aqueous therefore appears to lie between the point of equilibrium with arterial and that with venous blood, being much more closely related to the arterial. It has already been seen that capillary blood would seem in many respects to be more nearly related to arterial than to venous plasma; and in any case any remissness in the somewhat difficult technique of keeping the plasma absolutely excluded from air would tend to reduce the arterial plasma to some extent. At the end of each experiment the fluid in the aqueous cell is in equilibrium with the plasma. The deduction which necessarily follows is that the osmotic pressure of the aqueous is equal to that of a dialysate of the blood in the arterial capillaries: *it is therefore less than that of the plasma* by an amount which is determined in part by the difference in the distribution of the ionic activities (see page 67), and in part by the difference in the concentration of the colloid constituents. It is to be remembered, of course, that this difference is a small fraction only (about 0.3 to 0.5 per cent.) of the total osmotic pressure (6,000 mm. Hg).

V. THE PHYSICAL PROPERTIES OF THE ABNORMAL AQUEOUS HUMOUR.

As with the chemical composition so with the physical properties —all the variations from the normal that have been described as occurring in the aqueous humour can be explained on physico-chemical lines as being the direct consequence of either a change in the permeability of the capillary walls, or a change in the concentration of the constituents of the blood.

THE PLASMOID AQUEOUS.

The physical properties of the plasmoid aqueous, whether it has been formed after puncture of the eye or by any other method whereby the permeability of the capillary walls is increased, show a gradual and progressive change in the direction which we would expect to accompany an increase in the colloids and a decrease in the anions occurring in a virtually saline solution.

The Specific Gravity increases with the increase of colloids (Golowin, 1900, etc.).

The Refractive Index similarly increases. (See protein content; page 34).

The Surface Tension approaches more closely that of the plasma (Bardier and Cluzet, 1902; van Creveld, 1924).

The Viscosity also increases and approaches the value obtained in plasma (Scalinci, 1907; Mastrobuono, 1909; Löwenstein, 1911; Guglianetti, 1919; Dieter, 1925).

The Conductivity decreases assuming a value between that of the normal aqueous and the plasma (Scalinci, 1907; Hertel, 1909; van der Hoeve, 1912).

Measuring by the Kohlrausch method and using the aqueous of the rabbit, I have found the following variations:

TABLE XVI.

No. of rabbit.	Amount of aqueous removed at 1st paracentesis. in c.c.	Conductivity normal aqueous. $\lambda_{18^\circ C} \times 10^5$.	Conductivity plasmoid aqueous.	Difference in conductivity normal–plasmoid.
1	0.10	1335	1281	54
2	0.25	1272	1174	98
3	0.32	1365	1217	148

The decrease in conductivity running parallel with the increase of protein is as we have seen due to an increase in viscosity impeding the migration of the ions. Applying the correction

formula of Bugarsky and Tangl to the plasmoid aqueous we find that the corrected value of the conductivity does not compare with the estimated value, but is higher. Thus, in rabbit No. 1 the refractive index showed a difference between the plasmoid and the normal aqueous of 0.001844, which corresponds approximately to 1 per cent. of protein.

$$\text{Hence } \lambda_c = 1281 \times \frac{100}{100 + 2.5 \times 1} = 1307,$$

while the value of the normal aqueous was 1335. The difference is due to the concomitant decrease in the concentration of negative ions.

Osmotic Pressure.—The osmotic pressure of the plasmoid aqueous was found by Scalinci (1907) and Dieter (1925), within the limits of the error of its determination by cryoscopy, to be equal.

A series of experiments was conducted on the plasmoid aqueous as obtained by a paracentesis of the anterior chamber, using the same technique as has already been described in the determination of the osmotic pressure of the normal aqueous humour. Rabbits were again used; and measurements were taken after removing progressively larger fractions of the contents of the anterior chamber up to its complete evacuation.

TABLE XVII.

1. *Colloid Osmotic Pressure.*

	No. of rabbit.	Amount of aqueous removed at 1st paracentesis in c.c.	Manometer reading mm. Hg.	Difference in level mm. plasma.	Capillarity of tube.	Corrected osmotic pressure difference.
With arterial blood	1	0.10	17.5	+3.2	−1.2	19.0
	2	0.25	14.5	+3.5		16.2
	3	0.32	13.2	+3.5		14.9
Venous blood	4	0.20	15.5	+3.0		16.8

2. *Electrical Conductivity of Aqueous :* $\lambda_{18^\circ C} \times 10^5$.

	No. of rabbit.	Conductivity normal aqueous.	Conductivity plasmoid aqueous. Before.	After.	Difference in conduct. Normal—plasmoid.
With arterial blood	1	1335	1281	1278	54
	2	1272	1174	1170	98
	3	1365	1217	1217	148
Venous blood	4	1313	1236	1262	77

3. *Glucose Content of Aqueous.*

	No. of rabbit.	Normal aqueous.	Plasmoid aqueous. Before.	Plasmoid aqueous. After.	Difference normal—plasmoid.	Mean difference.
With arterial blood	1	0.14	0.14	0.14	0.00	0.005
	2	0.11	0.12	0.11	0.01	
	3	0.16	0.17	0.18	0.01	
Venous blood	4	0.15	0.15	0.11	0.00	

4. *Refractivity.*

	No. of rabbit.	Normal aqueous.	Plasmoid aqueous. Before.	Plasmoid aqueous. After.	Difference normal—plasmoid.	Approx. protein per cent.
With arterial blood	1	1.335244	1.337088	1.337088	0.001844	1.0
	2	1.335168	1.339036	1.339036	0.003868	2.0
	3	1.335244	1.339834	1.339834	0.004590	2.5
Venous blood	4	1.335130	1.338428	1.338428	0.003298	1.8

From the results obtained it is seen that the difference in the osmotic pressure due to the non-diffusible constituents between the plasmoid aqueous and the plasma is progressively smaller as the colloid content of the former increases. The measurements of the electrical conductivity and the estimation of the glucose suggest that the concentration of the diffusible substances in the plasmoid aqueous bears the same relation to their concentration in the plasma as the corresponding constituents of the normal aqueous humour : that is, the molecular concentration in all stages of evacuation of the anterior chamber is slightly less than that of arterial blood, and somewhat greater than that of venous blood, and presumably, therefore, in osmotic equilibrium with the capillary blood.

VARIATIONS IN THE PHYSICAL PROPERTIES OF THE AQUEOUS HUMOUR ON VARYING THE CONSTITUTION OF THE BLOOD.

In a similar way, when the physical properties of the blood are made to vary, those of the aqueous follow suit. For example, it varies with the diet (Scalinci, 1907) : after the partaking of food the molecular concentration of dissolved substances in the blood is subject to great changes, owing to the introduction into it of the products of digestion. It further varies on the intra-venous injection of anisotonic solutions (Scalinci, 1907 ; Hertel, 1914 ; Dieter, 1925). In these circumstances the osmotic pressure varies in parallel with the blood, a question which I have elsewhere dealt with (1926, *a* ; where a full discussion will be found).

VI. THE VITREOUS.

The vitreous is a colloid gel lying in the meshes of a scaffolding composed of a network of long interlacing fibres whose structures can be seen objectively by the slit-lamp, or subjectively entoptoscopically with the aid of monochromatic light.

The vitreous fluid is almost identical with the aqueous.

Its solid content is 1.36 gms. per cent. (Lohmeyer, 1854); 1.116 (Cahn, 1881); 1.19 Michel and Wagner (1886).

Protein is present in comparable amount. Some of the earlier writers who did not use fresh material found a high percentage—0.053 gms. per cent. Lohmeyer (1854); 0.117 Portes (1880); 0.09 Michel and Wagner (1886). Deutschmann (1879) found 0.03 gms. per cent.; Giacosa (1882) 0.012; Dogiel (1879) found traces; Cahn (1881) found an amount equal to that in the aqueous. Later writers find them practically the same—Ascher (1922); Jess (1922); Gebb (1922). The difference is so small that to the refractometer the two appear equal. Moreover, on paracentesis, or on irritation of the eye, the proteins in both—aqueous and vitreous—increase to the same amount.

Fibrin is not found in appreciable quantities (Michel and Wagner, 1886). Immune bodies are found in the two in comparable amounts (Crondstedt, 1925), and are increased under all conditions wherein a plasmoid aqueous is formed.

Fat is present in traces: cholesterol is detectable, 0.005 per cent. (Jess, 1923)—both in the free form and in the form of ester (Valentin, 1919).

Urea is present in traces (Wöhler, 1848; Schneyder, 1855; Pautz, 1894).

Sugar is present in quantity comparable to the aqueous (Jesner, 1880; Jess, 1922) or in somewhat higher concentration (Hamburger, 1922).

Salt is also found in comparable concentration, being practically identical (Schneyder, 1885; Cahn, 1881; Michel and Wagner, 1886; Lohmeyer, 1854). Jess (1922) found the chlorides in the same concentration—0.73 per cent. in the ox; Ascher (1922) slightly less; Cohen, Killian, and Metzar (1925) slightly more.

Calcium and potassium are present in comparable amounts (Cohen, Killian, and Metzar, 1925).

The pH is practically identical with the aqueous (Gala, 1924; Baurmann, 1925), or slightly higher (Scalinci, 1924, *a*).

The physical properties are also strictly comparable.

The *specific gravity* is the same or slightly higher—1.005—1.009 (Chenevix, 1832; Cahn, 1881; Giacosa, 1882, *a*; Michel and Wagner, 1886; Jess, 1922).

The *refractive index* varies from 1.33403 (Freytag, 1907) to 1.337 (Hirschberg, 1874) in man. It has been variously given as less than that of the aqueous (Hirschberg, 1874; Freytag, 1907; Kunst, 1891; Hallauer, 1913), equal to it (Helmholtz, 1896; Becker, 1882; Gullstrand, 1891), or greater than it (Schiötz, 1913). In animals the general consensus of results shows that it is slightly less (Cyon, 1869; Fleischer, 1872; Valentin, 1879; Becker, 1882; Mönnich, 1883; Klingberg, 1889; Matthieson, 1891; Meyer, 1897; Freytag, 1907; Cirincione, 1913; van der Hoeve, 1914).

The *viscosity* is greater than the aqueous; Cavazzani (1905) found in the ox that it was equal to 1.366-1.376 while that of the aqueous was 1.029.

The *conductivity is slightly less*. Botazzi and Sturgio (1906) in the ox found that the ratio aqueous : vitreous was 181 :180 at 35° C., a result confirmed by van der Hoeve—178.24 :176.16 at 37° C.

The *osmotic pressure* appears to be practically the same : Kunst (1895) found that the osmotic pressure of the vitreous was greater than that of the aqueous, the ratio expressed as percentage concentrations of NaCl being aqueous : vitreous—0.955 :0.971. van der Hoeve (1912) found an opposite relation—aqueous : vitreous—1.001 :0.9817. Jess (1921), by the freezing-point method, found the two identical.*

*Since going to press I have received the papers of M. Cohen, J. A. Killian, and N. Metzar (*Contrib. to Ophthal. Science*; Ed. Jackson Birthday Book, 1926, pp. 216-228). They have carried out an analysis of the aqueous humour in horses, oxen, and pigs, in comparison with the fluid of the vitreous. The figures of the horse aqueous are largely comparable with those already given. Compared with the vitreous the results are practically all within each others limits, which are wide. In the aqueous they find more sugar (in the proportion—aqueous to vitreous of 83-87 to 63-76), more chloride (in the proportion, 656-695 to 648-682), more lactic acid (in the proportion, 17.5 to 21.5), and, on the basis of one estimation, more sulphur. The individual variations are large, and the material was all taken from dead eyes. The analysis of the aqueous was done on the pooled fluid of many animals, that of the vitreous (largely) on single specimens. In general terms the composition appears to be the same, and any differences found are explicable by the unavoidable lack of standardization in collecting the materials, and by the considerations which are dealt with on page 105.

PART II.

THEORETICAL.

"Nothing is so misleading as facts, except figures."

—SIR ROBERT PEEL.

"Hypotheses are cradle songs by which the teacher lulls his pupils to sleep."

—L. W. GOETHE.

I. THE THEORY OF MEMBRANE-EQUILIBRIA.

In the following pages, where theories are made use of, they are not to be thought of as an expression of ultimate knowledge, but are rather to be accepted in the light of a system of shorthand, or useful working hypotheses, by whose aid we are enabled to visualize forces of whose intimate nature we are ignorant, but whose effects we can to some extent appreciate. This applies even to simple unorganized systems; the more so is it evident in the enormous complexity of the reactions which characterize living tissues. At the same time, while an adequate explanation of these is beyond our knowledge, it seems most reasonable and scientific to reduce them as far as is practicable to the simple known laws of physics and chemistry, and elucidate them as far as may be through this medium. Thus while we speak of a force—osmotic pressure—and can measure its effects, we are ignorant of its true nature. It is a force caused by a difference which exists between the free energy or activity of a solvent in the pure state and in solution, and owing to this energy, equilibrium as such cannot exist when the two are put into such a relation that the one can react upon the other as when they are separated by a semi-permeable membrane. Although we may legitimately speculate whether the property of semi-permeability is due to an action comparable to an atomic sieve or a capillary tube, whether it depends on a chemical reaction involving the formation of hydrates, or depending on selective or preferential solubility or absorption, though we may even speculate whether osmotic pressure itself can receive a kinetic explanation or a hydrostatic interpretation, whether it is ultimately due to surface forces, to chemical affinities, to vapour pressures, or electrostatic conditions, yet it is undeniable that such a force—whatever its nature—exists and produces in its action concrete and determinable results which are capable of leading to pragmatic conclusions.

It is similarly true that in a system wherein two solutions containing electrolytes are separated by a membrane which is impermeable to at least one of the ions and permeable to the others, peculiar electrical, osmotic and other effects exist. First noted by Ostwald (1890), these effects were investigated and their thermo-dynamical consequences detailed by Donnan (1911). While in outlining this theory as enunciated by Donnan and applying it to the conditions obtaining in the eye, we use theoretical terms with specific theoretical connotations, it is to be remembered that they are used merely for convenience of expression. The validity of the theory does not depend upon the correctness of these theoretical postulates, but only requires two assumptions—

1. The existence of equilibrium;

2. The existence of certain constraints which resist the free passage of one or more electrically charged constituents (see Donnan, 1923). These constraints, which thus impose a restraint on the equal distribution of otherwise freely permeable ions on both sides of the membrane, give rise to certain concentration, osmotic and electrical effects, and a difference in reaction.

(1) *Differences in Concentration.*

We may take the conditions in the eye reduced to the simplest terms as follows : On one side (I, Fig. 4) of the membrane we have blood containing electrolytes (NaCl) and a protein salt (NaP) to the protein ion of which the membrane is impermeable. On the other side (II) we have the aqueous—a saline solution (NaCl) to the ions of which the membrane is permeable.

BLOOD. I.		AQUEOUS. II.	
z	P^-		
$z + y$	Na^+	Na^+	x
y	Cl^-	Cl^-	x

FIG. 4.

It follows from thermo-dynamical considerations, if the system is in equilibrium, that the product of the concentrations of a pair of diffusible cations and anions must be equal on both sides of the membrane.* If x, y, and z denote the concentrations, or more accurately, the activities of Na^+ and Cl^- in (II), of Na^+ and Cl^- in (I), and of Na^+ and P^- in (I), then the relation between the activities

*See Donnan (1911). When equilibrium is established the energy required to transport reversibly and isothermally 1 gm. molecule Na^+ from (II) to (I) equals the energy which can be gained by the corresponding reversible and isothermic transport of a gm. molecule of Cl^-. Considering the following infinitely small isothermal and reversible change of the system :

$$\left\{ \begin{array}{l} \delta n \text{ mol. Na (II)} \longrightarrow \text{(I)} \\ \delta n \text{ mol. Cl (II)} \longrightarrow \text{(I)} \end{array} \right\}$$

The energy which can thus be gained (*i.e.*, the diminution of free energy) is zero. Hence—

$$\delta n \text{ Rt. log.} \frac{[Na^+]_{II}}{[Na^+]_I} + \delta n \text{ Rt. log.} \frac{[Cl^-]_{II}}{[Cl^-]_I} = 0.$$

therefore $$[Na^+]_{II} \cdot [Cl^-]_{II} = [Na^+]_I \cdot [Cl^-]_I$$

where the brackets signify molar concentrations.

of the diffusible ions is expressed by the equality of their product on either side of the membrane:

$$i.e., \; x^2 = y\,(y + z)$$

$$\text{or } x^2 = y^2 + yz,$$

from this it follows that $x^2 \neq y^2$,

$$\text{or that } x \neq y,$$

$$\text{and that } x > y,$$

$$\text{and } x < y + z,$$

i.e., in the state of equilibrium, the different ions are not equally distributed, but there is more chloride (x) on the protein-free side of the membrane than (y) on the protein-rich side—in other words, in the aqueous than in the blood. Similarly there is more sodium in the blood than in the aqueous. A similar consideration applies to all other ions.

(2) *Osmotic Pressure Difference.*

Since the diffusible ions are unequally distributed a difference in osmotic pressure must exist between the two fluids. The osmotic pressure depends upon the sum of the molecules or fractions of molecules.

The sum of the diffusible ions in

$$\text{I} = 2y + z,$$

$$\text{and in II} = 2x.$$

Now since, as we have seen,

$$x^2 = y\,(y + z),$$

$$\text{hence } 2x = 2\sqrt{y^2 + yz},$$

$$= \sqrt{4y^2 + 4yz}$$

$$\text{Now } 2y + z = \sqrt{4y^2 + 4yz + z^2}.$$

Therefore $2y + z > 2x$ by a quantity depending on the value of z.

The osmotic pressure of the protein-rich side (the blood) must therefore be greater than that of the protein-free side (the aqueous), the difference (ϵ) being dependent on the quantity of indiffusible protein, where

$$\epsilon = 2y + z - 2x + \text{the osmotic value of P.}$$

(3) *Electrical Potential Difference.*

An unequal distribution of diffusible ions at equilibrium on two sides of a membrane must result in a difference of electromotive

force between the two solutions separated by the membrane. This electrical potential difference (E) is given by the formula of Nernst :

$$E = \frac{R\,T}{F} \ln \frac{x}{y}$$

Where E = difference of potential,

R = gas constant in electrical units,

T = absolute temperature,

F = number of coulombs in a farad of electricity,

ln = nat. log.,

$\frac{x}{y}$ = ratio of the concentration of any diffusible ions on the two sides of the membrane.

(4) *Difference in Reaction.*

Further, when the protein is in alkaline solution with a pH greater than the isoelectric point (as is blood) the protein existing as an ion, the hydrogen ion concentration on the protein-rich side must be greater than that on the protein-free side, *i.e.*, the pH of blood must be less than that of the aqueous.

II. THE PHYSICO-CHEMICAL EQUILIBRIUM IN THE EYE.

The Chemical Equilibrium.

We have seen that chemically the aqueous humour is in equilibrium with the plasma. All the constituents of the latter are found in the former in the proportions which we should expect to find them if we postulate a separating membrane relatively impermeable to the larger-sized molecules.

In the aqueous the colloid materials are represented merely by traces. The proteins in the aqueous are not new elaborations, and show no evidence of chemical alteration : they are specifically identical with those of the plasma, they are all present, and they are found in the same relative proportions as they occur in the blood stream. Similarly, these substances in the blood whose molecules are of colloidal aggregation are found in the aqueous in comparable proportions, and these proportions vary directly according to the simple laws of diffusion when the permeability of the membrane is varied.

Those constituents (sugar, urea, etc.) which are freely diffusible, and which, not being ionized, are consequently not subjected to the electrical constraints imposed upon the system, are found in quantities which may be considered as equivalent within the margin of error inseparable from biological estimations when these are represented as concentrations in watery solution. Those constituents which, being ionized and carrying an electrical charge, are brought under the influence of these constraints, are found in the concentrations which theoretical considerations demand. Those anions which are entirely dialysable (chlorides) are found in the aqueous in higher proportion than in the blood, and the cations (sodium, calcium, etc.) which are to a certain extent associated with the large-moleculed proteins are found in the reverse ratio. Thus we have found that the relative concentrations expressed as normal chlorine and sodium are :

$$Cl_{aq.} : Cl_{blood} = 123 : 103,$$

$$Na_{aq.} : Na_{blood} = 121 : 145.$$

The theoretical relation :

$$[Na^+]_{aq.} \times [Cl^-]_{aq.} = [Na^+]_{blood} \times [Cl^-]_{blood},$$

becomes— $121 \times 123 = 145 \times 103$

or $148.83 = 149.35$

In biological estimations, especially in dealing on the one hand with quantities so small as were available for the present analysis as the aqueous, and with material on the other hand so complex and liable to constant and ill-understood changes as blood, it is unjustifiable to hope for results of any more approximate accuracy. The agreement in the above is sufficient justification for it to be accepted as being within biological limits.

Those constituents of the plasma which are not freely diffusible (phosphates, etc.) are present in correspondingly smaller quantities in the aqueous. Further, it is seen that when the concentration of diffusible substances is altered artificially in the blood, their concentration in the aqueous varies similarly. Again, when the permeability of the membrane to colloids is increased, the plasmoid aqueous then formed, containing as it does a greater proportion of protein molecules, and therefore differing less profoundly from the plasma and so involving the existence of less powerful stresses, changes its composition in terms of the thermo-dynamical postulates we are considering—the anions (chloride) relatively decrease and the cations increase *pari passu* with the increase in concentration of colloids, while the non-ionized substances (glucose) remain unaltered.

Further, on introducing the foreign substances into the blood stream, these appear in the aqueous humour in corresponding concentrations: colloids are to all intents and purposes entirely retained in the blood, diffusible substances which are absorbed by the plasma proteins are partially retained, and freely diffusible substances are partitioned in the ratio of their diffusion constants. The pH of the blood, moreover, is less than that of the aqueous.

From the chemical point of view, therefore, the aqueous would appear to show both in its normal constitution and in the variations of its constitution from the normal, a composition which is difficult to explain in any other way but that it is determined by the thermo-dynamical considerations which govern the formation of a dialysate from the blood. There is no evidence of any chemical energy being expended as we would expect in the elaboration of a secretion, either in the formation of new substances, in the retention (apart from that on a physical basis) of substances already present, or in the abnormal concentration of any of its consituents.

The Physical Equilibrium.

If the aqueous is formed by a physical process of dialysation as its chemical constitution both in the normal and in the abnormal state would strongly suggest, it follows that the physical forces involved in its production must conform to the thermo-dynamical equilibrium which has been considered. If, on the other hand,

the terms of this equilibrium are not satisfied, it would seem that in the present state of our knowledge it will be necessary to postulate the intervention of some other force which for a convenient name we may call "secretory."

This physical equilibrium entails hydrostatic and osmotic forces and differences in electrical potential. It is through the endothelial cells of the capillary walls that all vital processes are mediated: through these the process of dialysis will take place. We have already seen that the osmotic pressure of the aqueous humour corresponds with that of a dialysate of the capillary blood—its molecular concentration thus forms a strong argument in favour of this theory of its origin. If the system is in equilibrium the blood pressure in the capillary circulation must exceed the hydrostatic pressure of the aqueous (*i.e.*, the intra-ocular pressure) by an amount which is equal to the difference between the osmotic pressures of the two fluids. Thus equilibrium is attained when the hydrostatic flow from the blood stream to the eye is exactly compensated by an equal and opposite osmotic attraction from the aqueous to the blood.

We have seen from theoretical considerations that the osmotic pressure of the aqueous must be less than that of the plasma, and by actual measurements we have found the difference to be 20 mm. Hg in the rabbit and 30 mm. in the cat and the dog. I have elsewhere (1926, *d*) discussed the question of the blood pressures in the eye, when I pointed out that although many observers have attempted to assess their value and a large proportion of their results appeared to indicate the impossibility of the existence of such an equilibrium, none of the methods they employed were above criticism; that no one had succeeded in measuring the pressure in the intra-ocular arteries, and that the methods of technique employed hitherto in measuring the venous pressure had been inadequate in that they involved in every case a wide departure from the normal conditions. Experimental technique was described whereby the first measurements which had been made of the pressure within these vessels were established by the employment of a micro-pipette introduced into their lumen with the aid of a micro-manipulator. It was shown that the mean pressure in the arteries entering the eye was 75 mm. Hg, and that the pressure in the veins leaving the eye is normally from 1 to 2 mm. Hg above the intra-ocular pressure. I further pointed out that no technique had been devised to measure the capillary pressure, and suggested that owing to the delicately balanced pressure conditions in the eye and their ready disturbance by any intra-ocular manipulation, this quantity seemed to be incapable of direct measurement. Having regard, however, to the dynamically active nature of the capillary circulation with its ever changing

pressure and wide range of variation, and arguing from the values of the pressure found experimentally in the arteries and the veins and the peculiar anatomical and physiological conditions which are found in the circulation here, reasons were adduced for ascribing to the blood in the ocular capillaries a hydrostatic pressure rising to 25 or 30 mm. Hg above the intra-ocular pressure. The conditions of the pressure equilibrium therefore seem to be fulfilled.

We have seen that when a membrane separates two solutions in equilibrium, the membrane being permeable to all the constituents of one solution, and to a part of the ionic constituents of the other, a definite potential difference should appear between the two solutions. Recently Lehmann and Meesmann (1924), using a capillary electrometer and 1/10 n. KCl electrodes, one of which was introduced through a canula into the jugular vein, and the other through a needle into the aqueous, found in cats, rabbits and dogs, that a difference of from 6 to 10 millivolts existed between the two, the aqueous being positive and the blood negative. When the second electrode was immersed in the blood in the other organs no difference in potential was seen, a sinking in its value occurred when it was inserted into any of the structures of the eye (*e.g.*, the iris), and when the animal was allowed to die under the anaesthetic, the current gradually faded until, 10 hours after death, one in the opposite direction was registered. Further, when the concentration of protein in the aqueous was made to rise, the difference in potential decreased, and by repeated punctures of the eye its value was made to sink to a few millivolts. Similarly, in inflammation of the eye the potential difference fell; and by diminishing the colloid concentration of the blood by perfusion (in frogs) a similar fall was induced.

