attempted, and have only very imperfectly managed, to present you with the broad aspects of the subject. Diseases of the coronary arteries present a varied picture, and certain of the more dramatic aspects are apt to blind one to the fundamental condition. These remarks, however, will have been justified if they lead to a very general discussion this forenoon.

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THE ETIOLOGY OF GLAUCOMA.*

BY

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FROM the days when ophthalmology was first a science the etiology of glaucoma has given rise to investigations and discussions innumerable; to-day, although our knowledge has advanced, we are still quarrelling over the matter. I do not imagine for a moment that we have solved the problem, or that we have ended our quarrels; it is more likely that we are starting them afresh. But I would suggest that the trend of modern thought is throwing some new light upon the subject, and is introducing us to a completely new aspect of it. For too long the attention of investigators has been focused upon the gross pathological changes which have been observed in eyes excised for established glaucoma. The findings in these have almost invariably been interpreted as the essential causal factors in the disease, while it is more than possible that they may have been merely subsidiary causes, or even results. The essential cause is almost certainly something deeper and more subtle, and to discover its nature we shall have to go more deeply into the problem. Before we are in a position to understand pathological changes in the tension of the eye we must investigate first of all the more fundamental question of the maintenance of the intraocular pressure at its normal level and the variations to which it may be subjected under physiological conditions.

At the outset of any problem which concerns itself with the intraocular pressure the first matter to be settled is the nature of the processes controlling the formation of the aqueous humour; for these essentially must play the most predominant role in the determination of any pressure conditions, and, until agreement can be reached upon this, we can never arrive at a satisfactory or generally acceptable theory of the etiology of glaucoma. This is, indeed, the most fundamental question in the physiology of the eye, and, strangely, it is a question on which there is, as yet, a great diversity of opinion. To it I propose to suggest a very definite answer: the aqueous is not a secretion, nor is it, in normal circumstances, a transudate. It is, on the other hand, a dialysate of the capillary blood, formed by the same processes as the other tissue fluids, the only difference being that the process is modified by the relative impermeability of the ocular capillaries in order to allow the physiological requirements of the eye to be met. If the eye is to be an efficient organ of vision it is essential that its fluid contents be kept clear and practically free from colloidal micelles to allow the light to pass through undisturbed, and this is accomplished by making the capillary walls relatively impermeable. If the dioptric apparatus of the eye is to be kept properly adjusted it is essential that

the various elements in the refractive system be kept each accurately in its own proper position, a condition which is brought about by making the eyeball tense and filled with fluid under pressure; this again is accomplished, as we shall see later, by the same process of making the capillary walls relatively impermeable. The permeability of the capillary walls varies within wide limits throughout the body from organ to organ, and, in each organ, from time to time, adapting itself to suit the requirements of each peculiar case; thus, for example, in order that the functions of the liver may be carried out efficiently, the capillaries here are extremely permeable. By a modification of the same universal physiological process in the opposite direction, the eye has become biologically adapted as an organ of vision; no more simple means could have been chosen, and I know of no more beautiful example of the purposive and teleological activities of the living organism.

The argument which has led me to adopt this view would take too long to go into in detail. It is essentially a physico-chemical one, and in essence it is as follows: A dialysate in equilibrium with its parent fluid must have a very precise and definite chemical composition, it must have a very definite osmotic pressure, a definite reaction, a definite electrical potential, and there must be a definite relationship between the hydrostatic pressure at which it is maintained and that of the parent fluid.

During the past few years we have analysed the aqueous humour chemically, comparing it with the arterial and venous blood. We have measured its osmotic pressure, its electrical potential, its reaction, and determined the pressures in the chambers of the eye and in the arteries and veins. We have done it in normal conditions and in experimental variations from the normal, taking minute precautions against sources of error, and we have satisfied ourselves that the aqueous in all conditions is in complete thermo-dynamical equilibrium with the plasma—chemically, osmotically, electrically, and hydrostatically.

It must be remembered that these relationships are very complicated and very precise, and if the aqueous shows all these very complex properties, it seems illogical to deny that it is a dialysate in the absence of any definite reason to the contrary. There is no evidence, experimental or otherwise, which I know, or which I can find in the literature, and which will bear legitimate criticism, which can detract from this conclusion; to my way of thinking, at any rate, we are forced to accept it. Indeed, I think that the physico-chemical evidence which we have put forward is the most unequivocal obtainable. In the last resort the formation of the aqueous humour is a physico-chemical process. In a case such as this, anatomical evidence must be subservient to physiological findings. In much of the physiological work which has been done upon the eye confusion has arisen from a failure to appreciate the ease with which the normal equilibrium is disturbed, and many of the results lay themselves open to the criticism of reasoning from the abnormal to the normal. From this criticism a physico-chemical method of inquiry is almost entirely free. We can separate the aqueous from the influences of the complex changes which beset it *in vivo*, and in the isolation of the test tube we can determine with a very great degree of precision what the normal really is. Similarly, after introducing abnormal conditions, we can repeat the same process, and by comparison construct a coherent picture of the train of events as they have actually occurred.

