

## VASCULAR CHANGES THAT OCCUR DURING THE PHASIC VARIATIONS OF TENSION IN CHRONIC GLAUCOMA\*

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It is abundantly clear that some relationship exists between ocular tension on the one hand and the state of the perilimbal episcleral vessels on the other. The ciliary congestion associated with acute and sub-acute attacks of congestive glaucoma, and the dilatation of the larger vessels of this region in absolute glaucoma, have long been recognized as examples of this relationship. Furthermore, the importance of these vessels in the drainage of aqueous from the anterior chamber has, by gradual stages, been established. The anatomical researches of Schlemm (1831), Rouget (1856), Leber (1873), Maggiore (1917) and Dvorak-Theobald (1934), have provided us with the basis of our knowledge of the vascular connections in the neighbourhood of the angle of the anterior chamber. More recently, the discovery of the aqueous veins by Ascher (1942) and Goldmann (1946), and the tracing of these to the canal of Schlemm by Ashton (1951), have confirmed a direct continuity between the anterior chamber and the vessels visible on the surface of the globe.

The more obvious changes in the episcleral vessels which follow gross changes in intra-ocular pressure have led to the inquiry whether there are also variations in the circulation on the surface of the globe in the less dramatic diurnal rise and fall of pressure which occurs in chronic glaucoma. The most detailed work on this subject is that of Thomassen (1947), who measured the pressures in episcleral vessels during these variations in tension. His method involved the direct compression of the vessel walls by a small transparent viewing chamber applied to the conjunctiva. He found that a rise in intra-ocular pressure was preceded by a rise in the pressure of the episcleral veins, and that a fall in the venous pressure initiated a fall in intra-ocular pressure. The pressure in the anterior ciliary arteries on the other hand did not vary with the changes in ocular tension.

### **Present Investigation**

The main object of this study was to observe the changes in calibre of episcleral arteries, veins, and capillaries during the diurnal fluctuations in tension and to record them by serial photographs. Methods had to be devised of recording the vascular changes without causing disturbances which might in themselves induce a hyperaemia. In most cases it was not necessary to know the precise height of the

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tension but merely the state of the cycle, whether rising, falling, or level. Advantage was taken of the fact that the rise and fall of pressure in two glaucomatous eyes in the same patient is (with certain reservations to be given later) almost synchronous, so where possible one eye was used for making observations and the other for tonometry. Altogether thirty glaucomatous patients and seven normal controls were examined.

### Methods

All the patients, except one, were observed over a full period of 24 hours. If miotics were being used these were stopped for 36 hours before admission. In the first four cases tonometry was done between five and eight times in the 24 hours, but in later cases, this was increased to ten or even twelve readings. Preferably tonometry was only done on one eye, usually that in which the tension was thought to be the lower. Occasionally, as for example when the tension changes in one eye were very slight, both tonometry and observation on the vessels were done on the same side; in these cases the observations were made first and the tension was taken afterwards with as little disturbance as possible. It has been found by observation in other cases that the chemical and mechanical irritation inevitable in tonometry quickly settles down, and it did not appear that in cases in which it had to be done the results were affected. Care was taken to choose a suitable group of vessels for observation. An area whose centre lay about 6 mm. from the limbus and which included the terminal part of an anterior ciliary artery and a large episcleral vein was required, and it had to be visible without undue movement of the eye or retraction of the lids, since either of these manoeuvres can in itself cause a hyperaemia. Records of the vascular events were made partly by direct visual observation with the slit-lamp microscope ( $\times 16$ ) and partly by serial photographs taken through the slit lamp. The visual observations provided accurate information regarding the number of smaller vessels conveying blood, and the photographs provided a means of measuring the changes in calibre in the larger vessels.

One of the earliest signs of an increased vascularity is the opening up of fresh capillary channels. It was found by counting the "islands" formed by intersecting capillaries in a well-defined area lying near the limbus that the variations in hyperaemia could be quite accurately assessed. The photographic records were obtained by mounting a reflex camera on one side of the slit-lamp binocular in place of one of the eye-pieces. Preliminary focusing with a narrow beam was done through the second eyepiece and when the required area was in the centre of the field the slit was opened to its full extent and the shutter was released. Great care was always taken to ensure that the conjunctiva was not exposed to the full strength of light for more than 5 seconds or so at a time. When the patients were awakened from sleep they were always allowed a period of 5 to 10 minutes for their eyes to adjust themselves to the lighting of the ward.