In addition to the fact of the existence of a chemical equilibrium, all the conditions of a physical equilibrium—hydrostatic, osmotic, and electrostatic—seem also to be fulfilled.

We therefore conceive of the eye as containing a fluid in membrane-equilibrium with the capillary blood. As such it must be essentially stagnant. If this conception is correct there are two large questions which it is advisable to clear up at the outset : the maintenance and variation of the intra-ocular pressure, and the circulation of the intra-ocular fluids.

THE MAINTENANCE AND VARIATION OF THE INTRA-OCULAR PRESSURE.

The most convincing argument in favour of a special secretory force responsible for the formation of the aqueous humour is the fact of the intra-ocular pressure. Curiously it is a consideration which has rarely been put forward. The existence of some special energy would seem at first sight necessary to explain why the pressure in the eye remains at 25 mm. Hg, while that of the other organs of the body generally remains at a pressure of a few mm. Hg, except in those organs (secretory glands, *e.g.*, salivary) where a specific secretory force may generate large pressures in periods of activity. It is outside the scope of the present monograph to deal exhaustively with the question of the intra-ocular pressure, but it would seem advisable to suggest the main lines on which the question may be answered.

The enucleated eye has a tension of 8 to 10 mm. Hg, which it retains for some considerable time, and only loses gradually on the disintegration of the lining cells. This residual tension is evident to everyone who palpates a human eye after excision. When an animal is killed or exsanguinated the intra-ocular pressure falls to the same level and remains there. Since it is found under these conditions, the maintenance of this tension cannot be due to the blood pressure, and since it remains in the enucleated eye, it cannot be due to any hypothetical secretory activity; there must be a lining structure which acts as a relatively water-proof membrane and retains within it fluid up to a pressure of 10 mm. Hg. Such a structure is not without parallel elsewhere in the body; it corresponds to the membranes or capsules surrounding glands such as the salivary glands, organs such as the tongue, muscle groups, etc., whose existence has been stressed by Leonard Hill (1920). When pressure is generated within these in pathological conditions, as in inflammatory processes, abscess formation, etc., a condition of tension is set up which may proceed to strangulation of the organ unless it is relieved by surgical incision of the membrane.

It may be suggested that such a "membrane" is formed by the endothelium of the cornea, which Leber (1873) showed to be impermeable up to relatively high pressures, the endothelium and epithelium covering the iris and ciliary body, and the retinal epithelium supported by the membrane of Bruch.

Between this relatively impermeable membrane and the slightly distensible sclerotic lies the vascular reservoir of the uveal tract. The normal condition may be represented diagramatically in

Fig. 5 (2) where the intra-ocular pressure is 25 mm. Hg. On enucleation of the eyeball the vascular reservoir empties, the apartment (*b*) collapses and the conditions of (1) occur. Here the lining cells retain the aqueous in (*a*) under a pressure of 10 mm. Hg, where it remains as long as they retain their functional activity. After exsanguination it is found that the intra-ocular pressure may be again raised experimentally to or above the normal level by the intra-venous injection of normal saline. On ligature of the carotid the pressure similarly falls to 10 mm. Hg, and on releasing this

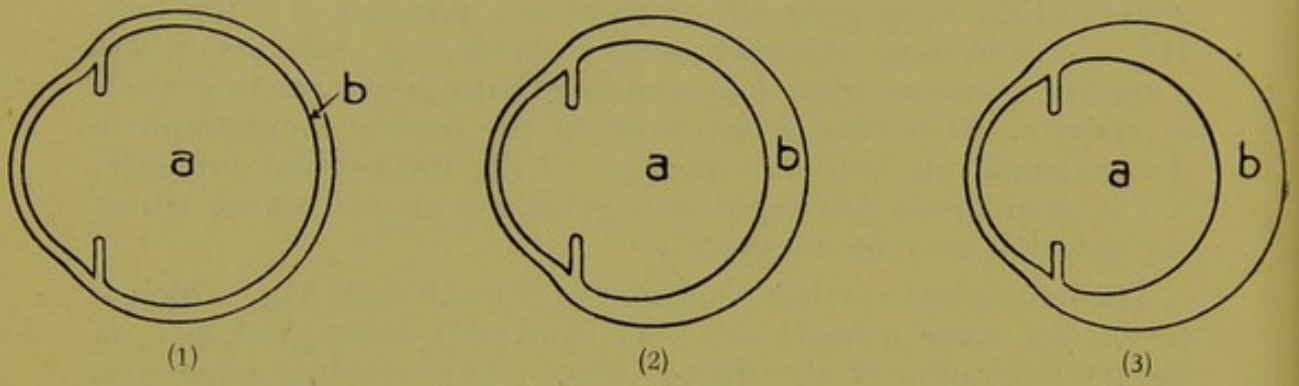


FIG. 5.

THE PRESSURE EQUILIBRIUM IN THE EYE (see text.)

(1) Representing distribution of volume-pressure either with a collapsed blood-pressure or with a turgescent vitreous.

(2) Representing the normal state.

(3) Representing the condition with raised blood-pressure and capillary dilatation.

vessel again it rises to the normal figure of 25 mm. When the blood re-enters the eye the apartment (*b*) must increase in volume to contain it. The sclerotic on the outside is unable to distend to any appreciable extent, and therefore room must be found for the additional volume by compressing the compartment (*a*). The feeding arteries will pile up pressure, and blood will therefore enter (*b*) opening out its vascular channels until an adequate circulation is maintained, at which point equilibrium will be reached. Meantime the compartment (*b*) is compressed, and at the equilibrium point (2) the pressure of the intra-ocular fluids will be determined by the height of the capillary pressure *minus* the difference in osmotic pressure between the two fluids (blood and aqueous). In the majority of cases this appears to be between 20 and 25 mm. Hg. If the blood pressure is then lowered (*b*) contracts and allows (*a*) to expand, when the condition represented in (1) is reached, where the pressure remains at 10 and does not fall lower. Pathologically when the continuity of the membrane

is broken or diminished in effectiveness it does so fall lower, as occurs in long continued moribund states or after trauma, induced either accidentally, or therapeutically in a trephining operation. Conversely when the blood pressure is raised the compartment (*b*) increases in volume and (*a*) is progressively compressed until the intra-ocular pressure rises to the point at which the available *vis a tergo* from the feeding arteries is exhausted, when it can rise no further (3). So far therefore there is no necessity to postulate any secretory energy in the maintenance of the intra-ocular pressure; the conditions are comparable to what occurs elsewhere in the body, with the difference that on increasing the blood pressure in these latter a considerable amount of swelling and expansion is allowed, while in the eye the vascular bed is confined between a physiologically impermeable cellular lining and an almost indistensible case—the sclerotic, an arrangement which necessitates an unusually high capillary pressure in order to maintain a circulation.

It is to be noted that this does not explain in any ultimate sense the fact of the intra-ocular pressure on purely mechanistic lines: it is merely a scheme to account for its existence without the intervention of a specific secretory force. We are left with a factor which in our present knowledge we cannot explain—the physiological impermeability of the lining cells. The normal tension is to be taken as that evolved as the optimum at which the eye is rendered optically rigid and at which its circulation and the metabolism of its tissues can at the same time proceed without disturbance. As to why this optimum is reached and maintained cannot be explained by any cut-and-dried scheme which gives the appearance of a definitive explanation to a physiological process which is much too complex to admit of such treatment. There is no physiological process which is so susceptible to simplification, although there seems no reason to doubt that the instability and plasticity of the physical and chemical structural constitution of protoplasm may yet permit of an interpretation of its ceaseless evolution, its histogenic powers, and its teleological attributes. At present the behaviour of living things can only be left as Pflüger postulated: the cause of every need of a living organism is at the same time the cause of the satisfaction of this need.

A further difficulty is that although in the laboratory the intra-ocular pressure has been found to vary with the blood pressure (Parsons, 1903; Henderson and Starling, 1904-6), yet in clinical practice this close association does not seem to obtain. The temptation was therefore to ascribe to those states of raised and lowered tension which could not be correlated with parallel changes in the blood pressure a causal factor depending on an increase or decrease of "secretory" activity.

There are, however, other factors of which cognizance has not been taken. We have seen that the equilibrium level of the intra-ocular pressure is maintained by the hydrostatic pressure in the capillaries *minus* the difference in osmotic pressure between the aqueous and the blood. From this point the pressure may be varied (Duke-Elder, 1927, *c*):—

1. By altering the equilibrium level:

   (*a*) By raising or lowering the blood pressure in the capillaries, either by varying the arterial blood pressure, or the venous pressure, or the local capillary pressure.

   (*b*) By varying the difference between the osmotic pressure of the capillary plasma and the aqueous. Since the capillaries are freely permeable to crystalloids, this is attained by increasing or decreasing the concentration of colloids in the former, or by increasing the colloid content of the latter.

2. By altering the volume pressure inside the eye:

   (*a*) By altering the state of capillary dilatation or contraction.

   (*b*) By increasing or diminishing the volume of the aqueous, the lens, and the vitreous. The volume of aqueous can be diminished by the application of external pressure applied to the globe; or it may be increased or decreased by the osmotic hydraemia or depletion of fluid following the establishment of a hypotonic or hypertonic condition in the blood, which respectively brings about an increase or decrease in the intra-ocular pressure quite independently of the blood pressure. The volume of the vitreous and the lens may be varied by altering their state of turgescence by variations in the concentrations of hydrogen ions and salts.

It is hoped in a future publication to deal in more detail with experimental work carried out upon this question. The matter is merely introduced here—with an apology for its premature introduction—to suggest that neither the maintenance of the intra-ocular pressure at its normal comparatively high level, nor its variation under physiological or pathological conditions necessitate the postulate of a specific secretory energy. Rather are there more than enough and to spare of physical forces already known, but as yet hardly explored, in the physico-chemical equilibrium of the eye to account for all the phenomena met with both in health and in disease.

THE CIRCULATION OF THE INTRA-OCULAR FLUIDS.

We have suggested that if the aqueous humour is in thermodynamical equilibrium with the capillary blood it is without an active circulation in the generally accepted sense of the term, but rather that it is essentially stagnant apart from the following reservations.

There is first an *external circulation* comprised of two factors.

(1) A primary metabolic interchange, a continuous process determined by the balancing hydrostatic and osmotic forces through the capillary walls. The capillary pressure may be taken as rising to 50 mm. Hg. Around this level it is constantly fluctuating, at one moment above it, at another below it; and in any one capillary the balancing hydrostatic and osmotic forces will render a flow of fluid possible outwards at one moment, inwards at another throughout its length, or in both directions contemporaneously in different parts of its length, the amount of fluid interchange being a function of the pressure head as the intensity factor, and the length of the path over which flow takes place as the capacity factor. While the fluid interchange in both directions is possible throughout the eye as a whole, we would expect from the direct vascular supply of the ciliary body and iris by the uninterrupted long posterior ciliary arteries, that the greater amount of diffusion outwards will take place from the capillaries in this region where the maximum pressure head is located. Conversely, it is probable that since the canal of Schlemm is favourably situated far down the venous pressure gradient and is surrounded by an endothelial wall resembling that of the capillaries, while osmotic re-absorption into the blood stream is possible throughout the eye generally, a large part of the process will take place here. Although no movement of fluid in mass thus results, these considerations will tend to impose upon what is essentially a reciprocal ebb and flow occurring throughout the eye a tendency towards a diffusion from the iris and ciliary body to the angle of the anterior chamber.

(2) A secondary pressure circulation, an intermittent circulation of fluid in mass in the same direction induced by pressure variations determined by the activity of the external and internal musculature, and assisted probably by the rhythmic variation of the ocular pulse. I have pointed out (1926, *b*) that under normal pressure conditions the venous pressure in the exit veins is slightly higher (1 to 2 mm. Hg) than the intra-ocular pressure, and a hydrostatic outflow of the intra-ocular fluids is therefore impossible; but that under conditions of raised intra-ocular pressure, the pressure here tends to fall below the chamber pressure. Under these conditions it is possible that the equilibrium is so altered that a hydrostatic outflow may occur temporarily

through the canal of Schlemm, which thus acts as a safety-valve mechanism to aid in the maintenance of the intra-ocular pressure at its normal level. Conditions of raised intra-ocular pressure are continually being realized by the contraction of the extra-ocular musculature, while the activity of the ciliary muscle may also aid by creating a relatively negative pressure in the canal of Schlemm through the pump-action of the scleral spur of Thomson (1910), and the influence of the pulse beat probably plays a not inconsiderable part, also. In addition therefore to the primary dialysation, these factors will impose secondarily an intermittent "pressure" circulation upon the intra-ocular fluids.

In addition to this there is an *internal circulation* within the anterior chamber itself caused by convection currents in the aqueous which determine a continuous flow upwards in the region of the iris and downwards in the region of the cornea—the thermal circulation.

This thermal circulation is readily demonstrable by the aid of the slit-lamp if the aqueous has been rendered slightly turbid, or after the injection of fluorescine. With the aid of ferro-constantin thermo-pile needles and a galvanometer, I have found a normal difference in temperature between the air-cooled cornea and the vascularized iris of 3° C. to 5° C. This temperature difference induces a convection current in the normal state which rises up in front of the iris, eddies round and descends behind the cornea. It is a purely physical phenomenon, and the conditions governing it and its effects have been studied by Leber (1903), Leber and Pilzecker (1906), Pflüger (1906), Türk (1906-11), Erggelet (1915), Berg (1915), Plocher (1917-19), van der Heydt (1923), and Trettereno (1924). A similar current can be produced in an artificial anterior chamber; by changing the position of the animal it can be modified to flow according to the requirements of gravity in any direction; and by altering the relative temperatures, as by heating the cornea to the general body temperature, it can be abolished, or by raising its temperature above that of the iris, it can be reversed.

This suggestion—the absence of a well-defined through-and-through circulation of the intra-ocular fluids—is by no means a new one. Doubts were expressed on the generally accepted view by Hamburger (1898-1914) on the ground of the "physiological seclusion of the pupil"—a theory originally propounded by Ulrich (1880). Weiss (1906) reasoning from the vascular pressures in the veins of the eye, came to virtually the same conclusion; and the evidence has been critically examined in favour of the absence of a circulatory current by Magitot (1917), Römer (1919), and Friedenthal (1924). Although it is almost universally taken as an accepted fact, there is no single piece of undisputed evidence that such a circulation of fluid does occur. The conception is based on experiments which are all physiologically unsound in that in no case have the conditions of the normal eye been approached: they have dealt with the opened eye, or with the dead eye, or with the eye subjected to some experimental manipulation, such as injection, which has completely altered the normal

equilibrium. None of them can support conclusions which can reasonably bear analogy with the living and normal organ; and all of them are alike in being of such a nature as is calculated to impose an abnormal circulation upon a fluid mass whose original state remains, as far as their evidence is concerned, entirely conjectural.

This evidence is based on two methods of experimentation: the determination of the site of origin of the aqueous and of its points of exit, and the demonstration of its actual circulation in the eye. These have been studied by the histological method of injection, and by physiological experiment.

(1) The Method of Injection.

(*a*) *The site of origin.*

This method depends on the injection of dyes or precipitable substances into the blood stream or subcutaneously, and the observation *in vivo*, or on histological examination after death, of the path taken by the dye in finding an entrance into the eye. This path is taken to indicate the site of formation of the aqueous humour. Many substances have been used for this purpose from time to time, among the most popular of which have been fluorescine, methyl violet, methylene blue, trypan blue, pyrrhol blue, and the indigo dyes. It is, however, unjustifiable to argue that the cells which these dyes stain preferentially in their passage from the blood to the cavity of the eye are those concerned with the formation of the intra-ocular fluids.

Throughout the body generally *intra-vitam* staining is largely of a specific nature, and each dye has a tendency to attach itself preferentially to various types of cell. The conditions which determine this individuality are complex and little understood. The permeability of the cell wall to the dye is one factor, to which must be added the relative solubility of the dye in the materials which form the surface layers of the cell on the one hand, and in aqueous solution such as forms the cell's surroundings on the other. Chemical affinity also enters into the question, and also the electrical forces set up between the cell constituents and the particles of the dye (see Michaelis, 1902; Evans, 1915). Moreover, the results obtained must be interpreted with caution, for few of these substances are entirely devoid of toxic properties, and we have no means of determining with certainty whether the dye found its way into the cell while it was still in its normal state, or whether it damaged or altered the cell first and subsequently found an entrance. Statements about the permeability of cells to dyes should not be accepted apart from a consideration of these possibilities.

It would appear that in the eye, were this reasoning to be followed in the case of each dye, every tissue in the organ—even the cornea—was responsible for the formation of the aqueous humour. Further with the same dye the staining varies with different animals. Thus fluorescine, the most commonly used substance, colours the ciliary body in most animals (owl, Wessely, 1907; rabbit, Ehrlich, 1882; cat, Wessely, 1911; dog, Nicati, 1890, etc.), while in the normal eye of the monkey and man it colours the iris only, and the ciliary body shows no trace (Hamburger, 1914; Thiel, 1922-24, etc.). Pyrrhol blue and the indigo dyes colour both and also the conjunctival cells near the limbus (Rados, 1913). Trypan blue colours the ciliary body and not the iris (Schnandigel, 1913); and so on. The staining effects are thus different with different dyes in the same animal, and with the same dye in different animals, a condition of affairs which is consonant with the behaviour of those substances throughout all animal tissues.

Using this method the following have demonstrated the origin of the aqueous from the ciliary body: Nicati (1890), Leber (1903), Wessely (1911), Rados (1913), Schnandigel (1913), Seidel (1916), Thiel (1922), Carrère (1923).

The following have similarly demonstrated the site of origin in the iris: Ulrich (1880), Schick (1885), Hamburger (1898), Rados (1913), Kumagai (1917), Nakamura, Mukai, and Kosaki (1922).

The following claim an origin from both: Nicati (1890), Niesnamoff (1896), Wessely (1911), Rados (1913), Angelucci (1915), Weekers (1924).

The choroid is also implicated. Nicati (1890) found it deeply stained and concluded that "la chorio-capillaire tout entière sert à la secretion de l'humour aqueuse." Rados (1913) and Angelucci (1915) corroborated this, and Magitot (1917) states that fluorescine colours the choroid more than any other part of the eye.

It would thus appear that the evidence of the injection of dyes would lead us to conclude as we have already suggested—*that entrance can be found into the eye through all the vascularized tissues*. Covered as it is by the retina, little or none probably comes from the choroid although it may be deeply stained, the greater portion enters *via* the ciliary body and iris.

Moreover, these dyes appear to enter the eye in the concentration required by a simple process of diffusion. We have already seen this to be the case with fluorescine (*vide* page 43). It is present in the aqueous in smaller concentration than in the blood, but the unequal distribution is due to its partial absorption in an indiffusible form by the plasma colloids (Trümpy, 1922); the diffusible portion partitions itself according to the laws of diffusion. A similar distribution in the blood is seen in the case of methylene

blue (Bechold, 1907). Further, de Haan and van Creveld (1921) found that in any process of dialysation, using blood and inanimate membranes, fluorescine appears to the dialysate in the same relative proportion as it appears in the aqueous. A similar partition is seen in freely diffusible substances as potassium ferrocyanide (Löhlein, 1910). Moreover, the behaviour of these substances in the eye is entirely consonant with the laws of diffusion. The aggregation of fluorescine (Ehrlich, 1882) and of other dye-stuffs (Hamburger, 1914) into a vertical line over the iris—sometimes offered as an indication of secretion by the iris—is a physical result of the thermal current and the action of gravity : the phenomenon is modified by all the conditions which alter the course of the convection currents, a similar appearance can be observed some time after death (Ehrenthal, 1887), and can exactly be reproduced by diffusion through an inert membrane (Leber, 1903). The concentration of the dye in the aqueous varies with the concentration in the blood, and the time of its duration in the eye is similarly determined (Schöler and Uhthoff, 1882) : both its entrances and its exits are determined by diffusion. Further, when the capillary walls are dilated or their permeability increased by inflammation, the entrance of dyes is aided even in those cases where it occurs normally with difficulty (Seidel, 1918; Thiel, 1924).

The evidence of the injection of dyes therefore demonstrates no actual entrance flow of fluid into the eye; but merely indicates that a reciprocal process of dialysation takes place between the blood and the aqueous humour, whereby foreign substances enter the eye from the capillaries by simple diffusion. A similar state of affairs occurs throughout the body generally. Schulemann (1917) studied the rate at which organic dyes injected into rabbits and mice were distributed over the organism and taken up preferentially by certain cells, and compared this with the rate with which the same dyes will diffuse through gelatine. He found a close correspondence, and showed that the passage of such dyes takes place by diffusion, and that the relative rates of their diffusibilities in the body were equal to those through gelatine.

(*b*) *The site of exit.*

This method depends on the injection of coloured fluid or particulate matter into the anterior chamber and the study of the paths of its elimination from the eye. Many various materials have been used—true solutions, colloidal solutions, particulate suspensions, and oils. In addition to the objections already considered in the previous case, the method involves a further

fallacy owing to the complete dislocation of the pressure equilibrium by the act of injection. Any conclusions drawn from its results must therefore lie open to still more severe criticism. The great diversity of conclusions arrived at by its use is alone sufficient for its condemnation; different observers have recorded different results, and where the same result has by chance been arrived at, since the evidence has not been free from artefact, it has been made to carry different interpretations, and, according to the bias of the observer, theoretical considerations in favour of any view have been pressed to fill the gap left by the deficiency of actually observed facts. I have already drawn attention to the flatly contradictory results that have been obtained by its use in studying the filtration system in the eye (1926,*d*). To get filtration Leber (1903) considered he required a pressure "a little over" the intra-ocular pressure, Hamburger (1914) a pressure of 30 to 40 mm. Hg, and Seidel (1922) a pressure 10 mm. Hg below the chamber pressure : all three experimented upon living rabbits' eyes, all three used indigo-carmine, and all three took as index of flow the discolouration of the episcleral veins. Thus we can prove anything —or nothing.

The transfixion of the tough cornea requires a considerable amount of force as a result of which the intra-ocular pressure is raised. The trauma to the cornea causes a noci-ceptive reflex vasomotor disturbance with a further disturbing effect on the intra-ocular pressure. This is further augmented once the needle is introduced by the additional volume required to accommodate it—a small volume in itself, but by no means inconsiderable when translated into terms of pressure, when the very small distensibility of the sclerotic is borne in mind. The summation of these three influences brings about an immediate anaemia which is followed by a marked hyperaemia when the eye resumes its normal state, and as this occurs, fluid is drawn into the temporarily depleted veins from all available sources including the aqueous with any dye-stuffs injected into it. Any immediate results of injection must therefore be discounted as far as legitimate conclusions regarding the normal equilibrium are concerned; and after the initial disturbance has subsided, if any of the injection mass at all flows into the eye, the pressure in the feeding reservoir is obviously higher than the intra-ocular pressure. Again the normal equilibrium remains quite conjectural.

In addition to the pressure disturbance, any histological evidence of the passage of dyes is to be interpreted with reserve. The preferential behaviour of these substances is to be considered. When the substances are colloidal or particulate their fate is not determined by hydrostatic forces alone, involving simple filtration, but osmotic action, electrical forces, and surface action enter largely

into the question. The phagocytic activity and the absorptive power of the endothelial cells lining the anterior chamber are more important still. The presence of any foreign matter necessarily excites a cellular reaction, and the endothelial lining actively absorbs all such material, just in the same manner as injected masses are absorbed from the subcutaneous tissues, the peritoneal cavity, or any other place in the body. In studying absorption from these places no one dreams of ascribing to their contents a definite circulation, and yet a similar occurrence in the eye has been responsible for the most far-reaching conclusions as to the behaviour of the normal aqueous, and that although the accompanying cellular reaction and phagocytic activity has frequently been noted at the same time (see especially Leboucq, 1913; and Hamburger, 1922, on the cellular reaction excited by Indian ink).

Using the method, drainage by the canal of Schlemm has been deduced by the following observers : Brugsch (1877), Pagenstecker (1878), Heisrath (1880), Gifford (1880), Priestley Smith (1886), Schwalbe (1887), Nicati (1890), Staderini (1891), Tuckermann (1892), Guttemann (1895), Leber and Bentzen (1895), Asayama (1900), Nuel and Benoît (1900), Leber (1903), T. Henderson (1910), Leboucq (1913), Seidel (1921-23), Hiroishi (1924), Weekers (1922-24).

The following have demonstrated drainage by the iris : Leplat (1889), Staderini (1891), Nuel and Benoît (1900), Leber (1903), T. Henderson (1910), Rochat (1911), Leboucq (1913), Hamburger (1914), Weekers (1922-24).

The following have noted drainage by the ciliary body : Schick (1885), Asayama (1900), Hotta (1906), Weekers (1922-24).

The choroid has been implicated by Schick (1885) and Asayama (1900), and the retina by Ovio (1892) and Gifford (1893). Wegefarth (1914), using the technique applied to the cerebral fluid channels by His (1865) perfected and amplified by Mott (1910), demonstrated perivascular and perineural paths here.

The optic nerve head also forms a channel of exit, considerable in the rabbit and less in man : Schwalbe (1870), Stilling (1885), Priestley Smith (1888), Knies (1894), Leber (1895), Leplat (1899), Nuel and Benoît (1900), Paterson (1904), Behr (1913), Wegefarth (1914), Schneider (1924). Priestley Smith (1888) estimated this posterior drainage as approximating 1/50 of the total.