The second fundamental question to be answered is that of the circulation of the aqueous humour. It is to be remembered that although I have used the word "equilibrium," the meaning is a dynamic and not a static equilibrium. All vital equilibria are of this nature. Three factors enter into the circulation of the fluid in the eye. There is in the first place a continuous metabolic interchange between the blood and the aqueous humour through the capillary walls, on either side of which the balancing hydrostatic and osmotic pressures are continually fluctuating, conditioning a flow of fluid now in one direction, now in another, so that the whole is continually renewed. Secondly, there is an internal thermal circulation caused by convection currents in the anterior chamber. More important, there is a through-and-through pressure circulation. We measured the pressure in the intrascleral

* The opening paper of a discussion in the Section of Ophthalmology at the Annual Meeting of the British Medical Association, Cardiff, 1928.

veins, and we found that, while in normal circumstances the venous pressure here was higher than the intraocular, when the intraocular pressure was raised it rose more rapidly than the venous pressure and readily exceeded it. The canal of Schlemm is in direct continuity with these venous exits, and it seems to follow that when the chamber pressure rises suddenly it exceeds the pressure here, and this excess will condition an outflow of aqueous. Such rises of pressure will be continually provided by the movements of the ocular muscles, for these have a larger effect on the tension of the eye than may be imagined. By stimulating the orbicularis to contract it has been found with a manometer inserted into the eye that pressures of the order of 40 to 60 mm. of mercury are easily attained. This action is doubtless assisted by the suction of the scleral spur described by Professor Thomson, and the result of the two factors will be an almost continuous, though very minute, circulation of fluid. This appears to act as a safety valve mechanism to maintain the intraocular pressure at its normal level, for in a globe like the eye, whose walls are feebly distensible, the expulsion of a very small quantity of fluid entails a large fall of internal pressure.

Based on our experimental studies we have thus arrived at the conclusion that the aqueous humour is in a state of continuous dynamic equilibrium with the capillary blood through the capillary walls, and that it is propelled through the eye with a small but efficient circulation. Using this as a basis for our inquiry into the cause of pathological rises of pressure, we may summarize the position from which we start under these three heads:

I. The intraocular pressure is maintained at its normal equilibrium by the height of the blood pressure in the capillaries, less the difference in osmotic pressure between the aqueous humour and the plasma.

II. Being maintained at this level the intraocular pressure may be varied:

1. By altering the equilibrium level: (a) by raising the blood pressure in the capillaries, either by varying the arterial blood pressure, the venous pressure, or the local capillary pressure; (b) by varying the difference between the osmotic pressure of the plasma and the aqueous. Since the capillaries are freely permeable to crystalloids, the only common clinical condition wherein this can occur is when the colloid (protein) content of the aqueous is raised.

2. Since the sclerotic is practically non-distensible, the pressure may also be raised by increasing the volume of the contents of the eye. The only common condition wherein this occurs is when the volume of the vitreous and lens are increased by physico-chemical influences involving changes in turgidity pressure.

III. In normal circumstances these changes in pressure are to a large extent compensated by the expulsion of some of the aqueous through what we have called the safety valve mechanism of the canal of Schlemm, the lens and vitreous partially filling up the anterior chamber. The aqueous thus acts, within limits, as an elastic cushion, tending to maintain the intraocular pressure at its normal level. If, however, the swelling is great, the anterior chamber may be abolished, in which case an acute rise of tension will ensue; and again, if the exit channels are rendered inefficient so that they cannot deal with an increased, or even with a normal, pressure circulation, whether it be by the formation of synechia, or by sclerosis, or by any other means, a rise in pressure will be evident at a much earlier stage. Not only will aqueous be pushed out under these conditions, but the uveal blood channels will be compressed as well, in which case the feeding arteries will pile up pressure to maintain the circulation at a higher level, until eventually their limit of effective pressure may be reached and finally overcome; in the first case the tension will be permanently raised, in the second the eye will be strangulated.

Starting, then, with these basic factors as a foundation, we can proceed to apply them to the clinical condition of glaucoma.