### Results

The early cases appeared to be showing conflicting results, but as more patients were examined it became clear that the fundamental vascular changes were best seen when the rise in ocular tension was moderate in degree. When the tension rose sufficiently to cause a definite corneal oedema, the main pattern became obscured by secondary vascular changes. Of the thirty cases examined, 26 showed definite alterations in the episcleral circulation; six of these came into the high tension group, and in the remainder the intra-ocular pressure was moderate or low (there are 21 records of this group as one high tension case was re-examined after operation).

**Eyes showing a Moderate or Low Degree of Tension (21 cases).**—For the reasons given above, in most cases only the relative values of tension were known.

There were twelve cases in which it seemed probable (from observations made previously) that the highest tension lay somewhere between 30 and 60 mm.Hg, and nine in which it probably did not rise beyond 30 mm.Hg. Six of this latter group had had the pressure normalized by iris inclusion operations.

There were fifteen cases of simple chronic glaucoma (medium and wide angles), and the other six were cases of chronic congestive glaucoma (narrow angles). No essential difference between the two types was found in the vascular changes.

One of the main features which distinguished cases in this series from the high tension cases was that the greatest vascularity of the episclera always occurred when the tension was at a low level and that a relative vasoconstriction was present when the tension was in an increased phase. The variations in the vessels were found to affect only the venous side of the circulation. During the period of low tension many new capillaries opened up (Figs 1a b, overleaf), and the diameter of the veins increased to a marked degree. No evidence was found of arterial dilatation, but the technique was not sufficiently exact to be certain that minor variations in calibre did not occur.

In order to determine whether the vascular changes were affected by the tension itself, some cases were studied in which the pressure had been reduced by operation on one eye only. It was found that the operated eye underwent fluctuations similar to those of its fellow (Figs 2a b, overleaf), and this led to the conclusion that the variations in the episcleral circulation were bilateral and part of a generalized vascular change.

As the tension was taken at approximately 3-hourly intervals, it was not possible to relate the vessel changes to the tension cycle as accurately as one would have wished but certain facts emerged quite clearly from these 21 reviews. The most marked vasodilation, for example, occurred in all cases somewhere between 8 p.m. and 6 a.m., that is, during the normal resting period of the body. The patient did not have to be actually asleep, but whenever the most marked vascularity occurred (in about half of the cases it was most marked between midnight and 3 a.m.) it coincided with the lowest pressure found in the 24 hours. The vasodilation appeared gradually during the descending phase, and faded again when the tension rose. It lasted in all some 4 to 7 hours, but in four cases may have been of shorter duration as it was seen during only one period of observation. Any secondary fall of tension which occurred during the day, which in this series was never so marked as that which occurred at night, was also associated with some degree of vasodilation. One case, for example, had two marked periods of vasodilation between two peaks of tension at noon and 5 p.m. The phase of highest tension, conversely, was always found during the period of relative vasoconstriction, which lasted much longer and appeared to be associated with the generalized increase of vascular tone found in the active state of the body. The usual time of highest tension was around 9 a.m. with extremes at 5.30 a.m. and 12 noon. It was unusual to find that the highest tension occurred before rising, which is the time usually accepted. It should be noted here that the times given for the highest and lowest tensions agree with those found by Langley and Swanljung (1951) in a series of thirty cases of glaucoma simplex. The dilation of the vessels is most pronounced in the phase of lowest tension. For example, the vasodilation occurring with a

tension of 20 mm. Hg was usually quite obvious to the naked eye, but in the same case the difference in vascularity between say, 30 and 50 mm. Hg was often relatively slight. In two-thirds of the cases, the vasodilation was quite obvious to the naked eye and the larger veins showed a definite increase in diameter. In the remainder, the vascularity was manifest only by an increase in the number of capillaries containing blood, and was only visible on slit-lamp examination. The four cases which showed no vascular changes in the 24 hours underwent very little rise and fall of tension. Three of them were cases of low tension glaucoma simplex which showed characteristic field defects but in which the tension in the control eye remained between 18–25 mm. Hg during the 24-hour review. The fourth case had a moderately high tension which fluctuated only between 37–45 mm. Hg. As a general rule, in glaucomatous cases, the fluctuation in tension was proportional to the degree of vessel dilatation.