In assessing the value of the results of these observers it is essential to remember firstly that the active elimination of foreign material does not necessarily give any information of the channels of exit of the normal aqueous, and secondly, that an outflow occurring under the artificial pressure conditions induced by an injection has nothing to do with the normal equilibrium. I have shown (1926, *b*) that under normal conditions the pressure in the

exit veins is higher than the chamber pressure : a hydrostatic outflow in this case is therefore impossible. Further under conditions of raised pressure an opposite condition holds good, and such an outflow may occur, probably largely through the canal of Schlemm. With these reservations, a study of the results of injection shows that when diffusible crystalloids are used, these diffuse more or less equally to all the tissues with which they come into contact. From the anterior chamber they have been traced to the angle of the iris and the canal of Schlemm, to the iris, the ciliary body, the deeper layers of the cornea, the vitreous, the choroid, the retina, the optic nerve, and the perichoroidal space. From the vitreous they have been traced to the optic nerve, the retina and choroid, the perichoroidal space, and the anterior chamber. When colloids are used they do not tend to travel from the anterior to the posterior segment of the eye. In their elimination forces of surface tension, adsorption, and electrical potential, as well as the active absorption of the endothelial cells are concerned. From the anterior chamber they find their way to the spaces of Fontana and into the iris; from the posterior chamber they traverse the perineural spaces of the retina and the lymphatics of the optic nerve. When solid suspensions are used (inks, carmine, etc.) the reaction of the cells becomes of a decidedly inflammatory nature involving phagocytosis and diapedesis. From the anterior chamber these are found largely accumulated in the iris massed round the walls of, but not entering the veins, and blocking the spaces of Fontana; from the posterior chamber their route of exit is largely by way of the optic nerve head. Oils on injection cause little of this tissue reaction : they become emulsified, and may be still recognized in the anterior chamber after a month; eventually they are carried away by the phagocytic action of leucocytes. Dialysable substances, therefore, appear to diffuse out over the eye generally, though preferentially from the canal of Schlemm; non-diffusible substances appear to be eliminated to a large extent from the posterior and anterior segments separately (see especially Leboucq, 1913), and correspond in their behaviour to pathological exudates—from the anterior chamber they mainly accumulate in the spaces of Fontana and the crypts of the iris; from the posterior segment they tend to be deposited in punctate form over the retina (Punctate Retinitis of Lister, 1921), or migrate to the optic nerve (Fisher, 1925).

If the evidence of injection has led to any conclusion at all it must be to the conclusion that *all parts of the eye are concerned in the formation and the absorption of the aqueous humour: that the ciliary body is to the largest extent implicated in the first process, and the canal of Schlemm and the anterior surface of the iris in the second.* The objection put forward so frequently in ophthalmological literature that the same structure is unlikely to be con-

cerned with two opposite functions is quite without weight—the flow of fluid in both directions occurs in every capillary throughout the body at the same time in different parts of its length, or at different times throughout its whole length.

The aqueous cannot be formed from the iris alone since in all cases of congenital aniridia this fluid is present, as it may also be when the iris is experimentally completely removed (Deutschmann, 1880; Leber, 1899). It cannot be formed from the ciliary body alone since many animals have no ciliary body (*e.g.*, teleosts), and cases have been reported of its congenital absence in man (Brunhaber, 1877; Pflüger, 1905). Normal aqueous has been found within the cavity of an iris cyst (Magitot and d'Autrevaux, 1924), and in a case when these authors satisfied themselves that a complete seclusion of the pupil existed, the chemical composition of the aqueous in the anterior chamber was similar to that in the posterior. There is no doubt that the secondary aqueous is formed from both. Collins (1918) showed that the plasmoid aqueous entering the posterior chamber came from the ciliary body, and that entering the anterior chamber from the iris. Leber (1903) demonstrated its formation from the former by artificially causing an occlusion of the pupil and observing an accumulation of fluid behind the iris, and Seidel (1918) was able actually to see under suitable magnification the formation of fluid droplets from the anterior surface of the iris.

(*c*) *The Circulation.*

The first experiments devised to determine the rate of production and circulation of the intra-ocular fluids were performed by Hovius (1702). They depended on the measurement of the amount of fluid which drained away when the anterior chamber was opened. Since under these completely abnormal conditions the intra-ocular pressure was equal to the atmospheric pressure, a rapid transudation of fluid necessarily took place from the blood-vessels whose quantity varied directly with the height of the blood pressure (see Henderson and Starling, 1904). By a similar procedure Jesner (1880) found a circulation rate of 44 cmm. per minute, Leplat (1889) 7 to 20 cmm., and Henderson and Starling (1904) 2 to 3 to 5 cmm.

There followed the experiments of Priestley Smith (1888), whose method of investigation depended on the rate at which fluid had to be fed into the freshly excised eye in order to maintain a constant pressure in it. Since, however, the pressure in the exit veins was nil instead of being 1 to 2 mm. Hg above the intra-ocular pressure, the contents of the anterior chamber which were maintained at the normal figure of 25 mm. Hg necessarily flowed out, and, moreover, the fluid escaped through channels quite

incomparable with those in the living animal. Priestley Smith thus obtained a filtration rate of 26 cmm. per minute in the sheep; Bentzen and Leber (1895), and Leber and Pilzecker (1906) of 5 cmm. per minute some hours after death in the human eye, and 6 cmm. in the rabbit. Niesnamoff (1896), 5.5 cmm. per minute in the human eye; 7 in the rabbit; 11 in the pig; 18 in the dog; 24 in the cat; 28 in the sheep; and 62 in the ox. Pflüger (1906) found 6 to 8 cmm. in the dog. Henderson and Starling (1906) performed experiments on the same principle in the eyes of recently killed cats *in situ*, and the inadequacy of the conditions are reflected in their being unable to obtain consistent results (5 to 15 cmm. per minute) and abandoning the method. Somewhat of a similar nature were the experiments of Troncoso (1909), who received the drops of fluid exuded from the partially dislocated eye in oil. He considered the filtration to vary from 3 to 9 cmm. per minute with an average figure of 5.2. Here again the experimental conditions had no relation at all with the pressure equilibrium in the normal eye.

A further method depends on the rate of return to normal after changes had been effected in the aqueous humour, *e.g.*, by the formation of a plasmoid aqueous. Thus Bauer (1896) found the protein in the fluids of the eye practically within normal limits within four hours after paracentesis; in 8 hours they were completely normal. Löwenstein (1915) found that the viscosity was normal in 4 hours. Seidel (1918) found a normal protein content in 8 to 10 hours after puncture, and Mestrezat and Magitot (1921) in from 12 to 24 hours. The argument that a return to the normal condition implies that the fluid contents of the eye have circulated through and have been entirely replaced by a fresh fluid, cannot be accepted. In addition to the fact that at the time of the puncture and for some considerable time thereafter the pressure equilibrium is completely disturbed and an artificial current is undoubtedly induced, the disappearance of protein bears no relation to the replacement of fluid. If the permeability of the dilated capillaries is sufficient to allow the entrance of protein, it is similarly sufficient to permit of its exit by the same channel. Further, proteolytic ferments are present in considerable quantity in the plasmoid aqueous; these act autolytically upon the proteins and convert their large molecules into smaller moleculed substances which can readily diffuse out. Thus, after the entrance of excess of protein into the aqueous, tyrosine, tryptophane and other freely diffusible hydrolytic products of protein are found in the intra-ocular fluids. A similar action accounts largely for the disappearance of the lens protein after discission (Goldschmidt, 1914; Hayano, 1921), an occurrence which has been cited as proof of a circulation (Collins, 1925). After needling, the lens proteins are hydrolysed by

proteolytic ferments into freely diffusible substances, which being thus present in the aqueous in higher concentration than in the blood, must necessarily diffuse out without any reference to the state of stagnation or circulation of the intra-ocular fluids. Moreover, these products of fermentation lower the surface tension considerably, an action which facilitates their dialysation. In a similar manner cholesterol when introduced into the aqueous in quantity is eliminated after emulsification and saponification to fatty acids (Meesmann, 1924). Lastly, apart from all these considerations, colloids act as foreign materials in the aqueous which is biologically adapted to be virtually colloid-free in order to serve as a homogeneous optical medium. Being foreign bodies, therefore, they will be taken up by the endothelial cells and actively eliminated, their disappearance bearing no analogy to the rate of disappearance of the normal contents of the eye. Thus any lens protein which is not hydrolysed will act as a foreign protein in the aqueous, and will be absorbed in this way. In an exactly comparable manner, foreign proteins are absorbed from any part of the body; for example, after subcutaneous injection, they appear in the blood stream in from 3 to 4 hours (Lewis, 1921).

None of these arguments can be held to invalidate the hypothesis that the aqueous humour is practically without a circulation under normal pressure conditions. That this is so was originally suggested by the adherents of the doctrine of the "physiological seclusion of the pupil," the hypothesis originally put forward by Ulrich (1880) and elaborated by Hamburger (1889-1914). The pressure of the iris on the conical anterior surface of the lens to which it is opposed by the action of the sphincter muscle, offers some resistance to the free passage of fluid from the posterior to the anterior chamber. If the aqueous were completely stagnant, such a passage is not required, the fluid in the posterior chamber being formed from the ciliary body, that in the anterior chamber from the iris. But inasmuch as we have seen that the greater proportion of the dialysation outwards from the blood probably occurs from the ciliary region, and since the intermittent pressure circulation which is imposed upon the intra-ocular fluid owing to changes in the pressure equilibrium in the region of the canal of Schlemm will necessitate an intermittent flow through the pupil, this physiological seclusion is not complete.

The doctrine of the physiological seclusion of the pupil in its absolute sense was based on experiments wherein dyes and particulate matter were injected either into the anterior or the posterior chamber, and the difficulty of inducing a flow through the pupil estimated. The a-physiological nature of all such procedures has already been pointed out; and it is not surprising that experiments based on these lines have led to no concordant results.

On this basis Hamburger (1898) demonstrated the comparative difficulty of obtaining a flow through the pupillary diaphragm, and Leber (1895), Levinsohn (1899), Nuel and Benoît (1899), and others, its free permeability. Since that time a wearisomely protracted controversy has gone on uninterruptedly to the present day, and a vast and unwieldy literature has been built up upon it; but since the greater part of it is occupied by discussions concerning unsound experiments upon abnormal conditions illogically applied to the normal, little benefit would seem to accrue from going into it. The greater part of the controversy is found in the writings first of Hamburger, Leber, Levinsohn, and Stock, and later of Seidel and Hamburger (see Bibliography). We cannot agree with Seidel that the aqueous is secreted from the ciliary body and circulates from the posterior chamber to the anterior and finds an exit by hydrostatic forces into the veins in the region of the angle of the iris; nor can we agree with Hamburger when he declares that circulation in no sense exists and that the canal of Schlemm has as much or as little significance in the traffic of the intra-ocular fluid "as the little finger or the little toe." As happens so often in similar controversies in different spheres of scientific literature, if one adds up the conclusion of both sides with mechanical impartiality and divides by two, one comes tolerably near to the truth.

There certainly is some obstruction to the passage of fluid from one side of the iris to the other. Hamburger (1914) claims that a pressure of 40 mm. Hg is required to force injected material from the posterior chamber to the anterior. Löwenstein (1912) similarly found little or no communication, and Kahn (1918) estimated that 50 mm. of Ringer were required in the cat and 30 in the rabbit to effect such a flow, the amount being dependent upon the state of tonicity of the iris. Conversely, Hamburger (1910) found that after the injection of neutral red into the anterior chamber, the pupillary area only of the lens was coloured and no dye seemed to have percolated through behind the iris; while Seidel (1920) in a similar experiment found the discolouration in this region to be so small that it was easily accounted for by a minimal diffusion. The artificial nature of these experiments, however, is obvious when it is recognized that the injection of the dye into the anterior chamber will raise the pressure therein, and forcibly oppose the iris to the lens whatever its state in the normal equilibrium might be. The literature abounds with such contradictory evidence. Hirschberg (1874), Schöler and Uhthoff (1882), Hamburger (1898), Hayasha (1911), and others find that no passage of dyes occurs through the pupil; Nakamura, Mukai, and Kosaki (1922) and Thiel (1924) consider that none occurs in the normal state but that such a passage is demonstrable in glaucoma and in

inflammatory states; while Wessely (1911), Leboucq (1921), Weekers (1924), and others affirm that their passage can be actually observed.

That a tendency for the passage of fluid through the pupil from behind forwards does exist is suggested by the formation of iris bombé in pathological states where the pupil is occluded, and by its relief by iridectomy. At the same time this evidence must be accepted with the proviso that, although the pressure equilibrium is here undisturbed by experimental manipulations, the analogy is based upon the behaviour of the pathological eye. The conclusions should be compared with the findings of Nakamura and his co-workers (1922), who found that while there was no passage of methyl violet or iodine preparations from the posterior chamber to the anterior in the normal eye, such a passage was easily seen in the glaucomatous or in the inflamed or irritated eye; and of Thiel (1923-24), who used the slit-lamp to trace the circulation of fluorescine after its systemic injection, and detected it coming forwards through the pupil only in glaucoma and iritis and never in the healthy organ. That any such flow even in these cases is extremely small is seen in the fact that in many conditions where pathological seclusion of the pupil appears to occur there is apparently no tendency for the formation of iris bombé or for the occurrence of increased tension. This is presumably due to the persistence of small channels which have remained open and are able to cope with such fluid traffic as does exist. The case of Stock (1909) is interesting: an occlusion of the pupil appeared to exist without iris bombé; on puncture of the anterior chamber the iris immediately bellied out, and as the eye refilled it gradually subsided. Stock argued that there was complete seclusion of the pupil, and that the iris-lens diaphragm was water-tight even when the cornea was opened; that the plasmoid aqueous refilling the anterior chamber was formed from the anterior surface of the iris, and that, once it was re-formed, the normal condition of seclusion of the pupil again existed. It might as well be suggested, however, that a minimal channel able to deal with a very small circulation found itself inadequate under the abnormal conditions following paracentesis. Similarly Winselmann (1909) noted that a hyphaema in the posterior chamber remained there until the pupil was dilated, when the blood at once flowed into the anterior chamber: there is evidently no current through the pupil strong enough to carry red blood corpuscles through. The cases of Ulbrich (1909) and Elliot (1918) probably give the truest conception of what does occur. In these a natural manometer of extreme delicacy was provided at the pupillary aperture, in the first case by a delicate membrane stretched across a coloboma of the iris, in the second by a patch of atrophied iris the result of inflammation.

In both there were only slight intermittent bulgings of the membrane at irregular intervals which Ulrich correlated with the movements of winking and accommodation. These would to some extent depend on changes of the shape of the lens; but the phenomenon shows in a strikingly convincing manner the pressure circulation imposed upon the intra-ocular fluids.

It is probable, moreover, that some difference of pressure may exist between the anterior and posterior segments of the eye, in any case temporarily, although the difference is usually so small as not to be susceptible to manometric registration. Monnik (1870) first showed that in excised eyes the pressure rose in both chambers coincidently until high levels were reached when the difference only amounted to 1—3 mm. Hg. Experiments on living animals have led to confirmatory results—Adamük (1869), Schöler (1869), von Schultén (1884), Höltzke (1883), Bödeker (1886), Bellarminoff (1886), Hamburger (1898). Thus Leber (1906) concluded that the pressure in the two was identical, and on experimental variations he could detect a difference of only 0.5 to 0.25 mm. Hg. Troncoso (1906), however, claimed to have registered a difference of 3-5 mm. on either side of the iris-lens diaphragm. Contrariwise Samojloff (1923) using a comparative manometer found in rabbits, after a subconjunctival injection of hypertonic salt solution, that the pressure in the anterior chamber could rise above that registered in the vitreous. That such a difference may exist seems to follow from the results of Priestley Smith (1888), who on injecting fluid into the vitreous, found that a small rise of pressure here (1 mm. Hg) pushed forwards the iris and lens, and almost obliterated the anterior chamber. A pressure difference is suggested also by the experiments of Collins (1918), who found that on trephining the eye in different localities, effusions of "serum" were found either before or behind the iris-lens diaphragm depending on the site of operation. It would appear, therefore, that a physiological seclusion of a degree sufficient to allow the occurrence of a pressure difference may be produced, at any rate for a time.

But the most conclusive direct evidence as to the absence of a well-defined circulation, apart from the essential fact of physico-chemical equilibrium, is chemical in nature. We have seen that the disappearance of proteins cannot be accepted as a criterion of renewal of the fluid contents of the eye, since apart from the other considerations already mentioned they are eliminated actively as foreign materials. At the same time albumen is reported to have persisted for over a year (Tschirkowski, 1911), and the "outstanding beam" of the aqueous is sometimes abnormally relucent several months after trauma (Graves, 1925). Oils on the other hand excite little cellular reaction, and Leboucq (1913) found that these remained *in situ* for over a month. Mawas (1912) found

that cholesterol took three weeks to get away from the anterior chamber; and Morax and Loiseau (1911) noted that an increase of antibodies which entered the eye after paracentesis still remained after three weeks. We have seen that with the formation of plasmoid aqueous the salt equilibrium is altered: according to Ascher (1922) and Magitot (1922), this substance is still found in abnormal concentration twelve days after puncture—an observation which demonstrates clearly the absence of a process of complete and rapid renewal and the non-existence of a well-defined current.

III. THE PLASMOID AQUEOUS.

We have seen that the normal aqueous appears to be a dialysate of the plasma through relatively impermeable capillary walls. The small amount of protein found is by no means incompatible with probabilities, but is comparable with the quantity experimentally produced in a similar manner in pulmonary oedema by Laqueur (1919), and with the results of a large amount of work on dialysation *in vivo* (Abel, 1914; Krogh and Harrop, 1919; Freund, 1922). When the capillaries are dilated or their permeability is increased in any other way, the colloidal material of the blood normally retained is now allowed through in increasing quantity. Such a reaction is well known throughout the body generally. The action does not appear to be due to actual openings between the endothelial cells, for on dialysing Indian ink (Krogh, 1922) of submicroscopical particles (200$\mu\mu$ diam.) these are held back quantitatively while clear plasma transudes through. The wall therefore appears to remain mechanically intact while permeability to colloids increases, the increase being a constant accompaniment of dilatation quite independent of the means by which it is brought about. Soluble starch gets through, however; the diameter of its particles is about 2$\mu\mu$; and while any sharp distinction between colloids and crystalloids is quite artificial, colloidal particles may be taken as being above the limit of 1$\mu\mu$ in diameter.

When the proteins in the aqueous are thus increased, we have seen that certain very definite adjustments are necessitated in the thermo-dynamical equilibrium. The most important and most easily measured of these is the coincident reduction in the concentration of chloride; moreover, since the difference between the osmotic pressure of the two fluids—aqueous and plasma— is now lessened, the intra-ocular pressure must rise. This will be dealt with in another publication; but it is evident that, however produced, the plasmoid aqueous always retains the characteristics of a dialysate. Its formation therefore corresponds to the local oedema which has been produced all over the body when capillary dilatation has been brought about by a variety of means, as by mechanical stimulation in the skin blisters of the manual labourer, or in the liver (Ebbecke, 1917, p. 31), or the tongue (Krogh, 1922), or by nerve stimulation (Bruck, 1909), or by the action of drugs (Hess and Muller, 1915; Dale and Richards, 1918).

It has often been stated that this plasmoid aqueous is of completely different origin from the normal aqueous—that the latter is a secretion and the former is a transudate of the serum (Collins,

wall's vessels formed when the capillaries
are dilated by anything suitable. - Prof Lassar
ovarian.

Subconjival. Salt injection
cauterization of limbus. &c.

~~Sanoffe~~ Sanofon. 1925.

1925). There is no evidence to suggest that two different modes of formation are called into activity : the one seems exactly comparable with the other, and by varying the extent to which the capillaries are dilated a gradual change takes place from the one to the other type of dialysate without any hiatus such as might suggest a dual mechanism. It is not due essentially to an increased pressure gradient from the capillaries to the chamber of the eye, since when permeability is increased with a negligible pressure disturbance, as by eserine or by inflammation, a typical plasmoid fluid is formed ; and where the pressure gradient exists and capillary dilatation is prevented, as by paracentesis after the injection of adrenaline, the aqueous formed is almost of normal composition. Its formation does not depend on the ciliary epithelium at all, for it is formed and collects behind this layer and in the tissues of the eye generally (Collins, 1918), and is responsible, for example, for post-operative sub-choroidal effusions. At the same time the epithelial cells must necessarily find some difficulty in allowing the passage, even in a passive manner, of the highly colloidal fluid in any quantity, and therefore, unsupported as they are after paracentesis by the intra-ocular pressure, they tend to be raised up in the form of vesicles (Greeff, 1894).

An alternative, and opposite, theory has also been put forward : that the plasmoid aqûeous formed after paracentesis was a true sêcretion. The evidence adduced depends upon histological changes in the ciliary epithelium, the large proportion of fibrin and the ready coagulability of the fluid, and the formation of the vesicles of Greeff. E. E. Henderson and Lane-Claypon (1908), however, disposed of this evidence by showing that the histological changes were passive ones indicating the disintegration of the cells rather than their secretory activity, and that the sub-epithelial vesicles were an oedema effect, while they suggested that the ready coagulability probably depended upon the liberation of thrombokinase from the damaged tissues. Vesicles may also be formed on the posterior surface of the iris (Carlini, 1910; Carrère, 1923); and vacuoles of a similar nature may be produced in the dead animal after paracentesis and perfusion of the aorta (Wessely, 1911).

It has been noted that the increase of protein in the aqueous after paracentesis is less marked in man than in the usual laboratory animals. This difference has led some to suggest that the plasmoid aqueous is formed in the two by quite different processes—a view which is expressed most decidedly by Elschnig (1920), who suggested that the aqueous was a secretion in man and a transudate in the lower animals. This assumption is obviously quite unlikely and seems as unnecessary. The difference is due in large measure to the difference in the relative volume which the

aqueous occupies with regard to the entire contents of the globe.* Wessely (1920) has shown that in the rabbit and cat the aqueous comprises about 1/5th of the total volume of the eye, while in man it only occupies 1/20th to 1/40th. On its withdrawal by paracentesis therefore a much smaller pressure difference and therefore a correspondingly smaller increase in permeability will occur in the latter, and the increase of protein will necessarily be less. It is probable indeed that in him the anterior chamber will to a very considerable extent be refilled by virtually protein-free fluid which will come forward from the vitreous. When the anterior chamber is opened fluid readily comes forward from the vitreous, as was originally suggested by Deutschmann (1879). If an eye is suspended by the optic nerve after a paracentesis the fluid of the vitreous drains rapidly away (Janin, 1788). On maintaining an artificial pressure between the vitreous cavity and the anterior chamber fluid readily passes (Priestley Smith, 1888). Diffusible substances injected into the former pass readily forward (Leboucq, 1913), such as iodides (Leplat, 1887) or strychnine (Ovio, 1895): even indiffusible substances, although with difficulty (Leboucq, 1913), find their way through the zonule—Berlin blue (Schwalbe, 1870) and Indian ink (Nuel, 1899).

On comparing the relative increase of protein in the plasmoid aqueous formed after puncture in different animals, it is found to vary directly with the comparative volume occupied by the aqueous in the normal eye; thus the increase in the rabbit is greater than that in the dog, and the increase in the latter is greater than that in man (Lehmann and Meesmann, 1924). Again on comparing the relative increase in the same species of animal, it is found to vary also with the relative volume; thus Wessely (1924) found that in dogs of nine days old whose aqueous occupies 2.8-3.5 per cent. of the volume of the globe the protein of the secondary aqueous rose to 0.4-0.8 per cent., while in adult dogs, whose aqueous occupies 12-14 per cent. of the total, the increase was 3.5-4.5 per cent. Moreover, in comparable individuals of the same species, the excess of protein after paracentesis varies directly with the volume of the fluid originally withdrawn just as formation of the vesicles of Greeff varies with the rate of withdrawal (Bauer, 1899; E. E. Henderson and Lane-Claypon, 1908); and those types of plasmoid aqueous whose formation depends not on changes of the pressure equilibrium but on a lessening of imper-

*The quantity of aqueous in different animals is very various. The following are the quantities occurring in animals: rabbit—0.2-0.35 c.c., cat—0.35-0.67, dog—0.4-0.5, pig—0.17-0.45, ox—1.6-1.7, horse—2.5, sheep—0.4-0.8 (see Hirschberg, 1874; Freytag, 1909; Wessely, 1920; Magitot and Mestrezat, 1921, etc.). In man it is given as 0.21-0.53 c.c. (Jäger, 1861), 0.233-0.325 (Krause, 1879), 0.3-0.35 (Petit, 1890), 0.4-0.45 (Shappey, 1890), 0.15-0.45 (Freytag, 1909), 0.2004 (Villasenor, 1901), 0.15-0.25 (Mestrezat and Magitot, 1921), 0.128 (Ascher, 1922).

meability due to inflammatory processes, and in whose formation volumetric considerations play no part, have always been found, in man as in animals, to contain a comparable excess of protein materials (see page 40).

The occurrence of Greeff's vesicles is relatively rare for the same reason after paracentesis in the human eye. In support of the thesis of a separate mode of formation of the plasmoid aqueous in the human eye Hagen (1921) and Rados (1922) have denied their occurrence altogether. This however is wrong. Greeff (1894) in his original description indicated their presence in man, an observation re-affirmed in 1920. von Hippel (1895) delineates them in similar circumstances. Bauer (1899) corroborates this, as also Seefelder (1906). They occur both on the ciliary body and the iris, and the fact that their relative rarity is associated with volumetric considerations is suggested by their more frequent incidence in conditions where the relative volume of the aqueous is increased, as in hydrophthalmia (Carlini, 1910; Stimmel and Rotter, 1912; Seefelder, 1920; Gilbert, 1921), and in myopia (Rados, 1922).