With regard to the first of these influences—the blood pressure in the capillaries—it is evident that the influence of both the arterial and the venous pressures will be felt only

in so far as their effects are manifested in this part of the circulation. There is a large amount of statistical evidence now available, which indicates definitely that a high blood pressure in itself is not an essential, nor even an important factor in the etiology of glaucoma. The reason for this is obvious when we remember that the arterio-sclerosis which usually accompanies a persistently elevated blood pressure damps down the capillary flow to such an extent that the circulation here is frequently less than normal. There is one important thing to be remembered in this connexion: in the normal individual the blood pressure is kept at a remarkably constant height, but in the high pressure subject the regulating mechanism has ceased to be adequate, and the pressure, in addition to being kept at an abnormally high level, is subject to sudden and extensive variations excited by influences so slight as would have little or no recognizable effect in the normal person. To this extent, therefore, a hyperpietic diathesis will predispose to an acute crisis in the eye. The venous pressure also is effective only in as far as its influence is felt in the capillaries. Since its variations, in comparison with the arterial side of the circulation, are less adequately damped down by a vasomotor mechanism, any local interference with the venous return from the eye readily produces a rise in capillary pressure which may precipitate a glaucomatous attack. The frequency with which phlebitis and peri-phlebitis of the vortex veins are seen in the pathological examination of glaucomatous eyes is significant in this connexion.

There remains for consideration the essential question of the capillary pressure itself. This is controlled by many factors as yet little understood—physical, chemical, nervous, hormonal, and psychical. The tendency for the occurrence of acute glaucoma in persons of an emotional temperament or during a nervous crisis is well known, and the etiological importance of the endocrine group of glands and their association with the sympathetic nervous system is also significant. Whatever the action of these ductless glands and the sympathetic nerve—and at present it can only be expressed as a vague and indefinite association—there is no evidence that any other action than vasomotor is called into play. The essential feature seems to be a state of capillary instability and a tendency to dilatation. There may be other factors than these: possibly the accumulation of some toxic material, of the nature and action of histamine, may have some influence. It is possible that such an injurious substance might be biochemical in nature, the result of faulty metabolism, such as might upset the delicately balanced mechanism of the endocrine glands or induce a condition of sympathicotonus. Whatever it is, it is unknown, and mere speculation is useless; all that we do know and can be sure about is the essential condition of capillary instability and dilatation.

We now come to the second factor—the difference between the osmotic pressure of the aqueous humour and the blood. The osmotic pressure may be considered to be made up of two components—that of the crystalloids and that of the colloids. Since the capillary walls are freely permeable to the former, only the latter can have a permanent influence on the tension of the eye. It may be of some significance, however, that there seems to be a tendency to hypotonicity in the blood of glaucomatous patients, for on the average in these subjects the total osmotic pressure is less and the sodium diminished in comparison with normal people. I do not think, however, that the changes which have been found are great enough or constant enough to entitle us to attach much etiological importance to them: such as they are, however, they tend to indicate a change in the general metabolism. Colloids, on the other hand, are normally unable to pass the capillaries of the eye, and therefore any tendency towards an equalization of the colloid osmotic pressure of the aqueous humour and of the blood will raise the pressure level in the eye. This may be done either by lowering the concentration of colloids in the blood or by raising the colloid content of the aqueous. The first of these is again unimportant clinically, and the blood of glaucomatous patients shows no decrease in its protein content. An increase in the protein content of the aqueous humour,

however, is a common occurrence in inflammatory states and cases of intraocular haemorrhage and thrombosis wherein pathological rises of tension are by no means unknown. It is to be remembered that in these cases the influence of the increase in colloids in raising the pressure level is increased by the obstruction to the free exit of fluid which the albuminous nature of the aqueous will bring about. Finally it is to be noted that the original cause of the entrance of colloid particles into the chambers of the eye is a dilatation of the capillaries involving an increase in the permeability of their walls; and thus we return again to our first consideration, the essentially important capillary circulation.

The remaining point to consider is the matter of changes in the volume of the contents of the globe, and among these the greatest interest centres round the changes which occur in the vitreous. The general appearance of a typical glaucomatous eye, with the anterior chamber shallow and the iris and lens pushed forward, strongly suggests that one of the commonest and most important changes which occur in this disease is an increase in the volume of the vitreous. The vitreous is a gel bathed in aqueous; its chemical constitution and its structure as seen under the ultra-microscope show that it is so. The main determinant of the volume of such a system is the amount of water which it retains in association with it—that is, the degree of hydration of its colloid particles. This question of the swelling of gels is an extremely interesting one, and, unfortunately, one about which little is known at present even in the domain of pure physical chemistry. We are working on it at the moment, but the experiments are long and take weeks of observation, and it is too early yet to dogmatize on the results. This much we know, however, that the pressures generated on occasion may be enormous; it is the same turgidity pressure which the Egyptians used to such good purpose in their gigantic building operations. They inserted dry wedges of wood into the crevices of rocks, and when they poured water upon them the swelling of the wood split the rock asunder. We are as yet unaware of all the factors controlling the swelling. One influence is a change in the reaction of the vitreous: within the limits compatible with life an increase of the pH causes an increase of turgidity pressure, while a decrease of pH has the opposite effect. The concentration of salts is another determining factor, and there are others about which we know less. Whatever the mechanism may be in clinical conditions, it is evident that pressures may be generated in the vitreous of sufficient magnitude to push forward the lens and the iris, to expel most of the aqueous, and to compress the uveal blood vessels to a degree which will strangulate the eye.