*Normal Controls.*—Six out of seven controls showed variations in the calibre of episcleral vessels comparable in duration and degree to that occurring in glaucomatous patients (Figs 3a and 3b). The “bleary-eyed” individual just awakened from sleep is familiar to all, and it was found that four out of the six normal cases in which vasodilation occurred showed a drop in tension ranging from 3 to 7 mm. Hg at the time when the vessel changes were most marked. It will be suggested later that this physiological dilation is the cause of the diurnal variations of tension in normal eyes.

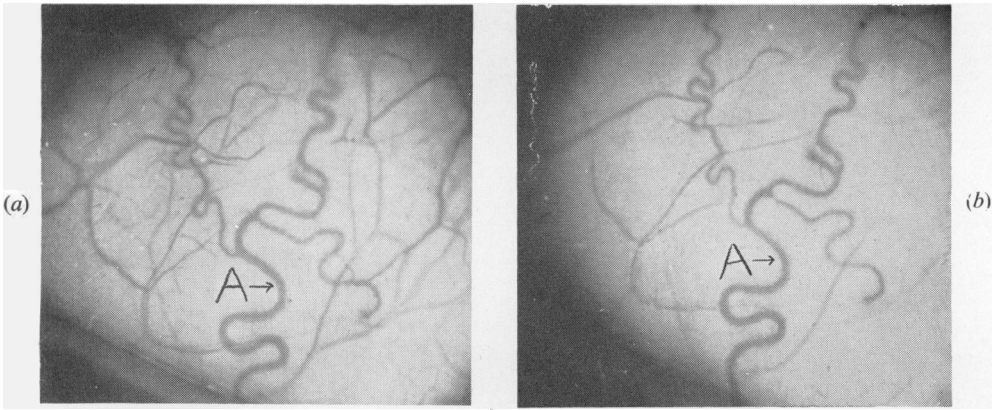
*Aqueous Veins.*—Observations on aqueous veins were made when possible. It was usually found that during the period of vasodilation, those vessels which were either pure aqueous veins, or contained a high proportion of aqueous, dilated in the same way as those containing pure blood. It was difficult to be sure whether more or less aqueous was flowing out during the reduced phase, because there was usually an increased blood content at the same time. In three cases (notably the vessel in the normal control shown in Figs 3a and 3b) photographs provided evidence that the stream of aqueous was wider in the dilated than in the constricted phase. This probably implies that facilitation of aqueous outflow is occurring.

To summarize the results so far, it would appear that there is a physiological variation of vascular tone in the episcleral vessels which is associated with variations in ocular tension of a greater or lesser degree in both glaucomatous and normal eyes. The relationship between these changes will be discussed presently, but first it is advisable to consider the group of six high tension cases in which the physiological pattern was not followed, and in which the hyperaemia was probably influenced by local factors.

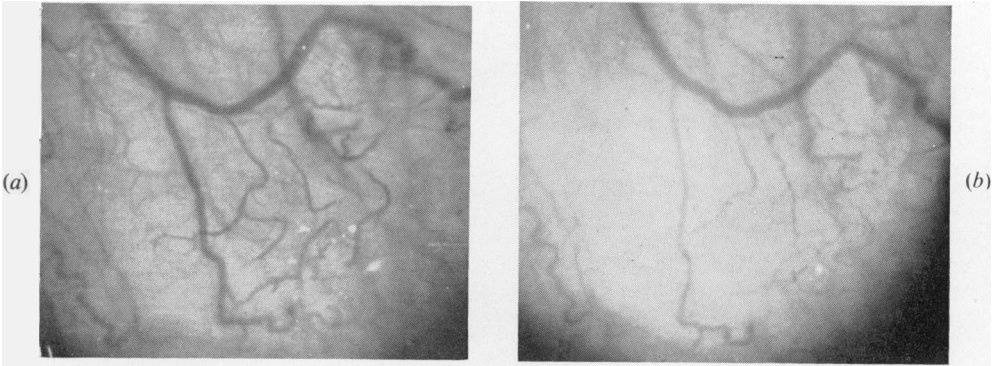
**Eyes showing a High Degree of Tension (6 cases).**—These were all cases of the narrow-angle congestive type, and all showed a considerable rise of tension with a marked corneal oedema at one stage in the cycle.