In addition to the difference in relative volume, other considerations may well play some part. The permeability of the capillaries of different animals is known to vary quite considerably; the aqueous of the rabbit contains more protein, and injected substances (as fluorescine) enter it more readily than the human eye. Further, the size of the molecular complexes into which the plasma proteins are aggregated varies with different animals (Krogh, 1922), and their relative diffusibility therefore varies correspondingly. And again the dilatation after paracentesis in addition to being a pressure phenomenon, is partly vaso-motor in its origin, and the vaso-motor response to the same stimulus is not necessarily comparable in man and the lower animals under the conditions of the experiment.

IV. THEORIES OF THE NATURE OF THE INTRA-OCULAR FLUIDS.

(1). THE SECRETORY THEORY.

Secretion is a term which has been used in the present connection with the freest possible licence: it is essential to state definitely what it connotes. A secretion may be taken to be the elaboration of a substance by certain specialized cells for some specific purpose in the body mechanism in such a way that, in its formation, work in one form or another is done, the energy for this work being derived from the protoplasmic activities of the secreting cells. The source of the energy is derived from chemical reactions in the cell systems, which entail the oxidation of substances of high chemical potential to substances of low chemical potential. Although in the present state of our knowledge we are ignorant of the intimate nature of these cellular activities, the essential feature in the process is the active part taken by the cells of the secretory gland involving the expenditure of energy. This energy may be evident either as chemical work, as when new substances are elaborated, as for example, the productions of the enzymes of the alimentary juices or the hormones of the internal secretions, of the acid or alkali of the stomach or pancreas, of poisons for offence or defence by insects or snakes, of pigments by cuttle fish, of gas by the swim-bladder of fishes, of luminous substances by insects and bacteria, and so on; or as hydrostatic work, as when the salivary gland secretes against a pressure in the duct greatly in excess of that in the carotid artery; or as osmotic work, as when the kidney produces urine, which is under normal conditions of approximately molar concentration, from blood, which is about 0.3 molar; or as electrical work as in the electrical organ of malapterurus. Accompanying this active process changes in the microscopic appearance of the gland cells occur. The interpretation of these phenomena is difficult (see Metzner, 1907), but the most common occurrence is the appearance and growth in the more or less homogeneous protoplasm of the resting cell of "zymogenic" granules, and their solution or emission from the active cell. There are further electrical changes, changes in the permeability (Garmus, 1912), and differences of absorption (Macallum, 1911, p. 644) accompanying the secretory process. Further, the process of secretion can usually be modified either qualitatively or quantitatively by stimulation of the nerve fibres which terminate in the secretory cells, or by the action of chemical substances supplied through the blood stream. Chemical excitants may induce a normal secretion, as secretin, or produce a violent, increased, and pathological one,

Semmelroth. 1927.

as for example, pilocarpine, which is capable of stimulating practically all the glands of the body into abnormal activity, while others, such as atropine, exert an opposite and restraining influence.

There is no evidence whatever that the aqueous humour is in any sense a secretion as defined by this standard. Various arguments, few of them apposite, have, from time to time, been put forward to champion such a view. The main fact is that in its elaboration there appears to be no expenditure of energy of any kind. On the other hand, we have seen that chemically, electrostatically, osmotically, and hydrostatically, this fluid is in equilibrium with the blood. Further, all the evidence points to the fact that the maintenance and the variations of the intra-ocular pressure can be explained by simple hydrostatic laws involving the equilibrium between the capillary blood and the intra-ocular fluids and the state of turgescence of the vitreous and lens, and that none of the phenomena met with in the normal or the abnormal state need reasonably be ascribed to any specific mechanism resembling secretory activity. If indeed the aqueous is essentially in static equilibrium with the blood having merely a minimal circulation imposed upon it secondarily, it is obvious that the whole conception of secretion is unnecessary and illogical. And when it can be shown that all the vascular structures in the eye are concerned in the formation of the intra-ocular fluids, more especially the iris as well as the ciliary body, the location of any specialized structures becomes a problem of considerable difficulty.

The evidence in favour of a secretory origin of the aqueous is largely anatomical in nature, depending on the structure of the ciliary epithelium and its arrangement as ciliary "glands." The earlier observers (Méry, 1707; Haller, 1757; Zinn, 1780; Vetch, 1820) regarded the ciliary body as a whole as a gland. Later, Boucheron (1883) differentiated the anterior and posterior parts, and ascribed to the former the function of secreting the aqueous, and to the latter that of secreting the vitreous. Nicati (1890-91) described minutely the histology of the so-called gland, and adduced physiological and pathological evidence in favour of its activity. Collins (1891-98) brought forward anatomical and pathological evidence that the primary seat of the secretory process was located in specialized outgrowths of the ciliary epithelium; and Panas and Rochon-Duvignaud (1898) further elaborated the doctrine of secretion from anatomical data, and Angelucci (1904) and Scalinci (1907) from physiological deductions. At this time ophthalmologists seemed to have been about equally divided between the secretory theory and the filtration theory elaborated by Leber (1903) and his school in Germany, and corroborated by the work of Parsons (1903) and

Henderson and Starling (1904-06) in this country : the evidence for and against has been summarized by Parsons (1903-8), who concluded that "all the experimental evidence is consistent with a transudation of fluid by a simple process of filtration." There followed the detailed histological work of Mawas (1909-10), and the physiological studies of L. Hill, T. Henderson, and M. Flack (1910-13), which were interpreted as favouring the theory of secretion. At the present day this is probably the most generally accepted hypothesis, and finds its most ardent advocates in Seidel in Germany and Collins in this country—a change over from the widely-accepted views of Leber which is astonishing when we reflect that there is no definite evidence to support it.

The evidence given may be rapidly summarized :

1. Anatomical Evidence.

The gross anatomy of the ciliary epithelium was first adequately noticed by Schwalbe (1870), and Nicati (1890) first described minutely its intimate histological structure. From his studies the latter deduced that the entire epithelium from the ora serrata to the root of the iris was of the nature of an actively secreting gland, and he divided the glandular apparatus into three parts—the secretory epithelium, a contractile apparatus (the ciliary muscle), and a secretory nerve centre (the ciliary ganglion). Collins (1891) went a step further ; and having demonstrated in bleached sections that the pigment epithelial layer which continues over the ciliary body from the retina sends off numerous little processes each consisting of a group of cells with a central lumen protruding towards the ciliary muscle, he regarded these as the ciliary "glands" responsible (but only in part, however) for the secretion of aqueous. For this view there is no direct evidence at all. Collins himself says (1896, p. 60) : "there is no evidence to show to what extent they are concerned in it (the secretory process), that they are the sole source of the fluid seems improbable." The criticisms of Greeff (1893) may be not altogether apposite, but several observers have described them as in no way resembling true glands (Griffith, 1894 ; Alt, 1896 ; Parsons, 1904 ; etc.). Alt describes them as processes of cells with no central lumen and no glandular structure. Ruttemann (1914) in a study of 80 eyes found that in 39 there was no evidence which would indicate a glandular nature, in 18 the evidence was very slight, and in 23 only could the structures of Collins be recognized, and these appeared as clumps of cells without any lumen, and having nothing in common with true glands. Finnoff (1915), after a detailed study came to the same conclusion. Examining bleached sections from man and animals cut equatorially, meridionally, and transversely at various levels,

he found the resemblance of a lumen in one section only, and that a bad one; and he concluded from anatomical evidence that it was highly improbable that the cellular clumps were glands, and that the demonstration of a lumen was probably an artefact in histological technique. In structure they resemble no other gland in the body either in their form or in their relation with the neighbouring blood-vessels. They are formed of the deeper layer of the epithelium alone, have no connection with the superficial layer, and none with the cavity of the eye. It may or may not be a matter of argument whether or no they are possessed of a true lumen, but the lumen, if it does exist, appears to lead nowhere, for anything of the nature of a duct to deliver the secreted fluid into the eye has never been found. In some animals they are completely absent—rabbits (Collins); and in those where they appear to be found most characteristically (man), it can be shown that the aqueous is by no means exclusively formed from them or the region where they exist. If the intra-ocular fluids are formed in their absence, and in their presence are not essentially associated with them, it seems that to ascribe to them a predominant secretory function is imaginative rather than scientific. Collins himself says 1896, p. 71): "processes . . . which I can imagine to be nothing else than glands concerned with (the) elaboration . . . . of the aqueous and the nutrient fluid of the vitreous." Griffith (1893) imagined them to be associated with the regulation of pigment. Scalinci (1922), with as much evidence and a more modern imagination, has called the ciliary body a ductless gland in fact, and ascribed to it the function of elaborating an internal secretion. Finally, these "glands" are not stained with fluorescine before the eye is punctured, and any evidence that can be obtained from the passage of dyes shows that in the ciliary region the aqueous is formed largely from the apices of the ciliary ridges where the epithelium is thin and diffusion presumably easier, and where the "glands" appear to be completely absent. We have seen that fluorescine enters the eye *via* the ciliary body in some animals, but in the normal eye of man it does not pass the ciliary body at all in detectable quantity (Hamburger, 1910; Magitot, 1917; Thiel, 1924; and others), but is associated rather with the iris. Moreover, we have seen that it enters the eye according to the laws of simple diffusion (Wessely, 1905; Löhlein, 1910) in the same proportional concentration relative to that in the blood as occurs in any dialysation through an inanimate semipermeable membrane (*e.g.*, collodion; de Haan and van Creveld, 1921). In its behaviour it thus corresponds with the diffusion of dyes through cells throughout the body generally (Schulemann, 1917). There is little evidence, therefore, of its association with the ciliary body in man, and none at all of its secretion.

2. Cytological Evidence of Functional Activity.

The minute histology of the ciliary epithelium has been studied by Mawas (1910), Seidel (1918-20), Carrère (1923), and Albrich (1924). Seidel (1920) described the presence of definite staining bodies (mitrochondria), and associated them with a secretory function. Such mitrochondria, however, are not a peculiarity of glandular cells. To what extent they are an artefact of histological technique we do not know, but they are a common possession of many types of cellular tissue—nerve cells, muscle cells, cartilage cells, and others (see Benda, 1902). They cannot be accepted as proof of a glandular function, and they have never shown any evidence of activity typical of a true zymogenic nature. Such histological evidence of activity is completely lacking, and the formation of vacuoles which has been described after paracentesis is almost certainly merely an oedema effect following the excessive filtration outwards of the plasma, comparable to the accumulation of fluid in vesicles under the epithelium first described by Greeff (1894).

3. Electrical Evidence of Activity.

By placing one electrode upon the ciliary epithelium and the other outside the sclera, Seidel (1920) claims to have demonstrated a current of action indicative of secretory activity. Doubt has been cast upon his findings by Lullies and Gulkowitsch (1924). But in any case such a difference of potential is necessarily found between any two solutions of different ionic composition or different ionic concentration.* Here one electrode is in a bath of aqueous and the other is immersed in a mixture of lacrymal and conjunctival secretion. For a similar reason we have seen that a potential difference exists between the intra-ocular fluids and blood. A similar phenomenon would be observed were the electrodes placed on either side of the cornea, and to it cannot be ascribed any secretory activity; and the galvanometric deflection would be observed in an inanimate cell arranged similarly.

---

* See Nernst.—The electromotive force (π) called into being at the interface of two similar electrolytic solutions of different concentrations is given by the formula:

$$\pi = \log. \frac{u - v}{u - v} \times 0.0001983\ T. \log. \frac{c_2}{c_1}$$

That occurring at the interface of two solutions of the same concentration but holding different ions by the formula:

$$\pi = \log. \frac{u_1 + v_2}{u_2 + v_1} \times 0.0001983\ T.$$

Grönholm (a. f. O., XLIX, 620. 1900)
contraction vessels of iris c̄ eserine.

Knape (Arb. Physiol. Instit. Helsingfors. Festschrift. p 215. 1910.
dil. + hyperaemia of iris c̄ eserine /.

4. The Stimulation of Secretion.

(*a*) *By drugs.*

After the instillation of eserine and pilocarpine there is a slight increase of tension in the normal eye accompanied by an increase in the protein content of the aqueous. This action is undisputed. The increase of tension has been described by Höltzke (1883), Graser (1883), Schlegel (1886), Stocker (1887), Golowin (1895), Grönholm (1900), Wessely (1909). The accompanying increase of protein has been observed by Wessely (1900), Scalinci (1907), Mawas (1910), Kumagai (1917), Seidel (1920), Mukai (1922) Biagio (1923), Dieter (1925), and Adler and Landis (1925). At the same time the aqueous becomes more quickly coloured on the subcutaneous injection of fluorescine (Ulrich, 1883), and this dye disappears from the eye more rapidly than usual (Schöler and Uhthoff, 1882; Ulrich, 1883; Wessely, 1908). Inasmuch as these drugs are known to excite most glands of the body to secrete, Seidel (1920) claims that this reaction demonstrates that the ciliary body is a true gland and the aqueous a true secretion—the increase in pressure showing an increase in quantity, and the increase in protein a concentrated "stimulated" product comparable to that which occurs in other glands.

It has, however, been shown by Wessely (1913), Köllner (1916-21), and Thiel (1923-24) that eserine causes a marked vaso-dilatation in the vessels of the ciliary body and iris. The alternative explanation may be advanced that the increased pressure is due to the capillary dilatation and that the increased protein is due to the increased permeability that accompanies this dilatation, which factor may be aided by the stretching of the vessels of the iris. The latter explanation is the correct one. The action of eserine in stimulating secretion is on the peripheral endings of secretory nerves, and no adequate evidence of the presence of secretory nerves in the eye has ever been adduced. If these exist at all they must be contained in the ciliary nerves, and Adler and Landis (1925) have conclusively shown that removal of the ciliary ganglion does not affect the increase of protein which follows the exhibition of eserine. If the action of eserine persists after the nerves have degenerated it cannot in this case be nervous but is purely vascular, and it cannot therefore be accepted, as Seidel contends, as providing evidence of glandular activity. Seidel (1920) further found that the increased protein which followed the instillation of eserine was prevented by the prior exhibition of atropine, and this he interpreted as evidence of the well-known general action of paralysis of the secretory nerves by this drug. Adler and Landis (1925) were able to confirm the observation, but the negative results which followed destruction of the nerves at the

same time demonstrated that, whatever its mode of action, atropine did not act through a nervous agency. Thiel (1924) has shown that although the afferent vessels become engorged after the instillation of this drug, the capillaries at the same time become anaemic and bloodless. The action is again probably largely vascular, although there is a considerable amount of evidence, hitherto almost uninvestigated, which points to those drugs having some action as yet little understood upon the permeability of the capillary walls themselves. Such considerations apply even to inanimate systems: thus Brinkman and György (1923) have shown that a collodion membrane normally impermeable to protein is rendered permeable by the addition of atropine, pilocarpine, caffeine, strychnine, or quinine.

(*b*) *Stimulation by nerves.*

The increase of intra-ocular pressure and of the protein content of the aqueous after nerve stimulation has from time to time been represented as demonstrating the presence of secretory nerves subserving the formation of the intra-ocular fluids. It has, however, been fully demonstrated that all the various phenomena which have been recorded are directly attributable to the action of the nerves on the blood-vessels, and that none of them provides evidence of secretory activity. There are three nerves which may possibly be implicated—the fifth, the third, and the sympathetic. When the action of the trigeminal is dissociated from that of the sympathetic fibres which accompany it, section or stimulation of it or of the Gasserian ganglion has no effect on the aqueous (Henderson and Starling, 1904). Neither are there any secretory fibres associated with the third nerve (Landolt, 1906; Adler and Landis, 1925). Stimulation or section of the sympathetic in any part of its course causes profound changes, all of which are directly attributable to the dilatation or contraction of the capillaries which accompanies these operations.

The only evidence therefore which stands is purely anatomical, and this, as we have seen, is susceptible to various interpretations. While no one will deny the use of this form of evidence when interpreted in the light of all the facts, it can never take precedence over physiological evidence. The ciliary body is not always present; when it is present the aqueous is not formed from it exclusively. *It is therefore not essential for its formation. If it is accepted as a gland, then it must be admitted that it shows no activity as a gland, but merely allows the aqueous to diffuse through its cells passively; that is, it must be admitted that it secretes nothing, for the intra-ocular fluids are in thermo-dynamical*

equilibrium with the capillary blood, and in their passage through the epithelial cells no work of any kind—chemical, hydrostatic, osmotic, or electrostatic is done. On the other hand, the anatomical configuration of the ciliary body can be looked upon as providing every facility for dialysation with its abundant and direct blood supply and with its surface area multiplied with reduplications and plications. Its apparent complexity is explained by the fact that it is the continuation forwards of the still more complex retina. Magitot (1917) has brought forward a considerable amount of evidence, embryological and comparative, to support his suggestion that it is a structure differentiated to support the lens and to serve as an organ of accommodation, with its mass of muscle and its epithelial layer which represents the supporting cells of Müller in the retina, to which are attached, and from which may have been developed, the fibres of the suspensory ligament of the lens. It is a suggestion at any rate as rational as that of a gland of secretion to which no secretory function can be ascribed.

2. THE TRANSUDATION THEORY.

The transudation theory—that the aqueous is formed by a pressure transudation from the ciliary body, that it circulates through the eye, and that it finds exit by the canal of Schlemm—was first adequately presented by Leber (1895-1903), whose main thesis was supported by the experimental work in this country of Parsons (1903) and E. E. Henderson and Starling (1904-6). We have seen, however, that there is no evidence that the intraocular fluids have a definite circulation through the normal eye governed by a pressure head at their site of origin, but that on the other hand all the evidence points to their being in a state of equilibrium, although such a circulation, to a minimal degree, it is true, may be imposed upon them secondarily. To mention one consideration which disproves that the aqueous is a simple filtration: such a process could not give rise to an excess of anions in it (*e.g.*, chloride). Leber (1903) sought to explain this by postulating a concentration of the aqueous in the anterior chamber by backward diffusion of water into the blood stream, by taking up of solids from the tissues, and by drying from the surface of the cornea. But Leber considered that the aqueous was hypertonic to blood, in which circumstance it is difficult to see how a backward diffusion of water could occur; it is also difficult to see from what tissues and why the aqueous should preferentially take up salts; and this investigator showed that the corneal endothelium was waterproof up to pressures of 200 mm. Hg. Weiss (1877) advanced an explanation as highly improbable—that the excess of salts was due to an inflow of this substance through

the cornea from the lacrymal secretion which is rich in chloride (1.3 p.c.). Such diffusion inwards would be easier after subconjunctival injection than from fluid merely lying free in the conjunctival sac; and Wessely (1908) found no change in the chloride content of the aqueous in living eyes after such an injection of 5 per cent. salt, and a rise of only 0.1 per cent. when solutions of a concentration of 20 per cent. were employed. It is impossible that a process of simple filtration should produce a fluid with a higher concentration of salt than the parent one—a consideration of the first importance which seems to have been neglected by the earlier workers. With the knowledge of physics which was available at the time, the Italian school of physiologists took up the only rational attitude (Botazzi and Sturgio, 1906; Scalinci, 1907) when they laid down that this excess of salt proved the intervention of the secretory activity of a gland actively secreting saline. On the other hand we can take it to-day as forming one of the most powerful arguments in favour of the hypothesis of dialysation: such an increase of salt is the constant result of the dialysis of any protein-salt mixture, and is the necessary consequence of the forcing away of the negatively charged chlorine ions from the negatively charged protein ions in order to maintain thermodynamical equilibrium.

3. THEORIES OF DUAL ORIGIN.

From time to time the opinion has frequently been expressed that the aqueous and the fluid of the vitreous are of different origin. Among the earliest to state the conception definitely was Boucheron (1883), who concluded that the anterior part of the ciliary body and the posterior part of the iris subserved the secretion of the aqueous while the posterior ciliary body secreted the "mucin" of the vitreous (*l'epithelium aquipare et vitréipare*). Hamburger (1922, *b*), reasoning from the differences in the chemical constitution which some workers have found between the two (Cahn, 1851; Mörner, 1884; Jacoby, 1920), is the most prominent exponent of such a dual origin to-day. But such differences in the chemistry of the two are small, and other investigators have been able to detect none at all (Magitot and Mestrezat, 1921; Jess, 1922). In any case, we would expect such differences to exist owing to the thermo-dynamical stresses prevailing in the vitreous. At the interfaces of this structure forces are existent which necessitate changes in the distribution of the constituents of the fluid percolating it just as surely as if a semipermeable membrane was in being: adsorption, solid solution, the development of electrostatic stresses, etc. The physico-chemical properties of the vitreous have already been alluded to, and any differences between it and the aqueous fall well within the limits of such an explanation. In

this is too hard an exercise.

In his letter (filed) of 25 · IV · 1928.

he says he uses the word "stagnant" figuratively

he is inclined now to put the ciliary epithelium,

not the neuroglicogenic cells (after reading this book)

to the credit of the formation of the spiral sprouts;

and ascribes their ++albumen to ++ permeability

at this stage.

He asks: what about vascular cells in vitro?

It seems to agree with me as must this go now

(i.e. IV/1928).

addition the comparison has rarely been made under comparable or adequately controlled conditions, and the differences are often within the normal variation. There is no need of a hypothesis ascribing to the two a different origin, but every reason to suggest that all the intra-ocular fluid is formed alike by dialysis from the capillaries. We would expect that the greater part of the dialysation of the fluid which reaches the vitreous would take place through the capillaries of the posterior part of the ciliary body, and that fluid interchange would occur to a slighter extent through the perineural spaces of the retina; and this expectation is borne out by physiological and pathological evidence.

4. "THE "NEUROGLIOGENIC" THEORY (OF MAGITOT).

Recently Magitot (1917), after extensive experimental and embryological researches, brought forward a theory of the origin of the aqueous humour, with the essential conception of which I agree, but from whose particulars I differ. He suggests that the aqueous was originally formed in the third-fourth month of foetal life as a true secretion by specialized neuroglial cells. It has no circulation in the eye whatever, and is absorbed with extreme slowness, that which is absorbed being replaced by the neuroglial cells of the ciliary region—Müller's cells, the cells of the ora serrata, and the clear cells of the ciliary epithelium. He takes the absence of cellular activity in these cells as "une des meilleures preuves" that this process of replacement is a dialysation. The "secondary" aqueous has a third and independent origin, and is a transudate from the capillaries.

It may be (see Mawas and Magitot, 1913) that the gel-like and fibrillar material which eventually develops into the vitreous body is probably formed embryologically by a process involving the formation of vacuoles in the neuroglial cells in the ciliary region and the subsequent extrusion of these vacuoles, but I can satisfy myself of no adequate evidence against the hypothesis that the aqueous humour in all circumstances is a product of equilibrium with the blood through the capillary walls, that its peculiar normal composition is due to the relative impermeability of the ocular capillaries, and that its variations from the normal can be expressed as a function of a relaxation of that impermeability. Magitot locates the dialysing membrane in the ciliary epithelium. But it has definitely been shown that this fluid is formed from other regions than the ciliary body—notably the iris. Moreover, its composition depends on the state of capillary permeability, and the plasmoid aqueous does not depend fundamentally on altered pressure conditions inducing a transudation. Where the pressure-fall is induced by paracentesis and at the same time dilatation is

prevented by adrenaline or sympathetic stimulation, a plasmoid aqueous is not formed; and where no pressure-fall occurs and dilatation or increased permeability is brought about, as by eserine or inflammation, a plasmoid aqueous is formed. The nature of the dialysate thus depends on the state of permeability of the capillaries. The primary separating membrane is therefore the capillary endothelium, and the ciliary epithelium seems to be a passive filter. As such, of course, it must have some influence on the fluid passing through it. The process, like all life processes, is more complicated than it may appear. Every cell which the fluid traverses in its passage from the capillary to the cavity of the eye, and every interface in every cell necessitates the establishment of a new thermo-dynamical equilibrium. A protein-rich fluid will have the same difficulty in passing the ciliary epithelium, as it will the capillary endothelium, and therefore when the pressure conditions require its rapid passage in quantity through the former, Greeff's vesicles will tend to be formed underneath it. But any part which it does play appears to be merely mechanical and always secondary. Magitot believes that there is a separate lymphatic system in the eye, distinct from, and never in contact or mixing with the aqueous. A true lymphatic system has never been adequately demonstrated within the sclerotic, but, as in the rest of the central nervous system, only perivascular and perineural channels; these like the perivascular and tissue spaces elsewhere in the body, will contain the dialysate from the capillaries, and it has never been shown that they contain a fluid differing in any way from the aqueous. Magitot himself admits that when diffusible substances are introduced into the aqueous they spread by diffusion equally to all the tissues within the eye with which they come into contact, and that non-diffusible substances readily obtain access to, and are actively eliminated by these paths. The aqueous drains freely from the sub-choroidal space; under raised pressure it is forced into the tissues of the eye and oedema results, which is observable in the cornea; and under conditions of lowered tension there are formed the plasmoid aqueous, and at the same time a similar protein-rich fluid in the ciliary body and the iris (Greeff's vesicles) and behind the choroid (Collins, 1918). Containing as it does all the diffusible constituents of the blood, this intra-ocular fluid is quite adequate to nourish the tissues of the eye, for the protein material is carried, as it is carried elsewhere, as diffusible amino-acids.

Magitot denies to the aqueous any circulation at all. But the evidence, physiological and pathological, forces one to accept, in addition to the continuous interchange with the blood by dialysation, a secondary intermittent "pressure" circulation: not only are the intra-ocular fluids formed by a process comparable to the

tissue fluids elsewhere, but like them they rely almost entirely upon muscular activity for the "circulation" which they possess.