These, then, appear to be the main mechanisms whereby the intraocular pressure may be raised. When the pressure is raised the "pressure circulation" makes its influence more markedly felt, and by the expulsion of some of the aqueous the normal pressure equilibrium is still maintained. With the anterior chamber rendered shallow, however, the margin of safety is lowered and a comparatively small increase of pressure, one with which the normal eye could deal quite safely, becomes a source of real danger. When, in addition, the exit channels lose their efficiency, the danger becomes greater; small rises of pressure become cumulative and large rises lead to complete and sudden strangulation of the globe. Probably many influences may act, either together or severally, in obstructing these channels; the formation of peripheral synechiae, sclerosis of the pectinate ligament, the deposition of iris pigment in the meshwork of the filtration angle, a defective inward pull of the ciliary muscle, or the pressure and obstruction of a gradually growing lens—each or all of these may be present and obstruct the exit of fluid, but it seems obvious that in the majority of cases their influence is adjuvant rather than primary, consequential rather than causal.

It will be realized from what has been said already that the etiology of glaucoma is not to be sought in one direction alone. The rise of pressure which we call glaucoma is a symptom common to many clinical conditions; further, there are clinical conditions wherein many of the symptoms characteristic of glaucoma are present in which no rise of

pressure can be detected. It is easy to argue that in these cases rises of pressure may occur intermittently at times when they have not been detected, but this can hardly explain the fact that it frequently happens that the progress of symptoms does not by any means run parallel with the tension, and frequently continues after its efficient operative relief. If we admit that physico-chemical changes do occur in the vitreous in some of these cases, it does not seem improbable that they continue after the mere mechanical relief of tension. After all, the nerve processes in the retina are ultimately physico-chemical in nature, and it is conceivable that they also may be deranged coincidentally. There is a considerable amount of experimental evidence, for example, that scotomata can be formed by inducing retinal oedema, but this question raises matters upon which so little has been done that their discussion seems unprofitable at the present time.

Taking glaucoma, then, as a pressure symptom merely, I would suggest that the two main factors in its etiology are these: first, a derangement of the capillary circulation, involving a capillary dilatation, which produces a rise in capillary pressure, or an increased permeability of their walls allowing an excess of colloids in the fluids of the eye; secondly, changes of a physico-chemical nature in the vitreous. About the first we know little, but are rapidly learning more; about the second we know less, but are slowly finding out more. These two may act either alone or together, and their effectivity in causing a permanent rise of pressure depends directly on the efficiency of the drainage channels in the region of the angle of the iris.

MERCUROCHROME 220 SOLUBLE.

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IN 1920 E. C. White¹ obtained from dibromo-fluorescein and mercuric acetate an insoluble amorphous substance which he regarded on analytical grounds as dibromo-hydroxymercuri-fluorescein. He also analysed some commercial specimens of its di-sodium salt, "mercurochrome 220 soluble," obtaining results which differed considerably from the theoretical values for the formula:

Allowing for the water content of his samples, the agreement was better, but it is obvious that slight modifications in the method of manufacture might lead to the presence of one or more of the following impurities: (a) dibromo-fluorescein, (b) dibromo-di-hydroxymercuri-fluorescein, (c) mercury salts, and (d) sodium acetate. Contamination with appreciable quantities of (a), (b), or (c) might considerably modify the therapeutic properties of the drug (cf. Macht and Harden²). Elementary analysis affords the only criterion of purity for a non-crystalline substance of this type, and mercury determinations alone are not sufficient for this purpose, since, for example, the presence of (b) or (c) might be masked by that of (a) or (d). Accordingly it became of interest to examine a number of commercial samples of mercurochrome 220 more thoroughly, in order to determine first how nearly they approach in composition to the above formula, and, secondly, whether the purer specimens are pharmacologically superior to the others. The analytical results given in Table I for what purport to be four samples of the same compound are surprising. A, B, and C were obtained from ordinary trade