The first point of difference between this and the preceding series was that the vascular changes, which were marked in every case, were not necessarily bilateral, so that unless both corneae were oedematous, the changes were more obvious in the eye with the higher pressure.

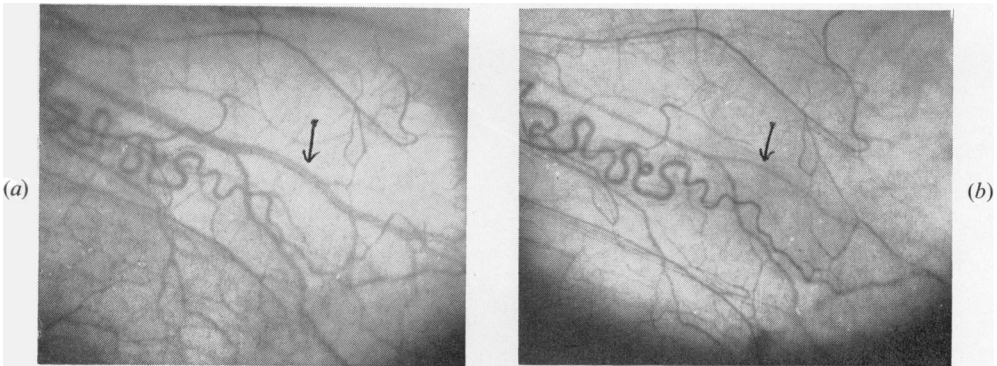
The second point of difference was that the vascular changes were related to



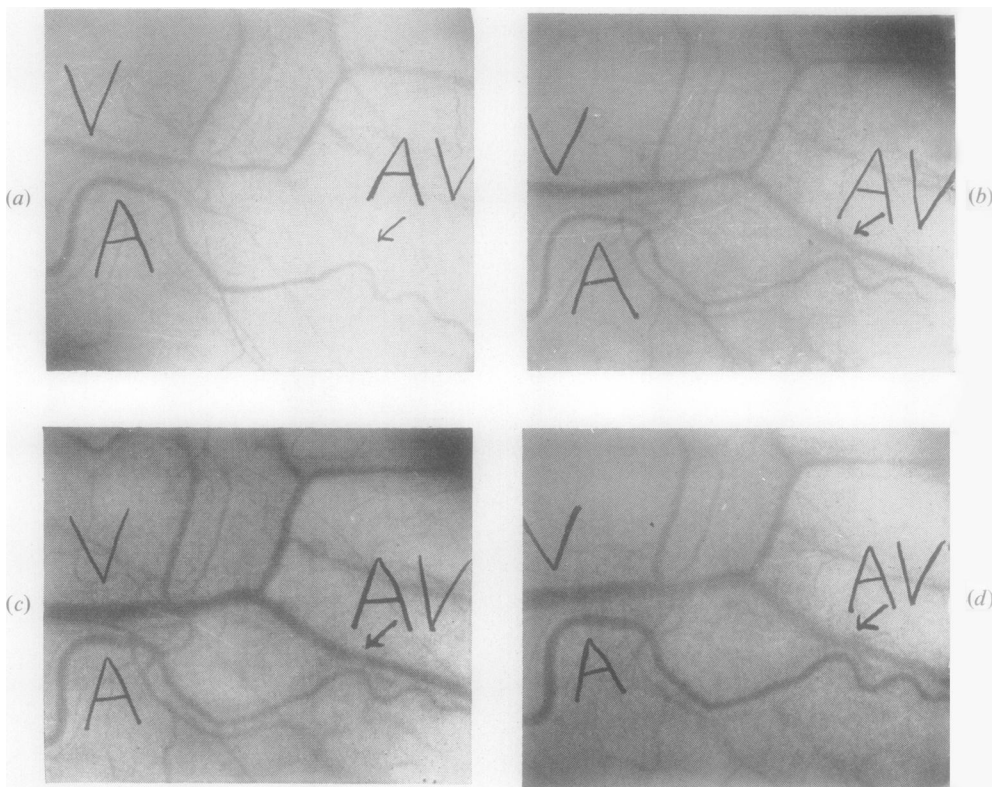
**FIGS 1(a) and 1(b).**—Calibre variations in glaucoma simplex, an anterior ciliary artery (A), and a group of venules.  
 1(a).—4.30 a.m., tension 25 mm. Hg. 1(b).—10.00 a.m., tension 40 mm. Hg.