Magitot further considers that the diastolic and the systolic pressures in the entering arteries of the eye are 30 and 60 mm. Hg respectively, and that the capillary pressure is little above the intra-ocular. I have elsewhere suggested that fallacies were involved in his method of inquiry (1926, *d*); but it is inconsistent to suggest that in these circumstances the aqueous is formed by dialysation without the intervention of some cellular activity of the nature of secretion to provide the necessary hydrostatic energy to overcome the unbalanced osmotic pressure of the blood (30 mm. Hg). If his estimates of the vascular pressures are correct, then the aqueous must be a secretion. Magitot considers that the intra-ocular pressure is a function of the state of turgescence of the choroidal blood-vessels (1917, *b*), that glaucoma is largely a question of vaso-motor disturbance and venous obstruction (1925), and that in the maintenance and variation of the tension of the eye the aqueous plays little or no part. The intra-ocular pressure depends for its maintenance on the point of hydrostatic-osmotic equilibrium between the capillary blood and the aqueous, and for its variation, in addition to this, upon the volume-pressure of the contents of the globe. This latter involves the volume occupied by the aqueous and the vitreous and lens as well as that accounted for by the blood-vessels; and if the aqueous is made to accumulate, or the vitreous or lens to swell, the tension will rise. I have shown that after the depletion of aqueous following the intra-venous injection of hypertonic saline, a lowered tension is coincident with capillary dilatation (1926, *a*). When the aqueous is largely pressed out by the application of external pressure to the globe, and the pressure is maintained for some time, the condition of marked hypotension which follows is accompanied by maximal vaso-dilatation: the state of tension may therefore be inversely proportional to the state of turgescence of the choroid. In the normal eye, if an incision be made post-equatorially through the tunics into the vitreous, a haemorrhage from a congested and pressure-sustaining choroid does not take place, but a bulging through of the vitreous into the wound occurs, obliterating the blood-vessels and preventing haemorrhage; and in the eye of chronically raised tension, the same phenomenon occurs, while the choroidal reservoir, instead of being especially in evidence as the source of the high pressure, is thin and atrophied and obviously pressed out of existence by something else. Hypotension can thus be associated with a state of turgescence of the choroidal blood reservoir, and hypertension with its virtual obliteration. Clearly there are many cases where the vascular element is subsidiary.

V. THE THEORY OF DIALYSATION.

The theory of dialysation has evolved from the views so strongly advocated by Hamburger since the end of last century that no circulation existed in the eye, but that its metabolism was carried on by a process of "cellular interchange" ("cellulärer stoffwechsel"). Hamburger associated the iris predominantly with the process; others have located the dialysing membrane in the ciliary epithelium; and the biochemical aspects of the interchange have been dealt with by Meesmann (1924-25) and Baurmann (1924-25). It would seem, however, that the existence of a circulation, as elaborated by Leber, cannot altogether be denied, and that the truth is to be found in a reconciliation and unification of the two schools of thought.

The theory suggested regarding the origin and metabolism of the intra-ocular fluids is that they are a simple dialysate from the capillary blood, the dialysing membrane being the capillary walls. They are thus comparable with the tissue fluids elsewhere in the body in their mode of origin, and differ from them qualitatively only as a direct consequence of the relative impermeability of the capillaries of the eye. The permeability of the capillaries varies widely in different species of animals and in different regions of the body in the same animal—a biological adaptation to meet the requirements of the case. It is essential that the media of the eye be kept as far as is possible optically homogeneous, and therefore the capillaries here have become biologically adapted to almost complete impermeability to colloidal micelles. This is merely one of a myriad of functional adaptations which characterize every manifestation of living organisms, and which cannot be put into any logical relation with our present knowledge of physico-chemistry.

The term so often used in ophthalmological literature—that the aqueous is the "lymph" of the eye—is wrong. Lymph is the fluid contained in an anatomically closed system which seems to be altogether unrepresented in the eye.

As with their formation so with their metabolism and circulation the intra-ocular fluids and the tissue fluids of the body are regulated by the same factors. There is a continuous process of reciprocal interchange on either side of the capillary walls, made up of filtration outwards determined by the difference in the hydrostatic pressures, an osmotic flow in the opposite direction, conditioned by the relative osmotic pressures, a diffusion out or in of the diffusible substances according to their several differences in concentration, and a readjustment depending on colloid impermeabilities. On to this is superimposed a "circulation in mass" conditioned by muscular activity.

h This omits Meotiegat who completed his work on the physico-chemical equilibrium in 1914. on C.S.F. a compared it to D.O.F.
cf. Meotiegat et Leddbt. Soc. Bil. 1921).

I take it that the intra-ocular fluids are a dialysate of the capillary plasma because they have all the very definite physico-chemical properties both in their normal and their abnormal state which such an origin demands, because there is no evidence of the expenditure of any energy or demonstration of any activity in their formation beyond the stresses set up by the restraint placed upon the equal diffusion of colloidal molecules by the dialysing membrane, and because they are in chemical, hydrostatic, osmotic, and electrostatic equilibrium with the capillary blood.[9] Such a physico-chemical method of enquiry is much more susceptible to adequate control and much less open to experimental fallacy than are the abnormal incidentals of physiological experiment or the equivocal deductions of histological technique upon "normal" or pathological structures. There are no experimental findings that I am aware of which are not above criticism and which at the same time invalidate this hypothesis. I take it that the capillary walls and not the ciliary epithelium form the essential dialysing membrane, because the intra-ocular fluids are in equilibrium with the capillary blood, because the properties of the aqueous vary directly with the state of their permeability, and because the ciliary region is not the only site of the process of dialysation.

On either side of the capillary walls there is a balancing hydrostatic and osmotic pressure equilibrium, around which level the mutually compensating pressures are continually fluctuating, and in any capillary these balancing forces will determine a flow of fluid outwards at one moment and inwards at another.[4] This fluid will percolate throughout all the structures within the sclerotic, through the stroma and cellular elements of the ocular tissues, and eventually through the epithelium and the endothelium lining the anterior and the posterior chambers, filling these cavities and percolating the interstices of the vitreous. Throughout its passage, although it is modified by metabolic activity and the stresses to which it is exposed, no evidence of any expenditure of energy can be detected : but although the process seems to be a purely passive one, at the same time it must be remembered that at all points of its course, between each cell and between the interfaces in each cell, fresh membranes have to be traversed, each involving a new series of stresses with the corresponding adjustments that these entail, and each necessitating a fresh state of thermo-dynamical equilibrium. While such fluid interchange occurs in both directions throughout the eye as a whole, the location of the greatest pressure head in the circulation in the region of the distribution of the long posterior ciliary arteries will determine the greatest outward diffusion from the ciliary body and iris, and the position of the canal of Schlemm far down the venous pressure gradient, with its wall resembling the capillary endothelium, will

favour an inward diffusion at the angle of the anterior chamber. The pressure equilibrium which has been indicated at the canal of Schlemm will allow changes of pressure, such as will be produced by muscular contraction and sudden alterations in the vascular pressures, to initiate a minimal and temporary through-and-through circulation. At the same time an internal thermal current is constantly maintained by differences in temperature in the anterior chamber.

Viewed in the light of this hypothesis many of the problems of ophthalmology will require revision. To mention two merely—and these admittedly speculatively, for it is hoped to deal with them more adequately in the near future—glaucoma and cataract.

A scheme whereby the intra-ocular pressure is maintained at its normal level has already been suggested. The equilibrium point—that at which the eye is rendered sufficiently rigid to function as an optical instrument and at which its circulation and metabolism can at the same time proceed without disturbance—is normally maintained by the difference between the hydrostatic pressure in the capillaries and the osmotic pressure called into being by the excess of colloidal material in the plasma in comparison with the aqueous. The equilibrium point may be raised if the capillary pressure is raised to a higher level, or if the difference in colloid content between the two fluids is lessened, as occurs, for example, when the protein material in the aqueous is increased, as in inflammation. The equilibrium may be disturbed by an increase in the volume-pressure of the contents of the globe—an increase in the aqueous, or in the volume occupied by the vitreous or the lens or the uveal blood reservoir. Any such disturbance is normally compensated within very wide limits by the safety-valve action of the canal of Schlemm, and the aqueous thus acts as an elastic cushion, its quantity being in inverse proportion to the volume occupied by the blood-vessels and the vitreous. If for any reason this safety-valve action is rendered inefficient or abolished, then disturbances of the equilibrium become cumulative and tend to be permanently effective, and the intra-ocular pressure rises. If the disturbance is due to vascular conditions, then the resultant rise of pressure is limited to the effective limits of the intra-ocular blood pressure. The causes of such a disturbance are to be found in the factors which control the general state of the circulation, and in the pathological state of the capillary walls and the physical, hormonal, nervous, and chemical influences which preside over their physiological activity. If the disturbance is due to an increase of volume

in the vitreous then the resultant rise of pressure is practically without limits. The vitreous is a gel, and our knowledge of the turgescence and turgidity pressures of gels is as yet by no means as extensive as we might wish. One of the most potent factors which determine variations in the volume of such a system is the quantity of water it retains in association with it, and this depends largely upon the concentration of hydrogen and hydroxyl ions and of electrolytes in the fluids bathing it. To deal with the first of these only, we have seen that the isoelectric point of the colloid system of the vitreous is pH 4.4, at which point ionization, conductivity, osmotic pressure and turgescence are at a minimum. In the normal state, when the pH is 7.5 to 7.7, it is in a condition of partial swelling and any variation in the hydrogen ion concentration from the normal, either towards or away from the isoelectric point, will necessarily entail volumetric changes in it. In considering these it is to be remembered that the vitreous occupies four-fifths of the volume of the globe, and its variations in this manner will have a profound effect. In conditions of alkalaemia when the pH rises higher than this value, the degree of turgescence will increase. It is to be remembered also that exactly similar considerations apply to the lens, whose colloidal system under similar conditions undergoes a similar turgescence. The swelling and the turgidity pressure of the vitreous can be measured experimentally, and that of the lens can be seen in the beam of the slit-lamp. The turgescence may progress to such an extent as to push out practically all the aqueous and abolish the anterior chamber, and to force out the blood from the choroid reservoir, until it may overcome the effective blood pressure of the feeding arteries and strangulate the eye. Variations in the turgidity balance play a very important part in a wide range of biological processes, and pushed beyond pathological limits the potential force involved in turgidity pressure is enormous. Rocks can be split asunder by inserting dry wood into existing crevices and making the colloids in the wood swell by pouring a little water over it—a fact well known to the ancients.

Thus glaucoma interpreted as a pressure symptom merely. It is probably much more. For example the same or parallel physico-chemical processes which produce changes in the physical equilibrium of the vitreous, may as well and as reasonably derange the still more complex physico-chemical basis of the mechanism which converts radiant energy into nerve impulses in the retina and which mediates the functional activity of the nerve fibres in the retina and the optic nerve. Glaucomatous symptoms sometimes appear to be almost independent of pressure, and at other times to progress after the pressure has been efficiently relieved.

If the intra-ocular fluids are a dialysate of the capillary blood it is improbable that the primary cause of cataract is to be associated with physiological or pathological alterations in the epithelial cells of the ciliary body, which, by altering the nature of the "secretion,"

induce degenerative changes in the lens. The intra-ocular fluids play the part only of a vehicle in the transport of the diffusible constituents of the blood to this tissue, whose metabolism presumably is regulated in very large measure by the efficiency of its own internal autoxidation system wherein glutathione appears to act as a hydrogen donator and β- crystalline as a thermostable residue. I have elsewhere (1926, *e*) advanced the thesis that the primary cause of cataract in all its clinical forms is probably to be associated with the direct action of incident radiant energy of any wave-length upon the lens itself, increasing the lability of its colloid system by denaturing its proteins and deranging the autoxidation system upon which its metabolism depends, and with the coagulating effect of changes in the concentration of hydrogen ions and electrolytes, osmotic changes, and possibly in some cases, with a process of continuous photosensitization.

Although it is somewhat dogmatically stated it is not to be imagined that the thesis of this monograph is offered in any sense as Ultimate Truth. Of such, science at present has no cognizance. There seems no adequate reason for doubting that all living processes will ultimately be explained in terms of the same physical laws which govern the behaviour of non-living things. But no physiological process with its purposive, histogenic, and teleological characteristics is by any means amenable as yet to such treatment; and although we may here and there study in a crude manner isolated energy transfers, we must limit our deductions by the knowledge that ideally normal processes are beyond observation. Even were they not so, we are dealing with agents whose activities are imperfectly understood, and measuring results with standards of most uncertain accuracy; we are applying methods merely of approximation to materials of unknown composition and to reactions modified by an infinity of unrealized and uncontrollable variables. Where this is the case there enters the further difficulty in presenting any thesis of viewing the matter impersonally, detaching it from the peculiar system of philosophy to conform to which one unconsciously tends to mould all one's thoughts. The literature of this particular subject will always remain a vast and portentous mausoleum to the Loyal Slaves of Theory. It forms a striking example of how transparently true is the saying of Demosthenes: "What we wish that we believe," and of Aristotle: "What we

expect that we find''—in other words: believing is seeing. In extenuation for myself, I think it must be agreed that the physico-chemical method of approaching the problem is the most legitimate in that it involves the introduction of few extraneous influences, and is the least equivocal in the interpretation of its results.

If it is dogmatically stated, the reason is that it is difficult to deny myself the pleasure of so doing. However that may be, it is to be accepted in the light of a working hypothesis which may, or may not, aid after the manner of a temporary scaffolding in the erection of a building of whose very design we are ignorant. And as such it is to be treated. For the whole progress of knowledge is strewn with the wrecks of such systems.

PART III.

BIBLIOGRAPHY.

The preparation of this monograph entailed the study of a considerable amount of scattered literature on the physico-chemistry of the intra-ocular fluids which may be of some value. For economy of space and time only abbreviated titles of papers are given in English. There are, of course, omissions.

> "Those who have occasion to enter into the depths of what is oddly, if generously, called the literature of a scientific subject, alone know the difficulty of emerging with an unsoured disposition. The multitudinous facts presented by each corner of Nature form in large part the scientific man's burden to-day, and restrict him more and more, willy-nilly, to a narrower and narrower specialism. Much that he is forced to read consists of a record of defective experiments, confused statements of results, wearisome description of detail, and unnecessarily protracted discussion of unnecessary hypotheses. The publication of such matter is a serious injury to the man of science; it absorbs the scanty funds of his library, and steals away his poor hours of leisure."
>
> J. N. LANGLEY, *British Association*, 1899.

Accardi. V (1926) Il bismuto nei tessuti e liquidi oculari.
Boll. d'ocul. vol. V. f. 232.

k.P. - Ber. ü. d. 42 Vers. d. deutsch. Oph. Ges. Heidel. 1920. f. 63, 85.
Hygiea. 1923. Bd. 85. f. 924.
K. m. f. A. 1927. Bd. 78. Beilageheft. 33-44.
"Sugen in agreono."

ABDERHALDEN, E. (1922).
Fermentforsch, Bd. VI, S. 230.

ABEL, J. H., L. G. ROWNTREE, and B. B. TURNER, (1914). *In vivo* dialysation.
Jl. Pharmacol., Vol. V, pp. 275-316.
Trans. Amer. Assoc. Phys. 1913.

ADAMÜK, E.—Intra-ocular pressure and filtration.
1866: *Centralbl. f. d. med. Wissenschr.*, No. 36; 1867, ibid, No. 28.
1867: *Ann. d'Ocul.*, T. LVIII, p. 8.
1868: *Klin. Monatsbl. f. Augenheilk.*, Bd. VI, SS. 386-393.
1869: *Sitzungsberichte d. Wiener Akad. d. Wissenschr.*, Bd. LIX, Feb. 2.
1870: *Ann. d'Ocul.*, T. LXIII, pp. 108-113.

ADDARIO, C. (1899). Subconjunctival injection.
Arch. f. Ophthal., Bd. XLVIII, H. 2, SS. 362-375.

ADLER, H. F., and E. M. LANDIS (1925).—Studies on the protein content of the aqueous humour.
Arch. of Ophthal., Vol. LIV, pp. 265-279.

ALAJMO, B. (1923).—Influence of drugs on refractive index and protein content of aqueous and on intra-ocular pressure.
Arch. di Ottal., Vol. XXIX, pp. 509-531.

ALBRICH, K. (1924).—Histology of ciliary epithelium.
Klin. Monatsbl. f. Augenheilk., Bd. LXXI, S. 781.

ALT, A. (1896).—" Glands " of Collins.
Amer Jl. of Ophthal., 1st series, Vol. XIII, pp. 1-11.

ANDRESEN, K. L. G. (1921).—Urea content in the organism.
Bioch. Zeitschr. Bd. CXVI, SS. 266-302.

ANGELUCCI (1904).—*Physiologie gén. de l'oeil.*
Encyclop. franç. d'Ophtal.

——— (1906).—*Arch. di Ottal.*, Vol XIII, p. 309.

——— (1915).—On the nutrition of the eye.
Arch. di Ottal., Vol. XXII, p. 1.

ARLT (1868).—The secretion of tears.
Arch. f. Ophthal, Bd. XIV, H. 3.

ASAYAMA (1900).—The absorption of aqueous on the anterior surface of the iris.
Arch. f. Ophthal., Bd. LI, H. I, SS. 98-114.

ASCHER, K. W. (1922).—On the chemistry of the human aqueous.
Arch. f. Ophthal., Bd. CVII, SS. 247-297.

——— (1923).—The pH of the aqueous.
Deutsch. Ophthal. Gesell. Tschechoslow., Dec. 9.
Ref. *Klin. Monatsbl. f. Augenheilk.*, Bd. LXXXI, S. 771.

ASHER, LEON, and R. ROSENFELD (1907).—On the physico-chemical combination of various blood constituents.
Bioch. Zeitschr., Bd. III, SS. 335-358.

ASK, F. (1914).—The sugar of the aqueous.
Bioch. Zeitschr., Bd. LIX, S. 1.

AXENFELD (1905).—Serum therapy in eye diseases.
Deutsch. med. Wochenschr., S. 1886.

BACH, L. (1894).—Bactericidal content of aqueous.
Arch. f. Ophthal., Bd. XL, H. 3, S. 130.

BARDIER, E., et J. CLUZET (1902).—Surface tension of body fluids.
Comp. rend. de la Soc. de Biol., T. LIV, pp. 119-121.

BAUER, H. (1896).—The properties of the aqueous after emptying the anterior chamber.
Arch. f. Ophthal., Bd. XLII, H. 3, SS. 193-213.

BAURMANN, M. (1924).—Experiment on the properties of the vitreous.
Sitzungsberichte d. Göttingen Gesell., Nov. 29, 1923.
Münch. med. Wochenschr., Nr. 7, 1924.
Arch. f. Ophthal., Bd. CXIV, H. 2, SS. 276-303; Bd. CXVI, H. 1, SS. 96-113.

——— (1925).—The intra-ocular fluids.
Klin. Monatsbl. f. Augenheilk., Bd. LXXIV, S. 518.
Arch. f. Ophthal., Bd. CXVI, SS. 96-113.

BECHOLD, H. (1907).—Colloids and filtration.
Zeitschr. physik. Chem., Bd. LX, SS. 257-318; 1908, Bd. LX, SS. 328-342.

BECKER (1882).—Refractive index of aqueous.
Berl. Zeitschr. vergl. Augenheilk., Bd. I, S. 17.

BEHR, C. (1913).—Drainage at optic nerve head.
Arch. f. Ophthal., Bd. LXXXIII, S. 519.

BELLARMINOFF (1886).—The intra-ocular pressure.
Pflüger's. Arch. f. d. ges. Physiol., Bd. XXXIX, SS. 449-472.
Ann. d'Ocul., T. XCVII, pp. 181-198, 1887.

——— (1893).—The quantitative colorimetric method for investigating absorption from the anterior chamber.
Arch. f. Ophthal., Bd. XXXIX, H. 3, S. 38.

BELLAVIA, A. (1923).—The aqueous humour in compression of the eye.
Arch. di Ottal., Vol. XXX, pp. 252-266.

BENDA (1902).—Mitrochondria.
Ergeb. d. Anat. u. Entwickelungsgesch., Bd. XII, S. 743.

BENOÎT (1899).—The elimination of intra-ocular fluid at the posterior pole of the eye.
Internat. Cong. Ophthal., Utrecht.

BERG, P. (1915).—The visible current in the anterior chamber.
Klin. Monatsbl. f. Augenheilk., Bd. LV, S. 61.

BERNARD, CLAUDE (1859).—*Leçons sur les propriétés physiol. et les altér. path. des liquides de l'organism.* Paris II. (P. 409, sugar in aqueous.)

——— (1872).—*Leçons sur la diabète.* Paris.

BERZELIUS (1832).—*Lehrbuch der Chemie.* Reutlingen, Bd. IV, S. 442.

BIAGIO, A. (1923).—Dionin injection.
Arch. di Ottal., Vol. XXIX, pp. 509-531.

BLATT (1921).—Wassermann in aqueous.
Klin. Monatsbl. f. Augenheilk., Bd. LXVI, SS. 889-897.

BÖDEKER (1886).—The intra-ocular pressure.
Dissert., Berlin.

BOË (1886).—The chemistry of the vitreous.
Soc. franç. d'Ophtal., Avril 30.

BORDET (1909).—*Studies in Immunity.* Bordet-Gay, p. 525.

BOTAZZI e STURGIO (1906).—The source of the tension of the eye.
Arch. ital. de Biol., Vol. XLV, p. 198.
Arch. di Ottal., Vol. XIII.

BOUCHERON, (1883).—Anatomical and pathological studies on the "épithélium aquipare et vitréipare des procès cil."
Bull. et mem. de la Soc. franç. d'Ophtal., T. I, pp. 81-94.

BRINKMAN, R., u. VAN DAM (1923).—Measurement of surface tension.
Arch. Néerland. de Physiol., Bd. VIII, S. 9.
Ned. Tijdschr. v. Geneesk. Bd. II, S. 2905, 1921.

BRINKMAN, R., u. A. v. SZENT-GYÖRGYI (1923).—Studies on the physico-chemical basis of vital permeability.
Bioch. Zeitschr. Bd. CXXXIX, SS. 261-269; 270-273; 274-279.

Bozzali (1926) Sulla circolazione dei liquidi endoculari.
Ann. di ottal. e. clin. ocul. VOL LIV. p. 7

(= sugar)

Bufano M. La determinazione contemporanea della glicemia e della glicoridia nell'occhio umano patologico e nell'occhio normale del coniglio (= rabbit)

Boll. d'ocul. VII. V p. 623.

BRUCK, C. (1909).—Aetiology and pathology of urticaria.
Arch. f. Dermat. u. Syphilis., Bd. XCVI, S. 241.

BRUGSCH (1877).—The absorption of dyes from the anterior chamber.
Arch. f. Ophthal., Bd. XXXIII, H. 3, SS. 255-287.

BRUNHABER (1877).—Congenital absence of the ciliary body.
Klin. Monatsbl. f. Augenheilk., Bd. XV, SS. 114-116.

BRUYNOGHE, R., et M. STAGNET (1924).—Complement in aqueous.
Comp. rend. de la Soc. de Biol. T. XC, pp. 1294-1295.

BUCHNER (1890).—The bactericidal properties of the blood.
Arch. f. Hygiene, Bd. X, S. 84.

BUGARSKY u. TANGL (1898).—Physico-chemical experiments on the molecular concentration of the blood.
Arch. f. d. ges. Physiol., Bd. LXXII, S. 531.

BURGERS, T. L. (1910).—Antibodies in aqueous.
Klin. Monatsbl. f. Augenheilk., Bd. XLVIII, H. 2, S. 497.

BURK (1910).—Fluorescine in the eye.
Klin. Monatsbl. f. Augenheilk., Bd. XLVIII, S. 445.

CAHN, A. (1881).—The physiological chemistry of the aqueous.
Arch. f. Ophthal., Bd. XXVII, H. 2, SS. 295-300.
Zeitschr. f. phys. Chem., Bd. V, SS. 213-232.

CALDERARO (1915).—Sugar in diabetes.
La Clin. Ocul., T. XV, pp. 1 et 88.

CARLINI (1910).—On formation of Greeff's vesicles.
Arch. f. Ophthal., Bd. LXXVII, S. 96.

CARRÈRE, L. (1923).—Experimental studies on the formation of the aqueous.
Comp. rend. de Soc. de Biol., T. LXXXVIII, pp. 475-476.

CASTRO, LOZANO Y. (1901).—*See* TRONCOSO (1901).

CAVAZZANI, E. (1905).—The viscosity of the aqueous.
Arch. di farmacol. sperim. e scienze affini., Vol. VI, pp. 401-405.
1909 : *Ibid.*, Vol VIII, p. 262.
1910 : *Arch. ital. de Biol.*, Vol. LIII, p. 479.

CHABBAS (1877).—On the secretion of the aqueous.
Pflüger's Arch. f. d. ges. Physiol., Bd. XVI, SS. 143-153.

CHENEVIX (1832).—On the specific gravity of the vitreous. In Berzelius: *Lehrbuch der Chemie*. Reutlingen, Bd. IV, S. 442.

CIRINCIONE, SP. (1912).—*Sull indice di rifrazione e dei mezzi oculari dell'uomo e degli animali all temperature normal.*
Palermo, 1912.

——— (1913).—*La Clin. Ocul.*, p. 1273.

COHEN, KILLIAN, and METZAR (1925).—Chemistry of the aqueous.
Proc. Soc. Exper. Biol. and Med., Vol. XXII, pp. 445-6.

COHNHEIM, O. (1900).—The chemistry of the vitreous.
Roscoe u. Schorlemmer's *Lehrbuch der Chemie*, Bd. IX, SS. 259-260.