**FIGS 2(a) and 2(b).**—Calibre variations in a low tension (operated) eye. A group of episcleral veins.  
 2(a).—11.00 p.m., tension in fellow (glaucomatous) eye 25 mm. Hg.  
 2(b).—9.00 a.m., tension in fellow eye 45 mm. Hg.



**FIGS 3(a) and 3(b).**—Normal control showing calibre variations in phase of vasodilation (3(a)) at 3.15 a.m. and during relative constriction (3(b)) at 6.15 a.m. Note vein indicated by arrow which is full of aqueous in Fig. 3(a).



FIGS 4(a) to 4(d).—Changes in a high tension attack.

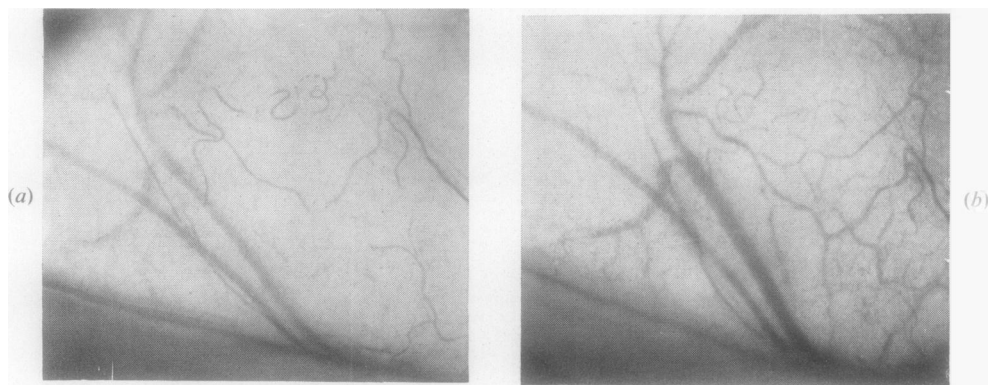
A.V.=aqueous vein. A=Anterior ciliary artery. V=Vein.

4(a).—2.00 p.m., tension 15 mm. Hg, A.V. contains pure aqueous and is invisible in this Figure.

4(b).—11.00 p.m., tension 60 mm. Hg, A.V. contains blood.

4(c).—5.30 a.m., tension 60 mm. Hg, A.V. contains blood.

4(d).—7.30 a.m., tension 32 mm. Hg, A.V. contains mixed blood and aqueous.



FIGS 5(a) and 5(b).—Effect of methonium on episcleral vein (above) and arteriole.

5(a).—Control eye before injection of 50 mg. hexamethonium.

5(b).—Control eye 45 min. after injection.

different points in the tension cycle. For example, some increased vascularity was always apparent at the highest point of tension, and it was most in evidence in the descending phase. Sometimes it was present in the latter part of the ascending phase.

A final point of difference was that several cases in this series showed dilatation of arteries as well as of veins.

The case shown in Figs 4(a) to 4(d), illustrates some of these points. The patient was a night worker and he remained up in a well-lit ward throughout the survey, so it is probable that a physiological dilatation did not complicate the vascular picture.