COLLINS, E. TREACHER (1891).—The glands of the ciliary body in the human eye.
Trans. Ophthal. Soc., U.K., Vol. XI, pp. 55-63.
Roy. Lond. Ophthal. Hosp. Reps., Vol. XIII, pt. i, p. 63.

——— (1896).—*Researches into the Anatomy and Pathology of the Eye.*
Lewis, London.

——— (1918).—Hypotony.
Trans. Ophthal. Soc., U.K., Vol. XXXVIII, p. 217.

——— and M. S. MAYOU (1925).—*The Pathology and Bacteriology of the Eye.*
Heinemann, London.

CONWAY, VERNEY, and BAYLISS (1923).—Comparison of methods of estimation of the pH of the blood.
Jl. of Physiol., Vol. LVIII, pp. 100-107.

COULTAR (1921).—Complement fixation and deviation reactions.
Jl. of Gen. Physiol., Vol. III, p. 513.

CRAWFORD and FOSTER (1918).—Antibodies.
Amer. Jl. of Pharm., Vol. XC, p. 765.

CREVELD, S. VAN (1921).— The chlorides in blood.
Bioch. Zeitschr., Bd. CXXIII, SS. 304-314.

——— (1924).—The surface tension of the aqueous.
Arch. néerland. de Physiol. de l'homme et des animeaux, T. IX, Nr. 1, pp. 60-66.

——— and R. BRINKMAN (1921).—Distribution of sugar in plasma and corpuscles.
Zittingsvers. Koninkl. Acad. van Weteirsch., Dec. 17.

CRONSTEDT, L. (1923).—Bacteriology of vitreous.
Svinska Läkar, Handlingar, Bd. XLIX, S. 157.

——— (1924).—*Acta Ophthal.*, Bd. II, SS. 168-175, 176-183, 267-274.

CULLEN and ROBINSON (1923).—pH of blood.
Jl. of Biol. Chem., Vol. LV, p. 533.

CYON (1869).—The refractive index of the aqueous and vitreous.
Sitzungsber. d. Wiener Akad. d. Wissenschr., Bd. LIX.
(see *Centralbl. f. d. med. Wissenschr.*, No. 50, 1874).

DALE, H. H. (1912).—Anaphylactic reaction of plain muscle of the guinea pig.
Jl. Pharmacol. and Exp. Therap., Vol. IV, pp. 167-223.

——— and P. HARTLEY (1916).—Anaphylaxis to serum proteins.
Bioch. Jl., Vol. X, pp. 408-433.

——— and A. N. RICHARDS.—The vaso-dilator action of histamine.
Jl. of Physiol., Vol LII, pp. 110-165.
Also with LAIDLAW, *Ibid*, p. 355.
Also with BURN, *Ibid*, Vol. XLI, pp. 185-215.

DEAN, H, R. (1923).—Serological tests.
Brit. Med. Jl., pp. 1033-1036, Dec. 1.

DEMONS.—See BOTAZZI e STURGIO (1906).—Subconjunctival salt injections.

DEUTSCHMANN, R. (1877).—Sugar in the aqueous of diabetics.
Arch. f. Ophthal., Bd. XXIII, H. 3, S. 143.

——— (1878).—The absorption of pathological matter in the anterior chamber.
Arch. f. Ophthal., Bd. XXIV, H. 2, SS. 213-234.

——— (1879, a).—The regeneration of the aqueous after paracentesis.
Arch. f. Ophthal., Bd. XXV, H. 1, SS. 99-114.

——— (1879, b).—Chemistry of the vitreous.
Arch. f. Ophthal., Bd. XXV, H. 2, S. 222.

——— (1880).—Source of the aqueous humour.
Arch. f. Ophthal., Bd. XXVI, H. 3, SS. 117-134.

——— (1881).—The physiological chemistry of the ocular fluids.
Arch. f. Ophthal., Bd. XXVII, H. 2, SS. 295-300.

DIETER, W. (1925, a).—On the surface tension of the aqueous and its relation to its protein content.
Arch. f. Augenheilk., Bd. XCVI, SS. 8-33.
Also *Klin. Monatsbl. f. Augenheilk.*, Bd. LXXII, S. 535.

——— (1925, b).—Relation between osmotic pressure, blood-pressure, especially capillary pressure, and intra-ocular pressure.
Arch. f. Augenheilk., Bd. XCVI, SS. 179-264.

DOGIEL (1879).—The protein content of the ocular media.
Pflüger's Arch. f. d. ges. Physiol., Bd. XIX, SS. 335-342.

DONNAN, F. G. (1911).—On Donnan's equilibrium.
Zeitschr. Electrochem., Bd. XVII,, S. 572.
Jl. of Chem. Soc., Vol. XCIX, p. 1554, 1911 ; Vol. CV, p. 1941, 1914.

DOR, L. (1901).—Reaction of the aqueous.
Bull. et mém. de la Soc. franç. d'Ophtal., T. XVIII, pp. 292-297.

DRESER (1892).—On diuresis and its fluid exchange by pharmacological means.
Arch. f. exper. Path. u. Pharm., Bd. XXIX, S. 304.

DUKE-ELDER, W. S. (1926, a).—Reaction of intra-ocular pressure to osmotic variation in blood.
Brit. Jl. of Ophthal., Vol. X, pp. 1-29.

——— (1926, b).—The blood pressures in eye.
Jl. of Physiol., Vol. LXI, pp. 409-419; Vol. LXII, pp. 1-11.
Brit. Jl. of Ophthal., Vol. X, pp. 513-572.

——— (1926, c).—Theory of the genesis of cataract.
Lancet, Vol. I, pp. 1188-1192, 1250-1255.

——— (1927, a).—Osmotic pressure of aqueous.
Jl. of Physiol., Vol. LXII, pp. 315-329.

——— (1927, b).—Biochemistry of aqueous.
Bioch. Jl., Vol. XXI, pp. 66-77.

——— (1927, c).—The pressure equilibrium of the eye.
Jl. of Physiol. (to be published).

DUNGERN, D. VON (1903).
Die Antikörper, Jena.

EBBECKE, U. (1917).—Local vaso-motor reactions.
Arch. f. d. ges. Physiol., Bd. CLXIX, SS. 1-81.

EGE, R. (1920).—The physiology of the blood sugar.
Bioch. Zeitschr., Bd. CVII, SS. 229-245.

——— and V. HENRIQUES (1925).—The sugar of arterial and venous blood and muscles.
Bioch. Zeitschr., Bd. CXIX, SS. 121-133.

EHRENTHAL (1887).—*Kritisches und Experimentelles zur Lehre vom Flussigkeitwechsel im Auge.*
Inaug. Dissert., Königsberg.

EHRLICH, P. (1882).—The appearance of fluorescine in the eye.
Deutsch. med. Wochenschr., N. 2.

EISLER (1923).—Properties of antibodies.
Bioch. Zeitschr., Bd. CXXXV, S. 416.

ELLIOT, R. H. (1918).—*A Treatise on Glaucoma.*
Oxford Med. Pub., London.

ELSCHNIG (1920).—On the secondary aqueous humour.
Ber. d. deutsch. Ophthal. Gesell., Heidelberg. Bd. XLII, S. 65.

ERGGELET (1925).—The thermal current in the anterior chamber.
Klin. Monatsbl. f. Augenheilk., Bd. LV, S. 229.

EVANS, H. M. (1915).—The macrophages of mammals.
Amer. Jl. of Physiol., Vol. XXXVII, pp. 243-258.

FALLOISE (1905).—Complement in aqueous.
Bull. de l'Acad. roy. Belge., Nr. 5.

FALTA u. RICHTER (1919).—Sugar in plasma and corpuscles.
Bioch. Zeitschr., Bd. C, S. 148.

FIELD and TEAGUE (1907).—Antibodies.
Jl. of Exper. Med., Vol. IX, p. 86.

FINNOFF, W. C. (1915).—The ciliary glands.
Arch. of Ophthal., Bd. XLIV. SS. 626-637.

FISCHER, P. (1862).—Sugar in aqueous in diabetes.
Arch. gén. de Méd., T. I, pp. 257-273, 413-443.

FISHER, J. H. (1925).—The intra-ocular lymph paths.
Trans. Ophthal. Soc. U.K., Vol. XLV, pp. 288-300.

FLACK, M. (1913).—The intra-ocular pressure.
Proc. of the Roy. Soc. of Med., Vol VI, pt. iii, p. 63.

FLEISCHER (1872).—*Neue Bestimmungen der Brechungsexponenten u. durchsichtigen flüssigen medien des Auges.*
Inaug. Dissert., Jena.

FOSTER, G. L. (1923) —The sugar content of capillary blood.
Jl. of Bioch., Vol. LV, p. 291.

FRASER, F. R., G. GRAHAM, and R. HILTON (1924).—Comparison between blood curves of venous and arterial blood.
Jl. of Physiol., Vol. LIX, p. 221.

FRERICHS (1848).—On cataract.
Hannover'sche. Annalen., S. 657.

FREUND, H. (1922).—*In vivo* dialysation.
Arch. f. exper. Path. u. Pharm., Bd. XCV, SS. 206-234.

FREYTAG, G. (1907).—*Vergleichende Untersuchungen über die Brechungsindices der Linse u. der flüssigen Augesmedien des Menschen u. der höheren Tiere in verschiedenen Lebensaltern.*
Wiesbaden, Bergmann, 1907.
——— (1909).—*Arch. f. Vergleichenden Ophthal.*, H. 1, S. 59.

FRIEDENTHAL, G. v. (1924).—Intra-ocular fluid change.
Zeitschr. f. Augenheilk., Bd. LII, SS. 15-57.

GALA, A. (1924, a).—Protein and salts in the regenerated aqueous of animals and in the normal and pathological human eye.
Bratis. lekársek listy, Vol. III, pp. 192-236.

——— (1924, b).—The micro-chemistry of the aqueous in hydrophthalmia.
Bratis. lekársek listy. Vol. III, pp. 383-390.

——— (1925).—The hydrogen ion concentration in the vitreous body of the eye with reference to glaucoma.
Casopis lékaru ceskycl., Vol. LXIV, pp. 409-413.
Brit. Jl. of Ophthal., Vol. IX, pp. 516-519.

GALA, A., and A. FABIAN (1926).— Wassermann reaction in aqueous.
Cas. lek. cesk., Bd. CLXV, SS. 1031-35, 1066-70.

GARMUS, A. (1912).—The permeability of gland cells to dye-stuffs.
Zeitschr. f. Biol., Bd. LVIII, SS. 185-236.

GATTI, A. (1902).—Bactericidal properties of aqueous.
Ann. di Ottal., Vol. XXXI, p. 3.

GAY and ROBERTSON (1912).—On the antigenic nature of proteins.
Jl. of Biol. Chem., Vol. XII, p. 233.

GEBB, H. (1922).—The protein content of the pathologically changed vitreous.
XLIII Sitzungsber. Ophthal, Gesell., Jena, SS. 21-23.

GIACOSA (1882, a).—The chemistry of the vitreous of the human eye.
Arch. per le Soc. med., T. VI, p. 29.

——— (1882, b).—On the albumen content of the human vitreous.
Giorn. di L. Accado. di Torino, Vol. XLV. p. 71.

GIFFORD (1886).—On the lymph stream of the eye.
Arch. f. Augenheilk., Bd. XVI, SS. 421-428

——— (1893).—*Ibid.*
Arch. f. Augenheilk., Bd. XXVI. SS. 308-336.

GILBERT, W. (1924).—Experiments on the aqueous.
Arch. f. Augenheilk., Bd. XCIV, SS. 101-103.

——— and F. PLANT (1920).—Serological reactions of aqueous.
Ber. d. deutsch. Ophthal. Gesell., Heidelberg, Bd. XLII, SS. 68-73.
Arch. f Augenheilk., Bd. LXXXVIII, S. 210.

——— (1921).—*Berl. klin. Wochenschr.*, Bd. LVIII, SS. 1097-1099.
Arch. f. Augenheilk., Bd. XC, SS. 29-42.

Haedertz a. o. Wittgenstein a., (1927)
"Über den Kationgehalt des Kammerwassers
im lebenden Warmblüterauge. Exp. Untersuchungen
a. f. Ophthal. CXVIII. S. 738

– do – 1928
Untersuch. ü. den Stoffaustausch vom Blut ins
K.W. a. f. O. (119) 395, 403, (1927), ~~733, 755~~ (192
755, 771.

GOLDSCHMIDT, M. (1914) —The mechanism of absorption of the lens proteins.
Münch med. Wochenschr., Bd. LXI, Nr. 12, S. 637.
Arch. f. Ophthal., Bd. LXXXVIII, SS. 405-412.

GOLDSCHMIDT, O. (1860).—Sugar in aqueous in diabetes.
Allg. med. Centralzeitung. No 51.

GOLOWIN (1895).—Ophthalmotonometric experiments.
Inaug. Dissert., Moscow (in Russian).
Ref. Michel's *Jahresber.*, S. 182.

——— (1900).—The specific weight of the aqueous.
Arch. f. Ophthal., Bd. XLIX, H. 1, SS. 27-35.

GRASER (1883).—Experiments on the intra-ocular pressure.
Inaug. Dissert., Erlangen.

GRAVES, B. (1925).—The visible beam in the aqueous.
Amer. Jl. of Ophthal., Vol. VIII, pp. 8-15.

GREEFF (1893).—New findings on the intra-ocular fluids and on the fibrin in the aqueous.
Sitzungsber. d. ophthal. Ges., Heidelberg, SS. 11-23.

——— (1894).—Findings on the ciliary body after puncture of the anterior chamber.
Arch. f. Augenheilk., Bd. XXVIII, SS. 178-192.

GRIFFITH (1894) —On the "glands" of Treacher Collins.
Ophthal. Rec., Vol. XIII, p. 247.

GRIGNOLO (1913).—Aqueous changes. Intravenous salt injections.
Klin. Monatsbl. f. Augenheilk.. Bd. LI, S. 157.

GRÖNHOLM (1900).—The action of eserine on the intra-ocular fluids and the intra-ocular circulation.
Arch. f. Ophthal., Bd. XLIX, SS. 620-711.

GRÜNHAGEN u. JESNER (1880).—The production of fibrin after nerve stimulation.
Centralbl. f. Augenheilk., S. 1781.

GRÜTER (1911).—Bacteriolysins in the aqueous.
Arch. f. Augenheilk., Bd. LXX, S. 241.

GUGLIANETTI, L. (1919).—The viscosity of the aqueous.
Arch. di Ottal. Vol, XXVI, pp. 109-122.

GULLSTRAND (1891).—The refractive index of the aqueous.
Svenska Läk. Sallsk. Handb., S. 73.

GUTTEMANN (1895).—The nature of Schlemm's canal and its relation to the anterior chamber.
Arch. f, Ophthal., Bd. XLI, H. 1, SS. 28-55.

HAAN, J. DE (1922).—The tension and consumption of oxygen in the aqueous.
Arch. néerland de Physiol., Bd. VII, SS. 245-250.

——— u. S. VAN CREVELD (1921, a).—On the relationship between the plasma and the tissue fluids with special reference to the aqueous and cerebro-spinal fluid.
Bioch. Zeitschr., Bd. CXXIII, SS. 190-214.
Also *Nederlandsch. Tijdschr. v. Geneesk*, H. 2, S. 783, 1921.

——— (1921, b).—Fluorescine in the aqueous.
Bioch. Zeitschr., Bd. CXXIV, SS. 172-184.

HAGEDORN, H. C., und B. N. JENSEN (1923).—Micro-estimation of blood-sugar.
Bioch. Zeitschr., Bd. CXXXV, SS. 46-58.

HAGEN, S. (1920, a).—The regeneration of the aqueous in the human eye.
Klin. Monatsbl. f. Augenheilk., Bd. LXIV, SS. 187-194.

——— (1920, b).—Experiments on the intra-ocular fluid in human eyes.
Klin. Monatsbl. f. Augenheilk., Bd. LXV, SS. 643-654.

——— (1921, a).—Experiments on the regeneration of the human aqueous.
Klin. Monatsbl. f. Augenheilk., Bd. LXVI, SS. 493-507.

——— (1921, b).—In reply to Wessely, 1921.
Klin. Monatsbl. f. Augenheilk., Bd. LXVII, S. 259.

HALLAUER (1913).—Refractive index of aqueous.
XXXIX Berl. Ophthal. Gesell., Heidelberg, Wiesbaden, S. 113.

HALLER, A. (1757).—Secretion of aqueous.
Element. Physiol., Bd. V, S. 412.

HAMBURGER, C. (1898).—Is there a communication between the anterior chamber and the posterior chamber ?
Centralbl. f. prakt. Augenheilk., Bd. XX, S. 225.

——— (1899).—The physiological seclusion of the pupil.
Deutsch. med. Wochenschr., No. 22.
Klin. Monatsbl. f. Augenheilk., Bd. XXXVIII, SS. 144-148, 227-229.

——— (1900).—The origin of the aqueous.
Klin. Monatsbl. f. Augenheilk., Bd. XXXVIII, SS. 801-823.

——— (1901).—*Ibid.*
Klin. Monatsbl. f. Augenheilk., Bd. XXXIX, SS. 312-313.

——— (1902) —The circulation in the eye.
Sitzungsber. d. Ophthal. Gesell., Bd. XXX, SS. 246-264.

——— (1905).—*Klin. Monatsbl. f. Augenheilk.*, Bd. XLIII, H. 1, S. 105.

——— (1909).—*Berl. klin. Wochenschr.*, S. 30.

——— (1910).—*Arch. f. vergl. Ophthal.*, H. 3, Nr. 3, S. 373.
Klin. Monatsbl. f. Augenheilk., Bd. XLVIII, S. 47.

——— (1914).—*Uber die Ernährung des Auges*, Leipzig.

——— (1920).—The nutrition of the eye.
Klin. Monatsbl. f. Augenheilk., Bd. LXIV, S. 737 ; Bd. LXV, S. 29.

——— (1921).—*Klin. Monatsbl. f. Augenheilk.*, Bd. LXVI, S. 403.

——— (1922).—*Klin. Monatsbl. f. Augenheilk.*, Bd. LXIX, SS. 249-258, 393-407.

——— (1922).—Injections into the eye : pathological effect.
Klin. Monatsbl. f. Augenheilk., Bd. LXIX, SS. 68-71.

——— (1923).—Effect of adrenaline
Med. Klin., Bd. XIX, S. 1224.

——— (1924).—The filtration theory and the treatment of glaucoma.
Klin. Monatsbl. f. Augenheilk., Bd. LXXII, SS. 47-56, 541, and 774-777.
Zeitschr. f. Augenheilk., Bd. LIII, S. 127.

——— (1925).—*Deutsch. med. Wochenschr.*, Bd. LI, S. 1397.

HAMBURGER, H. J. (1893).—Osmotic pressure.
Verhandl d. Koninkl. Akad. v. Wetenschr., H. 3, S. 5.

——— (1895).—*Virchow's Arch.*, Bd. CXL, SS. 517-518.

——— (1897).—*Centralbl. f. Physiol.*, Bd. XI.

——— (1902-4).—*Handb. d. osmotischen Druck und Ionenlehre.*
Wiesbaden, Bd. I-III.

——— (1918).—Migration of ions in serum and blood.
Bioch. Zeitschr., Bd. LXXXVI, SS. 309-324.

——— (1919).—Hyperglycaemia and glycosuria.
Brit. Med. Jl., Vol. I, pp. 267-271.

HARTLEY, P. (1914, a).—Variations occurring in serum proteins of animals, etc.
Memoirs of the Department of Agriculture in India : Veterinary Series, Vol. I, No. iv, pp. 178-270.

——— (1914, b).—Preparation of pure proteins.
Bioch. Jl., Vol. VIII, p. 541.

HAYANO (1921).—Ferments in aqueous.
Jubilee volume of Prof. Komoto.

HAYASHA (1911).—Circulation of the aqueous.
Klin. Monatsbl. f. Augenheilk, S. 154.

HECHT (1923).—Complement fixation and deviation reactions.
Zeitschr. Immunol., Bd. XXXVI, S. 321.

HEISRATH (1880).—The outflow of the aqueous by the spaces of Fontana and Schlemm's canal.
Arch. f. Ophthal., Bd XXVI, H. 1, SS. 202-243.

HELMHOLTZ, v. (1896).—Refractive index of aqueous.
Physiologische Optik., 2 Aufl., S. 98.

HENDERSON, E. E., and J. E. LANE-CLAYPON, (1908).—
Roy. Lond. Ophthal. Hosp. Reps., Vol. XVII, p. 97.

——— and E. H. STARLING (1904).—The influences of changes in the intra-ocular circulation on the intra-ocular pressure.
Jl. of Physiol., Vol. XXX, pp. 305-319.

——— (1906).—The factors which determine the production of the intra-ocular fluid.
Proc. Roy. Soc., Ser. B., Vol. LXXVII, pp. 294-310.

HENDERSON, T. (1910).—*Glaucoma*, Arnold, London.

——— (1913).—Discussion on the intra-ocular pressure
Proc. of the Roy. Soc. of Med., Lond., Vol. VI, pt. iii, p. 66.

HERTEL, E. (1909).—The electrical conductivity of the eye.
Arch. f. Ophthal., Bd. LXIX, SS. 126-144.

——— (1913, a).—Intra-ocular pressure in diabetes.
Internat. Cong. Ophthal., Ghent, 1913.
Münch. med. Wochenschr., Nr. 22, S. 1191.

——— (1913, b).—Changes in intra-ocular pressure with osmosis.
Klin. Monatsbl. f. Augenheilk., Bd. LI, S. 351.

——— (1914).—*Ibid.*
Arch. f. Ophthal., Bd. LXXXVIII, H. 2, SS. 197-229.

——— (1915).—*Ibid.*
Arch. f. Ophthal., Bd. XC, S. 309.

——— (1918).—*Bericht d. deutsch. Ophthal. Gesell.*, Heidelberg, S. 57.
Klin. Monatsbl. f. Augenheilk., Bd. LXI, S. 331

——— (1920).—*Bericht d. deutsch. Ophthal. Gesell.*, Heidelberg, S. 73.
Arch. f. Ophthal., Bd. CIV, S. 149, 1921.

——— (1921).—Estimation of hydrogen ion concentration in aqueous.
Arch. f. Ophthal., Bd. CV, SS. 420-431.

HESS, C. L. V., and MCGUIGAN (1914).—The condition of the sugar in the blood.
Jl. of Pharm. and Exper. Therap., Vol. VI, pp. 45-55.
See also ABEL, ROWNTREE, and TURNER, *Ibid.*, Vol. V, pp. 275 and 611, 1914.

HESS, L., u. H. MULLER (1915).—Pathology of oedema.
Zeitschr. f. exper. Path. u. Therap., Bd. XVII, S. 189.

HEUBNER, W., u. R. MEYER-BISCH (1926).—Sulphate in aqueous.
Bioch. Zeitschr., Bd. CLXXVI, SS. 184-188.

HEYDT, R. VON DER (1923).—Thermal current in the anterior chamber.
Amer. Jl. of Ophthal., Vol. VI, pp. 822-824.

HILBERT (1883).—The influence of iodine preparations on the tissues of the body, especially the eye fluids.
Schriften d. phys. ökon. Gesell. zu., Königsberg, Bd. XXIV.
Ref. in Michel's *Jahresber.* (1884), S. 147.

HILL, LEONARD (1913).—The physiology of the intra-ocular pressures.
Proc. of the Roy. Soc. of Med., Vol. VI, pt. iii, pp. 31-44.

——— (1920).—The blood pressure of the eye.
Lancet, Vol. I, pp. 359-366.

——— and M. FLACK (1912).—The relation between capillary pressure and secretion.
Proc. Roy. Soc., Ser. B., Vol. LXXXV, pp. 439-459.

HIPPEL, VON (1895).—Greeff's vesicles on ciliary body.
Arch. f. Ophthal., Bd. XLI, H. 3, S. 13.

——— (1920).—*Ibid.*
Klin. Monatsbl. f. Augenheilk., Bd. LXV, S. 85.

HIROISHI, H. (1924).—On the relation between the intra-ocular pressure and the blood pressure in the episcleral veins and vortex veins.
Arch. f. Ophthal., Bd. CXIII, SS. 212-222.

HIRSCH, E. F. (1922)—Precipitation reactions.
Jl. of Infectious Diseases, Vol. XXX, p. 666.

HIRSCHBERG (1874).—Refractive index of the ocular media of human eyes.
Arch. f. Augenheilk. u. Ohrenheilk., Bd. IV, H. 1, SS. 45-55.
Centralbl. f. d. med. Wissenschr., N. 13 u. 50.
Arch. f. Augenheilk., Bd. III, H. 2, S. 160.

HIS (1865).—*Ueber ein perivasculäre Canal system in den nervösen Centralorganen*, Leipzig.

HOEVE, J. VAN DER (1912).—The osmotic pressure and electrical conductivity of the intra-ocular fluids and the blood serum of animals.
Arch. f. Ophthal., Bd. LXXXII, H. 1, SS. 58-74.

HOLI (1921).—The physico-chemistry of the aqueous.
Jahr. d. japan. Ophthal. Gesell., Koyoto, April, 1922.
Jubilee volume of Prof. Komoto, 1921.

HÖLTZKE (1883).—The pressure in the anterior chamber.
Arch. f. Ophthal., Bd. XXIX, H. 2, S. 1.

HOMER (1920).—On antibodies.
Bioch. Jl., Vol. XIV, p. 42.

HOTTA, G. (1906).—The eyes of anthropoids (injections).
Arch. f. Ophthal., Bd. LXII, SS. 227-250.

HOVIUS (1702).—De circulari humorum motu in oculo.
Traj. ad. Rhen.