At 2 p.m. the vessels were constricted, the tension was 15 mm. Hg and a large aqueous vein contained pure aqueous (Fig. 4(a)).

At 9 p.m. the tension had risen to 40 mm. Hg, the veins showed a moderate degree of dilation, and the aqueous vein contained what appeared to be pure blood.

At 11 p.m. the tension had risen to 60 mm. Hg, a corneal oedema was present, and the veins and aqueous vein appeared to be as they were at 9 p.m. (Fig 4(b)).

The tension and the corneal oedema persisted throughout the night and at 5.30 a.m. were still present. At about this time the vasodilation became much more marked (Fig 4(c)). The tension began to fall shortly after this, the cornea cleared and aqueous eappeared in many of the episcleral veins.

At 7. 30 a.m. the tension had dropped to 32 mm. Hg, the veins were still very dilated and the aqueous vein shown in the pictures contained a large quantity of very dilute blood (Fig 4(d)).

At 10 a.m. the veins had returned to their original size and the aqueous vein contained pure aqueous again. It appeared therefore that no aqueous was escaping from the globe between the later part of the ascending phase and the beginning of the descending phase. The veins which previously contained aqueous had evidently become filled with blood through anastomotic channels.

The behaviour of the aqueous outflow was similar to that found in another patient also proved by gonioscopy to have an extremely narrow angle (reported by Thomassen, Perkins, and Dobree, 1950). Grant (1951) reported ten narrow-angle cases, and Weekers and Prijot (1952) six narrow-angle cases in which the resistance to outflow on compression of the globe increased greatly when the tension was high and decreased when it was low. The changes in all of these cases could be explained by an actual angle block shutting off the anterior chamber from the canal of Schlemm during the increased phase of tension.

### Discussion

Let us first consider the moderate and low tension cases in which the variations in the calibre of the episcleral vessels seem to have a physiological basis.

It may be that the vasodilation so constantly found in the phase of lowest tension is not directly related to the fall of pressure in the eye but that both have some common origin. The vasodilation is not dependent on sleep but it is possible that in the resting state there is a reduction in the formation of aqueous which coincides with, but is not directly related to, a general reduction in vascular tone including a vasodilation of the episcleral vessels. Although a diurnal variation in aqueous production has not yet been established, it is possible that it plays a significant part in the rise and fall of

tension. There is more positive evidence, however, that an obstruction to outflow of aqueous, even in wide-angle cases, plays an important role in the production of the tension in chronic glaucoma. Ascher and Spurgeon (1949) and Goldmann (1951) have demonstrated a diminished aqueous outflow in chronic glaucoma, and Grant (1951) found an increase in resistance to outflow in both wide- and narrow-angle cases. The intrascleral veins, which receive most of the "collectors" from the canal of Schlemm, and the episcleral veins, with which the former are freely connected (and which receive aqueous direct from the canal of Schlemm by the aqueous veins), could offer a varying degree of resistance to outflow, depending on their pressure. Now, when there is evidence of fresh capillary channels opening up and of a dilatation of veins, it is very likely that there is a drop in pressure in the venous side of the circulation, especially when there is little or no evidence of more blood passing through the area by reason of arterial dilatation. The fall of pressure which appears to occur during the period of vasodilatation would facilitate the outflow of both aqueous and blood from the interior of the globe. As variations in the calibre of the episcleral vessels have been shown to occur in normal as well as in glaucomatous eyes, it is unlikely that the phase of relative vasoconstriction in these vessels is the cause of the rise of pressure, but it is suggested that the phase of vasodilatation could play a part, and perhaps an important part, in reducing tension of whatever origin. Let us examine some experimental and clinical facts in the light of this hypothesis.

Thomassen's finding on the relationship between the episcleral veins and the intra-ocular tension would be explained, because the pressure at any particular point in an emergent vein would increase or decrease according to the changes of pressure in the veins into which it drained. At the same time, these would be altering the intra-ocular tension by varying the resistance to the outflow of aqueous. Further, the finding that the calibre of the arteries was unaltered throughout the cycle would agree with Thomassen's finding of a constant arterial pressure.