HOWE, L. (1925).—The protein of the blood.
Physiol. Rev. Vol. V, p. 452 (with bibliography).

IRVING, J. T. (1926) —The fate of sugar in shed blood.
Bioch. Jl., Vol. XX, pp. 613-619.

——— and H. D. KAY (1926).—The *in vivo* permeability of the red corpuscles of the rabbit.
Jl. of Physiol., Vol. LXI, pp. 113-121.

IWANOFF (1865).—The normal and pathological anatomy of the vitreous.
Arch. f. Ophthal., Bd. XI, H. 1, SS. 155-170.

JACINSKI (1924).—Proteolytic ferments in the aqueous.
Klinik Oczna, Bd. II, S. 112.
Abs. *Klin. Monatsbl. f. Augenheilk.*, Bd. LXXIV, S. 805.

——— (1925).—*Ibid. Soc. franç. d'Ophtal.*, T. XXXVIII.
Congress Brussels, May.
Ann. d'Ocul., T. CXLII, p. 461.

JACOBY, MARTIN (1920).—See Hamburger, C., 1922 (b).

JÄGER, E. VON (1861).—*Über die Einstellungen des dioptrischen Apparates. (Chemische Zusammensetzung der Augenflüssigkeiten nach Analysen von Kletzinsky.)* Wien.

JANIN, J. (1788).—*Mém. et obs. anat. physiol., et phys. sur l'oeil.*
2 Aufl., Berlin, S. 73.

JESNER (1880).—The relation of the aqueous to the blood pressure and nerve stimulation.
Arch. f. de ges. Physiol., Bd. XXIII, SS. 14-44.

Ikabata. T. (1927)
über die Zusammensetzung des Kammerwas
Biochem. Zeitsch. Bd. CLXXXII. S. 236.

Koller. artim † drop
Arch. Ophthal., (50) 550, 1921 ?!

a. of. Ophth.

JESS, A. (1922).—The chemistry of the normal and pathological vitreous.
Bericht. ü. d. XLIII Versam. d. deutsch. Ophthal. Gesell., Jena, SS. 11-21.

——— (1923).—The cholesterin content of the vitreous.
Arch. f. Ophthal., Bd. CXII, SS. 80-89.

——— (1925).—The cholesterin in the aqueous.
Bericht d. deutsch. Ophthal. Gesell., Heidelberg.

JOHNSTONE (1909).—The relation of conductivity to temperature.
Jl. Amer. Chem. Soc., Vol. XXXI, p. 1010.

JUSELIUS (1910).—Changes in the aqueous on applying heat.
Arch. f. Ophthal., Bd. LXXXV, S. 350.

KAHN, R. H. (1918).—On the seclusion of the pupil.
Arch. f. Ophthal., Bd. XCVIII, SS. 73-80.

KLEINER, I. S. (1918).—The rate of dialysis of the blood sugar, etc.
Jl. of Biol. Chem., Vol. XXXIV, pp. 471-487.

KLETZINSKY, see E. VON JÄGER (1861).

KLINGBERG (1889).—Refractive index of aqueous.
Programm. Domschule, Güstrow.

KNAPE (1910).—On the influence of atropine and eserine on the intra-ocular fluids.
Skand. Arch. f. Physiol., Bd. XXIV.

KNAPP (1909).—Opsonins in aqueous.
Arch. of Ophthal., July, p. 372.

——— (1912).—Chemical changes in aqueous after pressure.
Klin. Monatsbl. f. Augenheilk., Bd. L, S. 691.

KNAPP u. CARIUS (1863).—Lens extraction in diabetes: sugar in aqueous.
Klin. Monatsbl. f. Augenheilk., Bd. I, SS. 168-172.

KNIES (1875, a).—The resorption of blood in the anterior chamber.
Virchow's Arch., Bd. LXII, SS. 537-553.

——— (1875, b.)—The circulation in the living eye.
Virchow's Arch., Bd. LXV, SS. 401-409.

——— (1876).—On glaucoma.
Arch. f. Ophthal., Bd. XXII, H. 3, SS. 163-202; Bd. XXIII, H. 2, SS. 62-78, 1877.

——— (1878).—On the nourishment of the eyes and the channels of exit of the intra-ocular fluids.
Arch. f. Augenheilk. u. Ohrenheilk., Bd. VII, SS. 320-370.

KOCHMANN u. RÖMER (1914) —Experiments on the pathological fluid in the eyes.
Centralb. f. d. ges. Ophthal. u. ihre Grenz., Bd. I, S. 120.
Arch. f. Ophthal., Bd. LXXXVIII, S. 528.

KÖLLNER (1916).—Effect of eserine.
Arch. f. Augenheilk., Bd. LXXX, S. 245.

——— (1918).—*Arch. f. Augenheilk.*, Bd. LXXXIII, S. 135.

——— (1921).—*Arch. f. Ophthal.*, Bd. [illegible], SS. 550-555.

KOLMER, J. A. (1924).—*The human cerebro-spinal fluid.*
Hoeber, New York.

KOSKE, F. (1905).—Bactericidal properties of aqueous.
Arbeiten aus dem Kaiserl. Gesundheitsamt, Bd. XXII, S. 411.

KRAUSE, W. (1855).—*Die Brechungsindices des durchsichtigen Medien des menschlichen Auges.*

——— (1879).—*Handb. des menschlichen Anatomie*, 3 Aufl., Bd. II, S. 955.

KROGH, A. (1916).—Immunity.
Jl. of Infectious Diseases, Bd. XIX, S. 452.

——— (1922).—*The Anatomy and Physiology of the Capillaries*, New Haven.

KROGH, A., and G. A. HARROP (1920).—Some observations on stasis and oedema
Jl. of Physiol., Vol. LIV.
Proc. Physiol. Soc., Vols. CXXV, CXXVI.

KRUSIUS, F. (1910).—Specific sensitization in the eye.
Arch. f. Augenheilk., Bd. LXVII, SS. 6-35.
Zeitschr. f. Immunol., Bd. V, S. 6.

KUFFLER, O. (1912).—Antibodies in aqueous.
Bericht. u. d. Ophthal. Gesell., Heidelberg, S. 279.

——— (1913).—*Ibid.*
Arch. f. Ophthal., Bd. LXXXVI, S. 69.

KUHN (1887).—The chemistry of the aqueous.
Arch. f. d. ges. Physiol., Bd. XLI, S. 200.

KUMAGAI (1920).—Subconjunctival injections.
Mitteil. med. Fakultät der Kaiseri, Univer. Tokyo, Bd. XVIII, S. 103.
Nippon Gank. Zasshi, Oct.

KÜMMELL, R. (1910).—The serology of the aqueous.
Arch. f. Ophthal., Bd. LXXVII, S. 393.

KUNST (1895).—*Beiträge zur Kenntniss der Farbenzerstrenung und des osmotischen Druckes einiger brechenden Medien des Auges.*
Inaug. Dissert. Freiburg, Br. u. Leyden.

LAGANA (1915).—Antibodies in aqueous.
La Clin. Ocul., T. XIV, pp. 1845 et 1913.

LANDIS, E. M., and H. F. ROBERTSON (1925).—Bactericidal power of aqueous.
Amer. Jl. of Ophthal., Vol. VIII, p. 572.

LANDOLT, M. (1906).—Does the ciliary gland play a part in the production of the aqueous?
Arch. d'Ophtal., T. XXVI, pp. 157-166.

LAQUEUR (1919).—On lung oedema.
Münch. med. Wochenschr., S. 1721.

LEBER, A. (1906).—Antibodies in aqueous.
Arch f. Ophthal., Bd. LXIV, SS. 413-444.

LEBER, TH. (1875).—Sugar content and reaction of aqueous in diabetes.
Arch. f. Ophthal., Bd. XXI, H. 3, SS. 124-129.
Also 1878, *Sitzungsber. d. Ophthal. Gesell.*, S. 39.

——— (1891).—Experimental secondary glaucoma.
Die Entstehung der Entzündung, u. s. w., Leipzig, SS. 131-133.

——— (1891).—Diastatic enzyme in aqueous.
Ibid, SS. 363-365.

——— (1893).—Discussion after Greeff.
Sitsungsber d. Ophthal. Gesell., S. 23.

——— (1895).—Schlemn's canal.
Arch. f. Ophthal., Bd. XLI, H. 1, SS. 235-280.

——— (1896, a).—The current in the anterior chamber.
XXIV Bericht d. Ophthal. Gesell., SS. 83-97.

——— (1896, b).—Summary of present knowledge on intra-ocular fluids.
Merkel u. Bonnet, *Ergebnisse der Anatomie und Entwicelungschrichte.*

——— (1903).—Die Cirkulations u. Ernährungs Verhältnisse des Auges. Leipzig.
In *Graefe-Saemisch Handb. d. ges. Ophthal.*, 2, Aufl., Bd. II, SS. 207-352.

——— u. A. PILZECKER (1906). Circulation and filtration of aqueous.
Arch. f. Ophthal., Bd. LXIV, SS. 1 and 127.

LEBOUCQ, G. (1913).—The lymphatic paths of the eye and orbit.
Thèse de doctorat ès sciences, Gand.

Kubik. J. (1928) Untersuch. über die Wasserstoffionenkonzentration des Kammerwassers. a. f. a. (96) 483.

Krause, O. C., Yudkin, Ann., - Morton. O. C.
On the experimental transmission of arsenic to the amnion human.
Proc. Soc. Exp. Biol. Med. xxiv. 384. 1927.

LEBOUCQ, G. (1920).—Does the aqueous circulate?
Bull. de l'Acad. roy. de méd. de Belg., T. XXX, No. 9. Ref. *Arch. d'Ophtal.*, T. XXXVIII, p. 252, 1921.

LEHMANN, G. u. A. MEESMANN (1924).—The intra-ocular fluids.
Pflüger's Arch. f. d. ges. Physiol., Bd. CCV, S. 210.

LEIBERMANN, F. (1921).—Antibodies in aqueous.
Deutsch. med. Wochenschr., Bd. XLVII, S. 1283.

——— (1925).—Microchemistry of the intra-ocular fluids.
Arch. f. Augenheilk., Bd. XCVI, SS. 355-384.

LÉPINE (1870).—On diastatic ferments.
Bericht. ü. d. Verhandl. d. k. Sächs. Gesell. d. Wissenschr. zu Leipzig, Math. physiol Kl., Bd. XXII, S. 332.

——— (1909).—*La diabète sucré*: Paris.

LEPLAT, (1887, a).—The regeneration of the aqueous after paracentesis.
Ann. d'Ocul. T. XCVII, pp. 75-84.

——— (1887, b).—The nutrition of the vitreous.
Ann. d'Ocul., T. XCVIII, pp. 89-108.

——— (1889).—Researches on the circulation of the intra-ocular fluids.
Ann. d'Ocul., T. CI, pp. 123-136.

LEPLAT, G. (1923).—The influence of local bleeding on the physiology of the eye.
Ann. d'Ocul., T. CLX, pp. 348-356.
See also *Bull. Soc. belge d'Ophtal.*, Nov. 1922.

LERCH.—See HAMMERSTEN, 1922. Chemical composition of tears.
Lehrb. d. Physiol. chem., 9 Aufl., S. 488.

LEVADITI, C. (1901).—Immunity.
Ann. de l'Institut Pasteur, T. XV.

——— et INMAN (1907).—Complement in aqueous.
Compt. rend. de la Soc. de Biol., T. LXII, pp. 725-728.

LEVENSOHN, G. (1899).—The question of a free communication from posterior chamber to anterior chamber.
Klin. Monatsbl. f. Augenheilk., Bd. XXXVII, pp. 52-61, 226-227.
——— (1901).—*Ibid.*, Bd. XXIX, S. 230.

LEWIS, J. H. (1921).—Rate of absorption of subcutaneously injected serum.
Jl. of Amer. Med. Assoc., Vol. LXXVI, p. 1342.

LILLIE (1907).—Osmotic pressure of protein.
Jl. of Physiol., Vol. XX, p. 127.

LINDAHL (1910).—Immunity of aqueous.
Arch. f. Augenheilk., Bd. LXVII, Ergänz, S. 1.

LISTER, W. T. (1921).—Punctate deposits in the retina.
Trans. Ophthal. Soc. U.K., Vol. XLI, p. 275.

LOBANOW (1899).—Bactericidal properties of aqueous.
Westnik. Ophthal., Bd. XVI, SS. 111 u. 215.

LODATA (1901).—The intra-ocular pressure and sympathetic stimulation.
Arch. di Oftal., Vol. IX, p. 105.

LÖHLEIN (1910).—Entrance of drugs into the eye.
Arch. f. Augenheilk., Bd. LXV, SS. 318-354, 417-460.

LOHMEYER (1854).—The chemistry of the aqueous.
Zeitschr. f. Anat. Med., Bd. V, S. 56.

LÖWENSTEIN, A. (1911).—The viscosity of the fluids of the eye under normal and pathological conditions.
Arch. f. Augenheilk., Bd. LXX, S. 26.

——— (1912).—*Arch. f. vergl. Ophthal.*, Bd. III, H. 2.

——— (1918).—The chemistry of the aqueous.
Bioch. Zeitschr., Bd. LXXXVI, S. 343.

LÖWENSTEIN, A. (1920).—*Klin. Monatsbl. f. Augenheilk.*, Bd. LXV, SS. 654-662.

——— u. J. KUBIK (1915).—Proteins of aqueous.
Arch. f. Ophthal., Bd. LXXXIX, SS. 197-227.

LUNDSGAARD (1922).—Oxygen content of blood.
Jl. Exper. Med., Bd. XXXVI, S. 559.
Compare *Ibid*, Bd. XXX, SS. 241, 215, 259, 271.

LULLIES, H., u. L. GULKOWITSCH (1924).—Changes in ocular fluids.
Zentralbl. f d. ges. Ophthal., u. i. Grenz., Bd. XIII, S. 463.

MACALLUM, A. B. (1911).—Surface tension and vital staining.
Ergeb. Physiol., Bd. XI, SS. 598-657.

MCGUIGAN, H., and E. L. Ross (1917).—Methods for the determination of blood sugar in reference to its condition in the blood.
Jl. of Biol. Chem., Vol. XXXI, pp. 532-547.

MCILROY, J. H. (1910).—The results of a short series of subconjunctival injections in rabbits.
Ophthalmoscope, Vol. VIII, pp. 614-618.

MAGITOT, A. (1917, a).—The aqueous humour and its origin.
Ann. d'Ocul., T. CLIV, pp. 65-94, 129-152, 211-239.

——— (1917, b).—The physiological ocular tension.
Ann. d'Ocul., T. CLIV, pp. 272-295, 334-356, 385-410.

——— (1917, c).—Traumatic variations of the intra-ocular tension
Ann. d'Ocul., T. CLIV, pp. 667-694.

——— (1923).—The ocular tension and some of its experimental modifications.
Ann. d'Ocul., T. CLX, pp. 1-15, 18-105.

——— et P. Bailliart (1919).—Modifications of intra-ocular tension by external pressure.
Ann. d'Ocul., T. CLVI, pp. 656-666.

——— (1925).—The circulation in glaucoma.
Ann. d'Ocul., T. CLXII, pp. 729-763.

——— et MLLE. D'AUTREVAUX (1925).—The aqueous humour in the pathology of the eye.
Soc. d'Ophtal. de Paris, February 21.
Arch. d'Ophtal., T. XLII, p. 445.

MAJISCHITA (1909).—Haemolysin and complement in aqueous.
Klin. Monatsbl. f. Augenheilk., Bd. XLVII, H. 1, SS. 62-72.

MANCA (1898).—The osmotic pressure of the aqueous determined by the haematocrit.
Arch. ital. de Biol., Vol. XXX, p. 178.

——— DEGANELLO (1898, a).—The osmotic pressure of the aqueous humour.
Arch. di Ottal., p. 438.

——— (1898, b).—*Arch. ital. de Biol.*, Vol. XXX, p. 172.

MARTHEN (1893).—Bactericidal properties of aqueous.
Beitr. z. Augenheilk., Bd. XII.

MASTROBUONO, L. (1909).—The viscosity of the aqueous.
Arch. di Ottal., Vol XVI.

MATTHIESSEN (1891).—The refractive index of the aqueous.
Beiträge z. Psychol. u. Physiol. d. Sinnesorgane.
Festschr. f. Helmholtz.

MAWAS, J. (1909).—*Sur la structure de la rétine ciliare et la sécrétion de l'humeur aqueuse.*
Ass. des Anatomistes, Nancy.

——— (1910).—*Sur la structure de la rétine ciliare.* Thèse de Lyon.
Rec. Ophtal T. XXXIII, p. 13.

MAWAS, J., et VINCENT (1925).—The pH and the alkaline reserve of the aqueous.
Bull. Soc. d'Ophtal. de Paris, pp. 190-192.

Waitoff 1926. L'humeur aqueuse. I
Ann. de physiol. et de physico. chem. biol.
No. 3. p. 363.

Waitoff. A. 1927 L'humeur aqueuse II
Annales de physiol. et de physicochemie biol.
~~No 3. p. 363~~ No. 4 p. 509.

MAYS, K. (1885).—The reaction of the aqueous.
Verhandl. d. Naturlist med. Versam., zu. Heidelberg, N.F. 111.

MEMORSKY (1865).—Experiments on diffusion in the eye.
Arch. f. Ophthal., Bd. XI, H. 2, SS. 112-128.

MEESMANN, A. (1924).—The dependence of the intra-ocular pressure on the pH.
Arch. f. Augenheilk., Bd. XCIV, SS. 115-142.

——— (1925).—The physico-chemistry of the intra-ocular fluids.
Arch. f. Augenheilk., Bd. XCVII, SS. 1-30.

MÉRY (1707).—Glaucoma and cataract; are they different or identical?
Mém. de l'Acad. des Sc., p. 498.

MESTREZAT, W., et MAGITOT, A. (1921, a).—The aqueous humour.
Compt. rend. de la Soc. de Biol., T. LXXXIV, pp. 185-187.

——— (1921, b).—Quality and quantity of the normal aqueous.
Ann. d'Ocul., T. CLVIII, pp. 1-4.

——— (1920).—The normal aqueous of man and some mammals.
Congrès de Physiol. de Paris, July 20.

——— (1922, a).—Origin and nature of the secondary aqueous.
Bull. de la Soc. de chim. biol., T. IV, pp. 279-286.

——— (1922, b).—*Ibid.*
Compt. rend. de la Soc. de Biol., T. LXXXVI, pp. 657-659

——— (1922, c).—*Ibid.*
Ann. d'Ocul., T. CLIX, pp. 401-415.

METZNER, R. (1907).—The histological changes in glands.
Nagel's *Handb. des Physiol.*, Bd. II, SS. 900-1024.

MEYER (1897).—Refractive index of aqueous.
Inaug. Dissert., Rostock.

MICHAELIS, L. (1902).—*Farbstoffchemie für Histologen.*
S. Karger, Berlin, S. 104.

——— (1922).—*Die Wasserstoffionkonzentration*, Berlin.
2 Aufl., Bd. I.

——— and P. RONA (1908).—On blood sugar.
Bioch. Zeitschr., Bd. XIV, SS. 476-483.

——— (1909).—*Ibid.*
Bioch. Zeitschr., Bd. XVIII, SS. 375-379.

MICHEL, v., u. WAGNER (1886).—Physico-chemistry of the eye.
Arch. f. Ophthal., Bd. XXXII, H. 2, SS. 155-204.

MONNIK (1870).—Pressure in excised eye: a new tonometer.
Arch. f. Ophthal., Bd. XVI, H. 1, SS. 49-89.

——— (1883).—Refractive index of aqueous.
Zeitschr. vgl. Augenheilk., Bd. II, S. 1.

MORAX et LOISEAU (1911).—The passage of diphtheria antitoxin and antitetanic antitoxin in the aqueous.
Ann. de l'Institut Pasteur, T. XXV.

MÖRNER (1893).—The proteins in the ocular media.
Zeitschr. f. Physiol. Chemie., Bd. XVIII, SS. 244-256.

MOTT, F. (1910).—Perivascular lymph spaces in brain.
Lancet, June 2 and 9.

MUIR and BROWNING (1910).—On complement.
Jl. of Path. and Bacteriol., Vol. XIII, p. 232.

MUKAI, H. (1922).—Einfluss von Jodcalciuminjektion auf des Kammerwassers.
Jahr. d. Japan. Ophthal. Gesell., Kyoto, April 2 and 3.

MUSY, TH. (1914).—Chemistry of aqueous.
Zeitschr. f. Augenheilk., Bd. XXXI, S. 124.

NAKAMURA, B., und MUKAI, H. (1922).—Intravenous injections and the protein content of aqueous.
Nippon Gank. Zasshi, Bd. XXIV, SS. 53-67 and 113-127.

——— H. MUTSAR u. S. KOSAKI (1922).—*Ibid.*
Klin. Monatsbl. f. Augenheilk., Bd. LXIX, S. 642.

NEAME, H., and F. W. BURY (1922).—Arsenic and the aqueous.
Trans. Ophthal. Soc. U.K., Vol. XLII, pp. 163-167.

——— and J. WEBSTER (1923).—*Ibid.*
Trans. Ophthal. Soc. U.K., Vol. XLIII, pp. 381-386.

NICATI (1890-91).—La glande de l'humeur aqueuse, glande des procès cil. ou glande uvée.
Arch. d'Ophtal., T. X, pp. 481-508; T. XI, pp. 24-52, 152-174.

——— (1909).—*Physiologie oculaire*, Paris.

NICOLLE (1920).—Precipitin reactions.
Jl. of State Med., Vol. XXVIII, p. 293.

NIESNAMOFF (1896).—The quantitative proportion between secretion and absorption of the intra-ocular fluid.
Arch. f. Ophthal., Bd. XLII, H. 4, SS. 1-35.

NIEWERTH (1904).—*Die elektrische Leitfähigkeit des Humor aqueus.*
Inaug. Dissert., Rostock.

NOGUCHI (1909).—Noguchi test.
Jl. Exper. Med., T. XI, p. 84.

NORDENSEN (1921).—pH of aqueous.
Upsala Läk Fordl., Bd. XXVI, Nr. 25, S. 5.

NUEL, J. (1905).—The osmotic pressure of the aqueous in the normal and abnormal state.
XVIII Soc. belge d'ophtal., June 5, 1905.
Arch. d'Ophtal., T. XXV, pp. 732-740.

——— et BENOÎT (1899).—The paths of elimination of the intra-ocular fluids, in the anterior chamber and at the back of the eye.
Arch. d'Ophtal., T. XX, pp. 161-228.
Also NUEL (1899).—*9th Internat. Cong. Ophthal.*, Utrecht.

NUTTALL, G (1888).—The bacteriolytic influence of the body fluids.
Zeitschr. f. Hygiene., Bd. IV, S. 353.

OBERMAYER u. PICK (1906).—Chemical basis of immunological specificity.
Wien. klin. Wochenschr., Bd. XIX, S. 327.

OHKUNI, J. (1924).—Sugar in the aqueous.
Centr. med. Jl., Japan, Vol. XLIII, Nr. 9.

OKAZAKI, G. (1920).—Wassermann reaction in aqueous.
Japan. Med. World, No. 315, p. 17.

OSBORNE, W. A. (1919).—Physico-chemical properties of aqueous.
Jl. of Physiol., Vol. LII, pp. 347-350.

OSSOWIDZKI (1869).—*Über die bei der Zuckerharnruhr vorkommenden Augenkrankeiten.*
Dissert., Berlin.

OSTWALD, W. (1890).—Electrical properties of semipermeable membranes.
Zeitschr. physik. Chem., Bd. VI, SS. 71-82.

OTTOLENGHI (1886).—Diffusion of potassium iodide.
Ann. di Ottal., Vol. XV, pp. 522-528.

OVIO (1895).—The nutrition of the vitreous.
Atti. del 11th Cong. med. internaz., Vol. VI, p. 85.

——— (1900).—On the nutrition of the lens.
Ann. di Ottal., Vol. VIII, pp. 62-102.
Ann. d'Ocul., Vol. CXXIV, p. 97.

agami (1926). Ricerca dell' urea ~~dell~~ nell'
umore acqueo.
Biochim. e terap. sperim. Vol XIII p. 274.

PAGENSTECKER, H. (1878).—Drainage of intra-ocular fluids.
Sitzungsber. d. Ophthal.Gesell., S. 92.

PANAS et ROCHON-DUVIGNAUD (1898).—*Recherches anatomiques et cliniques sur le glaucome*, Paris.

PANDIT (1923).—Complement fixation and deviation reactions.
Jl. Hygiene., T. XXI, p. 406.

PANDY (1910).—Pandy's reaction.
Neurol. Centralbl., Bd. XXIX, S. 915.

PARISOTTI (1908).—Experimental researches on aqueous in sympathetic ophthalmia.
Soc. franç. d'Ophtal., T. XXV, pp. 191-205.

PARSONS, J. H. (1904-8).—*The Pathology of the Eye*, London.
Vol. III, pp. 940-995, 1040-1070.
See also *Proc. of the Roy. Soc. of Med.*, Vol. VI, p. 3, 1913.

PASTEGA (1914).—*Gli anticorpi degli umori oculari.*
Instituto sieroterspico, Milanese.

PATERSON, J. V. (1904).—Drainage at optic nerve head.
Jl. of Bacteriol. and Path., Vol. IX, p. 323.

PAUTZ (1894).—Chemistry of the vitreous and aqueous.
Zeitschr. f. Biol., Bd. XXX, SS. 212-243.

PERLES, MAX (1895).—Bacteriological properties of the aqueous.
Virchow's Arch., Bd. CXL, H. 2.

PETERS, J. P., A. G. EISENMANN, and H. A. BULGER.—The plasma proteins in relation to blood hydration.
Jl. Clin. Investig :Vol. I, p. 435.

PETIT *vide* NICATI (1890).

PFEILER, W., u. G. KAPFBERGER (1913).—Serology of aqueous.
Zeitschr. f. Bacteriol. u. Infectionkr., 1 orig., Bd. LXIX, H. 4.

PFLÜGER, E. (1906).—On the mechanism of the formation of aqueous and its quantitative changes.
Arch. f. Ophthal., Bd. LXIV, SS. 446-481.

PIGNATARI (1909) —Bactericidal properties of aqueous.
Ann. di Ottal., Vol. XXXVIII, fasc. 6/7.

PLOCHER (1917).—The thermal current in the anterior chamber.
Klin. Monatsbl. f. Augenheilk., Bd. LVIII, SS. 371-375.

——— (1919).—*Ibid.*, Bd. LXII, SS. 491-492.

POLEFF (1914).—Immune bodies in aqueous.
Klin. Monatsbl. f. Augenheilk., Bd. LII, SS. 819-824.

PORTES et BEAUREGARD (1880).—Studies in the vitreous.
Jl. de l'Anat. et de la Physiol., T. XVI, p. 240.

POSSEK (1906).—Bactericidal properties of the aqueous.
Klin. Monatsbl. f. Augenheilk., Bd. XLIV, S. 500.

RADOS, A. (1922).—Chemical composition of the aqueous in man and animals.
Arch. f. Ophthal., Bd. CIX, SS. 342-386.

RAEHLMANN (1906).—The chemistry of the abnormal aqueous.
Ophthal. Klinik., July.

REINSTEIN (1903).—Absorption of aqueous from anterior surface of iris.
Inaug. Dissert., Halle.

RISSLING, P. (1908).—The osmotic pressure of the aqueous and the serum.
Arch. f. Augenheilk., Bd. LIX, SS. 239-264.

ROBERTSON, T. B. (1915).—Refractometric method of estimating proteins in serum.
Jl. of Biol. Chem., Vol XXII, p. 233.

ROCHAT (1911).—The absorption from the anterior chamber.
Rev. d'Ophtal. néerlandaise.

ROCHON-DUVIGNAUD et R. ONFRAY (1904).—Experimental investigations of the variations of the concentration of the intra-ocular fluids.
Soc. d'Ophtal. de Paris.
Arch. d'Ophtal., T. XXIV, pp. 618-620.

ROHRSCHNEIDER, W. (1925).—Cholesterol injections into the anterior chamber.
Virchow's Arch. f. path. Anat. u. Physiol., Bd. CCLVI, H.1, SS. 150-157.

RÖMER, P. (1901).—Experimental researches into the immunology of the eye.
Arch. f. Ophthal, Bd. LII, H.1, S. 72.

——— (1902).—*Ibid.*
Arch. f. Ophthal., Bd. LIV, H.1, S. 99.
Bericht. ü. d. XXX Versam. d. Ophthal. Gesell., Heidelberg.

——— (1903).—*Ibid.*
XXXI Versam.

——— (1905).—*Ibid.*
Arch. f. Ophthal., Bd. LX, H. 2.

——— (1907) —The osmotic pressure of the intra-ocular fluids and its variation with that of the serum.
Arch. f. Augenheilk., Bd. LVI, Ergänzungs, SS. 150-162.

——— (1919).—*Lehrb. d. Ophthal.* Urban u. Schwarzenberg, Berlin.

——— (1920).—Experimental hypotony.
Bericht. d. Ophthal. Gesell., Heidelberg, Bd. XLII, S. 66.
Klin. Monatsbl. f. Augenheilk., Bd. LXV, S. 378.

RONA, P., u. P. GYÖRGY (1913).—The distribution of ions in blood serum (sodium).
Bioch. Zeitschr., Bd. LVI, SS. 416-438.

——— and D. TAKAHASHI (1913).—The distribution of calcium in blood.
Bioch. Zeitschr., Bd. XLIX, S. 370.

ROSSI (1925).—Adrenaline in the aqueous.
Soc. franç. d'Ophtal., June.
Ann. d'Ocul., T. CLX, p. 594.

RÖTTH, A. v. (1922).—Lacrymal drainage.
Klin. Monatsbl. f. Augenheilk., Bd. LXVIII, SS. 598-604.

RUPPEL (1923).—Association of antibodies with globulins.
Deutsch. med. Wochenschr., Bd. XLIX, S. 40.

RUSZYNÁK, S. (1921).—Micro-method of estimating sodium chloride.
Bioch. Zeitschr., Bd. CXIV, SS. 23-26.

RUTTEMAN (1914).—The ciliary glands.
Dissert., Amsterdam.
Klin. Monatsbl. f. Augenheilk., Bd. LIII, S. 584.

RYMOWICZ (1902).—Bactericidal properties of aqueous.
Postep. okulist., Nr. 10, S. 6.
Westnik. Ophthal., Bd. XX, 1903.

SALUS (1910).—Antibodies in aqueous.
Arch. f. Ophthal., Bd. LXXV, H. 1.

——— (1911).—*Ibid.*
Klin. Monatsbl. f. Augenheilk., Bd. XLIX, SS. 322-337.

SAMOJLOFF, A. J. (1923).—Comparative manometry of eyes.
Russian Ophthal. Jl.
Abs. *Klin. Monatsbl. f. Augenheilk.*, Bd. LXX, S. 779.

——— (1925).—Greeff's vesicles after subconjunctival salt injections in rabbits.
Klin. Monatsbl. f. Augenheilk., Bd. LXXV, SS. 382-384.

SATTLER, C. H. (1912).—Abnormal aqueous after application of heat.
Versam. d. deutsch. Ophthal. Gesell., Heidelberg.

SCALINCI, NOE (1907, a).—The physico-chemical properties of the aqueous.
Arch. f. Augenheilk., Bd. LVII, SS. 214-255.

——— (1907, b).—The technique of viscosity measurements.
Arch. di Ottal., Vol. XV, p. 447.

Scalinci, Noë (1908).—The viscosity of the aqueous in glaucoma.
Arch. d'Ophtal., T. XXVIII, pp. 553-566.

——— (1922).—The function of the ciliary body.
Riforma Med., Vol. XXXVIII, p. 345.

——— (1924, a).—The reaction of the intra-ocular fluid.
Arch. di Scienze Biol., Vol. VI, Nos. 3 and 4, pp. 314-349.

——— (1924, b).—Study of changes in the vitreous.
Ann. di Ottal. e Clin. Oculist., Vol. LII, H. 11 and 12, pp. 964-974.

Schall (1925).—The reaction of the aqueous.
Arch. f. Ophthal., Bd. CXV, S. 666.

Schick, H. (1885).—Experiments upon the fluid traffic in the eye.
Arch. f. Ophthal., Bd. XXXI, H. 2, SS. 35-96.

Schiötz (1913).—Refractive index of aqueous.
Arch. f. Augenheilk., Bd. LXXV, S. 321.

Schirmer (1910).—The aqueous in inflammation.
Arch. f. Ophthal., Bd. LXXIV, S. 224.

Schläfke (1879).—Potassium iodide and calomel in ocular therapeutics.
Arch. f. Ophthal., Bd. XXV, H. 2, SS. 251-279.

Schlegel (1886).—The intra-ocular tension after pilocarpine.
Arch f. Exper. Path. u. Pharm., Bd. XX, S. 271.

Schmidt, H. (1873).—The sugar in diabetes.
Klin. Monatsbl. f. Augenheilk., Bd. XI, S. 492.

Schmidt (1912) —The filtration of complement.
Arch. f. Hygiene, Bd. LXXVI, S. 284.
Ibid., 1914. *Jl. of Hygiene*, Vol. XIV. p. 437.

——— and Bennet (1919).—The chemical basis for immunological specificity.
Jl. of Infectious Diseases, Vol. XXV, p. 207.
See also K. Landstein and H. Lampt. *Bioch. Zeitschr.*, Bd. LXXXVI, SS. 343-394.

Schnandigel (1913).—Vital staining of the eye with trypan blue.
Arch. f. Ophthal., Bd. LXXXVI, S. 93.

Schneider, R. (1924).—Drainage paths: optic nerve head.
Klin. Monatsbl. f. Augenheilk., Bd. LXXIII, SS. 210-211.

Schneyder (1855).—*Chemische Untersuchungen verschiedener Augen von Menschen u. Tieren.*
Inaug. Dissert., Freiburg.

Schöler (1869).—Differential pressures in eye.
Dissert., Dorpat.

Schöler u. Uhthoff (1882).—Fluorescine in relation to the eye.
Jahresber. über. d. Wirksamkeit d. Augenklinik., SS. 80-89.

Schönberg, M. J. (1914).—Serology of aqueous humour.
Ophthalmology, Vol. XI, p. 1.

Schulemann, W. (1917).—Vital staining with acid dyes.
Bioch. Zeitschr., Bd. LXXX, S. 1.

Schülten, v. (1888).—Intra-ocular pressure.
Arch. f. Ophthal., Bd. XXX, H 3, S. 1.

Schwalbe (1870).—The circulation of the eye.
Arch. f. mik. Anat., Bd. VI, SS. 1-61, 261-362.

——— (1887).—*Lehrbuch der Anatomie des Sinnesorgane.*
SS. 139 u. 332.

Seefelder (1906).—Greeff's vesicles.
Arch. f. Ophthal., Bd. LXIII, S. 480

——— (1920).—*Ibid.*
Klin. Monatsbl. f. Augenheilk., Bd. LX, S. 378.

SEIDEL, E. (1916).—Share of iris in secretion of aqueous.
Congress, Heidelberg.

——— (1918, a).—Physiology of intra-ocular fluids.
Klin. Monatsbl. f. Augenheilk., Bd. LXI, S. 330.
Arch. f. Ophthal., Bd. XCV, SS. 1-72.

——— (1919, b).—Physiological flow through pupil.
Arch. f. Ophthal., Bd. XCV, SS. 210-214

——— (1920, a).—*Ibid.*
Arch. f. Ophthal., Bd. CI, SS. 383-406.

——— (1920, b).—Structure of ciliary epithelium.
Arch. f. Ophthal., Bd. CII, SS. 189-202.

——— (1920, c).—Physiological absorption of aqueous.
Arch. f. Ophthal., Bd. CII, SS. 366-382.

——— (1920, d).—Secretion of aqueous.
Arch. f. Ophthal., Bd. CII, SS. 383-414.

——— (1920, e).—Pressure in glaucomatous eyes.
Arch. f. Ophthal., Bd. CII, SS. 415-420.

——— (1921, a).—Filtration on trephining.
Arch. f. Ophthal., Bd. CIV, SS. 158-161.

——— (1921, b).—Composition of aqueous in man and animals.
Arch. f. Ophthal., Bd. CIV, 162-170.

——— (1921, c).—Physico-chemical changes in secretion.
Arch. f. Ophthal., Bd. CIV, SS. 284-292.

——— (1921, d).—The outflow of the aqueous.
Arch. f. Ophthal., Bd. CIV, SS. 357-402, 403-410; Bd. CVII, SS. 101-104.
Klin. Monatsbl. f. Augenheilk., Bd. LXVIII, SS. 291-295; Bd. LXIX, SS. 773-786, 1922.

——— (1921, e).—The mechanism of glaucoma.
Arch. f Ophthal., Bd. CVI, SS. 176-186.

——— (1922, a).—The mechanism of protein absorptions from the anterior chamber.
Arch. f. Ophthal., Bd. CVII, SS. 105-108.

——— (1922, b).—The pressure gradient in the eye.
Arch. f. Ophthal., Bd. CVII, SS. 101-104; 496-506; 507-512; Bd. CVIII, SS. 285-294; 420-424.

——— (1923).—*Ibid.* Bd. CXI, SS. 167-195; Bd. CXII, SS. 252-260; Bd. CXIII, SS. 222-236.

——— (1924).—*Ibid.* Bd. CXIV, 159-162; 163-168; 388-392.
Klin. Monatsbl. f. Augenheilk., Bd. LXXII, S. 760.

——— (1925).—Origin and fate of intra-ocular fluids.
Deutsch. med. Wochenschr., Bd. LI, S. 851.

SERR, HERMANN (1924).—The properties of the blood in glaucoma.
Arch. f. Ophthal., Bd. XCIV, H. 2, SS. 393-440.

SHAPPEY *vide* NICATI (1890).

SMITH, PRIESTLEY (1879).—Glaucoma: London.

——— (1888).—On the escape of fluid from the aqueous and vitreous chambers under different pressures.
Ophthal Rev. pp. 193-208.

SÖRENSEN, S. P. L. (1909).—Hydrogen ion concentration.
Bioch. Zeitschr., Bd. XXI, S. 131.

Seidel (1927) Zur Methodik der klinischen Glaukomforschung
Arch f Ophthal. CXIX S. 15.

Seidel (1928) Neuere Anschauungen über den intraokularen Flüssigkeitswechsel und die Entstehung des Augendruckes.
Ic. m.-f. A. LXXX. p. 721.

Tron. E. (1926) Chem. untersuchungen über die Natur der intraokularen Flüssigkeiten

I. Arch f. Ophth. Bd. CXVII S. 677

(1927) II ibid CXVIII S. 713.

(1928) III " CXIX 659.

STADERINI (1891).—The lymphatic circulation of the vitreous.
Ann. di Ottal., Vol. XIX, pp. 523-524.

STEINBORFF (1908).—Specific gravity of aqueous.
Oppenheimers *Handb. Bioch.*, 2 Aufl., Bd. II, S. 4, ~~1921~~. 1910.

STIMMEL u. ROTTER (1912).—Greeff's vesicles.
Zeitschr. f. Augenheilk., Bd. XXVIII, S. 114.

STÖBER (1862) —Sugar aqueous : diabetes.
Ann. d'Ocul., T. XLVIII, p. 192.
Gaz. méd. de Strasbourg, S. 109-110.

STOCK (1905).—Secretion of aqueous after puncture.
Klin. Monatsbl. f. Augenheilk., Bd. XLIII, H. 1, S. 86.

——— (1909).—Seclusion of pupil.
Klin. Monatsbl. f. Augenheilk., Bd. XLVII, H. 2, SS. 602-604.

STOCKER (1887).—Influence of miotics and mydriatics.
Arch. f. Ophthal., Bd. XXXIII, H. 1, SS. 104-158

SUGITA, Y. (1922).—Cholesterol in aqueous.
Japan. Ophthal. Soc., April 2.
Centralbl. f. d. g. Ophthal. u. i. Grenz., Bd. VII, S. 500.

SWEET (1903).—Complement in aqueous.
Centralbl. f. Bakteriol., Bd. XXXIII.

TERRIEN, F., and A. DANTRELLE (1913).—Coagulability of aqueous.
Arch. d'Ophtal., T. XXXIII, p. 607.

——— (1914).—*Ibid.*
Soc. franç. d'Ophtal., T. XXX, p. 503.

THIEL, R. (1922).—The entrance of fluorescine into the eye.
Klin. Monatsbl. f. Augenheilk., Bd. LXVIII, S. 244.

——— (1923).—*Ibid.*
Klin. Monatsbl. f. Augenheilk., Bd. LXX, S. 76.

——— (1924).—*Ibid.*
Zusam. d. deutsch. Ophthal Gesell., Heidelberg, Bd. XLIV.
Arch. f. Ophthal., Bd. CXIII, SS. 347-358.

THOMSON, A. (1910).—The scleral spur.
Ophthalmoscope, Vol. VIII, pp. 608-614.

TORNABENE (1904).—Aqueous proteins on mechanical irritation of the cornea.
Arch. di Oftal., Vol. XI, p. 277.

TRETTENERO, A. (1924).—Thermal currents in anterior chamber.
Ann. di Ottal. e Clin. Oculist., Vol. LII, pp. 466-480.

TRISTAINO, B. (1923).—Refractive index of aqueous after milk injections, etc.
Boll. d'Ocul., Vol. II, pp. 173-193.

TRONCOSO, M. URIBE Y. (1901).—Pathogenesis of glaucoma.
Ann. d'Ocul., T. CXXVI, pp. 401-454.

——— (1905).—Experiments on the filtration from the anterior chamber.
Ann. d'Ocul., T. CXXXIII, pp. 5-31 ; T. CXXXIV, pp. 250-263.

——— (1907).—*Ibid.* T. CXXXVII, pp. 132-140.

——— (1909).—Nature of canal of Schlemm.
Ann. d'Ocul., T. CXLII, pp. 237-265.

——— (1910.)—Composition of aqueous in glaucoma.
Arch. d'Ophtal., T. XXX, pp. 91-102 ; 151-170.

——— (1915).—Lymph circulation.
Arch. de Oftal., Bd. XV, S. 49.

——— (1921).—Nature of Schlemm's canal.
Amer. Jl. of Ophthal., Vol. IV, pp. 321-326 ; also *ibid.*, Vol. VIII, 433-439, 1925.

TRÜMPY, see FREUNDLICH (1922).—*Capillarchemie:* Leipzig, S. 233.

TSCHIRKOWSKI (1911).—Antibodies after operation.
Westnik. Ophthal.,

TÜCKERMANN (1892).—The absorption of aqueous seen by dyes.
Arch. f. Ophthal., Bd. XXXVIII, H. 3, SS. 60-92.

TÜRK, S (1906).—Thermal currents in anterior chamber.
Arch. f. Ophthal., Bd. LXIV, SS. 481-501.
——— (1911).—*Ibid.*
Klin. Monatsbl. f. Augenheilk., S. 300.

ULBRICH (1907) —Seclusion of pupil.
Ber. d. deutsch. Ophthal. Gesell., Heidelberg, S. 105.
——— (1908).—*Ibid.*
Arch. f. Augenheilk., Bd. LX, S. 283.

ULRICH (1880).—Circulation of aqueous.
Arch. f. Ophthal., Bd. XXVI, H. 2, SS. 29-49; H. 3, SS. 35-82.

——— (1883).—Fluorescine injections.
Arch. f. Augenheilk., Bd. XII, SS. 153-163.

VALENTIN (1879).—Refractive index of aqueous.
Pflüger's Arch. f. d. ges. Physiol., Bd. XX, S. 283.

VALENTIN, F. (1919).—On the fats in the vitreous.
Zeitschr. f. Physiol. Chem., Bd. CV, SS. 33-57.

VERDERAME (1913).—Subconjunctival injections.
Ann. di Ottal., Vol. XLIII, p. 73.

VERNEY (1926).—Osmotic pressure of serum proteins.
Jl. of Physiol., Vol. LXI, p. 319.

VERZÁR, F., u. F. KELLER (1923).—The reaction of capillary blood.
Bioch. Zeitschr., Bd. CLXI, SS. 21-27.

VETCH, J. (1820).—*A practical treatise on the diseases of the eye*, London.

VILLASENOR, F. (1901).—See TRONCOSO, 1901.

VINCI (1901).—Diffusion of substances into the eye.
Ann. di Ottal., Vol. XXX, p. 523.

VIRCHOW, R. (1852).—Note on the vitreous.
Virchow's Arch., Bd. IV, S. 468.
Verhandl. d. Phys.-med. Gesell., Würzburg, Bd. II, SS. 160 u. 317.

VLADESCU, R., et A. BABES (1914).—The physico-chemistry of the aqueous.
Compt. rend. Soc. de Biol., T. LXXVI, pp. 320-321.

VOLLARO, R. DE L. (1907).—The pathological aqueous.
Arch. di Ottal., January, February, March.

WADA (1921).—Chemical constituents of lacrymal fluid.
Nippon Gank. Zasshi, May, June, August.

WASHBURN, E. W. (1911).—Theory of solutions.
Amer. Jl. of Chem., Vol. XXXIII, p. 1436.

WEBER, A. (1881).—Pathological changes with glaucoma.
Trans. of 7th Internat. Congress, London, Vol. III, pp. 75-83.

WEED, L. H. (1914).—*Re* Drainage of aqueous.
Jl. of Med. Research, Vol. XXXI, pp. 51-91.
See *Phys. Review*, Vol. II, p. 171, 1923.

WEEKERS, L. (1921).—The intra-ocular fluids, and their elimination.
Arch. Intern. de Physiol., T. XVIII, p. 200.

——— (1922).—*Bull. de la Soc. belge d'Ophtal.*, T. XLV, pp. 58-64.
Arch. d'Ophtal., T. XXXIX, pp. 513-522.

——— (1923) —*Arch. d'Ophtal.*, T. LX, pp. 269-282.

——— (1924).—*Arch. d'Ophtal.*, T. LXI, pp. 400-419; 652-656.

Yudkin. a.m. The aqueous humour.
J. Amer. med. ass. 87. p. 1910, 1926.

Yudkin. a.m., Kramer. A.C., Goldstein, H.H., & Berman M.B.
A chemical study of the normal aqueous humour
Proc. Soc. f. Exp. Biol. & med. xxiv. 451. 1927.

WEGEFARTH, P. (1914).—Drainage of the intra-ocular fluids.
Jl. of Med. Research, Vol. XXXI, pp. 147-149; 149-166.

WEISS, O. (1877).—The circulation of fluid in the eye.
Verhandl. d. Naturlist. med. Versam., Heidelberg, Bd. II, S. 1.

——— (1879).—*Arch. f. Ophthal.*, Bd. XXV, H. 2, SS. 243-250.

——— (1904).—In *Nagel's Handb. d. Physiol.*, Bd. III, SS. 438-468.

——— (1906).—*Arch. f. d. ges. Physiol.*, Bd. CXV, SS. 602-611.

——— (1911).—*Zeitschr. f. Augenheilk.*, Bd. XXV, SS. 1-14.

——— (1920).—*Zeitschr. f. Augenheilk.*, Bd. XLIII, SS. 141-143.

——— (1923).—*Arch. f. d. ges. Physiol.*, Bd. CXCIX, SS. 462-470.
Deutsch. med. Wochenschr., Nr. 4, S. 134.
Med. Klin., S. 97.
Klin. Monatsbl. f. Augenheilk., Bd. LXX, S. 257.

——— (1924).—*Arch. f. d. ges. Physiol.*, Bd. CCII, SS. 642-644.

——— (1925).—*Deutsch. med. Wochenschr.*, Nrs. 1-2, SS. 21-23; 63-65.

WELLS, H. G. (1908).—Specificity of proteins.
Jl. of Infectious Diseases, Vol. V, p. 449.

——— (1913).—Immunity.
Zeitschr. f. Immunität., Bd. XIII, S. 519

——— (1916) —*Ibid.*
Jl. of Biol. Chem., Vol. XXVIII, p. 11.

——— (1925).—*The Chemical Aspects of Immunity*, New York.

WESSELY, K. (1900).—Action of adrenaline on eye.
Sitzungs. d. Ophthal. Gesell., Heidelberg, Bd. XXVIII, SS. 69-80.

——— (1902).—Subconjunctival injections.
Verhandl. d. Naturforschen. u. ärzte., S. 74.
Vers. z. Karlsbad, Bd. II, S. 387.
Klin. Monatsbl. f. Augenheilk., Bd. XL, H. 2, S. 267.

——— (1903).—The eye and immunity.
Berl. klin. Wochenschr., S. 27.
Deutsch. med. Wochenschr., Nrs. 7 u. 8.
Berl. Klin., Nr. 182.

——— (1905).—The exchanges of the intra-ocular fluids.
Ascher-Spiro Ergebnisse d. Physiol., Bd. IV, SS. 637-641.

——— (1908, a).—*Ibid.*
Arch. f. Augenheilk., Bd. LX, SS. 1-48; 97-160.

——— (1908, b).—*LXXX Versam. deutsch. Naturforschen u. ärzte.*, Köhn, SS. 411-414.

——— (1908).—*Experimentelle untersuchungen ü. d. Augendruck, u. s. w.*, Bergmann: Wiesbaden.

——— (1911).—*Zeitschr. f. Augenheilk.*, Bd. XXV, S. 315; Bd. LXXVIII, SS. 247-278.

——— (1916).—*Zeitschr. f. Augenheilk.*, Bd. LXXXI, SS. 102-119.

——— (1920).—*Klin. Monatsbl. f. Augenheilk.*, Bd. LXV, S. 376.

——— (1921).—The composition of the intra-ocular fluids.
Arch. f. Augenheilk., Bd LXXXVIII, SS. 217-253.

——— (1924).—(With C. FASSIN).—*Arch. f. Augenheilk.*, Bd. XCIII, SS. 184-203.

WINSELMANN (1909).—Seclusion of pupil.
Klin. Monatsbl. f. Augenheilk., Bd. XLVII, H. 2, SS. 203-208.

WITTGENSTEIN, A., u. A. GAEDERTZ (1926).—Lactic acid in aqueous.
Bioch. Zeitschr., Bd. CLXXVI, SS. 1-17.

ZADE (1909).—Serology of aqueous.
Arch. f. Ophthal., Bd. LXXII, S. 507.

——— (1910).—*Arch. f. Ophthal.*, Bd. LXXV. S. 43.

ZINN (1780).—Secretion of aqueous.
Descr. anat. oc. hum. Wrisberg, S. 130.

ZINSSER (1923).—The nature of antibodies.
Infection and Resistance, p. 319.
See also: NICOLLE. *Compt. rend. de la Soc. de Biol.*, T. CLXIX, p. 1433, 1919.
NICOLLE et CESARI. *Ann. Institut. Pasteur*, T. XXXVI, p. 463, 1922.
RAMON. *Ann. Institut. Pasteur*, T. XXXVIII, p. 1, 1924.
WEIL. *Jl. of Immunol.*, Vol. I, p. 19, 1916.

ZUR NEDDEN (1908).—Serology of aqueous.
Zeitschr. f. Augenheilk., Bd. XX, S. 380.

——— (1920).—Proteins of aqueous.
Klin. Monatsbl. f. Augenheilk., Bd. XLIV, S. 605.