The effect of the methonium compounds on the reduction of the ocular tension in both normal and glaucomatous eyes has been noted by several observers, notably Rycroft and Romanes (1952), and Cameron and Burn (1952). The former state that the tension may fall so low that it will not register on a tonometer.

Caution has to be exercised in correlating the results with the foregoing, as these compounds cause a profound drop in the arteriolar as well as the general blood pressure. Photographs of a non-glaucomatous subject (Figs 5*a* and 5*b*) taken before, and three-quarters of an hour after, the injection of 50 mg. hexamethonium are of interest because they show a similar dilatation of the venous channels associated with a drop in tension of 5mm. Hg in the control eye.

There are several clinical findings which this hypothesis would explain. The reduction of tension by miotics in wide-angle subjects and in aniridia,



for example, may be partly due to the fact that both pilocarpine and eserine, which are known to have a direct vasodilator effect on vessels, may reduce the pressure in the scleral and episcleral veins. Thomassen (1946) and Grant (1951) found that in wide-angle cases the resistance to outflow was decreased after the instillation of miotics. Furthermore, the beneficial effect of sleep, with its attendant physiological vasodilation, and of local heat in the relief of sub-acute glaucomatous attacks may be significant in this connection.

In the high tension cases it is clear that the vascular pattern is much more complex and is probably much influenced by local ocular changes. It has been suggested that an angle block occurs in high tension narrow-angle cases, and if this is so some of the vascularity could be explained by axon reflexes caused by the periphery of the iris being forced against the back of the cornea. This would explain the vascular changes occurring in the later part of the ascending phase in the case illustrated. The explanation of the vasodilation, which was so constant a feature of the descending phase of tension in this series of narrow-angle cases, offers an intriguing subject for speculation. The explanation may possibly lie in the raised tension itself. This may, for example, cause a relative intra-ocular ischaemia, which might result in anoxia, or in the formation of histamine, both of which are known to cause a local vasodilation. This vasodilation may be of considerable importance in lowering the tension and may act as a kind of safety-valve. A second factor worthy of consideration is that the increased vascularity may be caused by the difficulty experienced by the arteries in pumping blood into the eye in face of considerably increased pressure; blood may be "shunted off" through the minute superficial branches to limbal loops, paralimbal conjunctiva and sclera, which eventually drain back into the episcleral vessels without having entered the globe at all.\*

In conclusion, it is suggested that the changes in calibre described provide further evidence that variations in vascular tone play an important part in the rise and fall of tension in glaucoma. It must be remembered that only the changes in calibre in the episcleral vessels have been studied, and that there may well be other changes either in these or in deeper vessels which may be found to play a more important role than those described. For example, our knowledge of the rate of flow and of the capillary permeability, even in the vessels which can be directly observed, is fragmentary. The recurring theme throughout the investigation is that of an association between a dilatation of the venous side of the circulation and a lowering of the ocular tension; it is hoped that this will prove to be a pointer towards the more effective medical treatment of glaucoma.

### Summary

(1) The vascular changes occurring during the diurnal tension variations in thirty patients suffering from chronic glaucoma and seven normal controls are described.

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\*The reader is referred to a previous communication for an anatomical basis for this argument (Dobree, 1950).

(2) The majority of cases showed a rise of tension which was not sufficiently high to cause a corneal oedema. In these cases, and in the normal controls, it was found that a vasodilatation, mainly affecting the venous side of the circulation, was associated with the lowest tension level. Conversely, when the tension was raised, the vessels were relatively constricted. Both eyes showed similar changes suggesting that these phenomena have a physiological basis.

(3) A series of six cases in which the tension was markedly raised showed quite different changes in the vessels. These were probably due to local vascular disturbances.

(4) The suggestion is made that the changes described facilitate the outflow of aqueous by causing a reduction in pressure in the venous outlets from the canal of Schlemm.

(5) This hypothesis is discussed in the light of several experimental and clinical findings.

I should like to record my indebtedness to Dr. T. Thomassen for the interest aroused in this phase of glaucoma research during his sojourn at the Institute of Ophthalmology three years ago and to Sir Stewart Duke-Elder for his interest and helpful criticism during the investigation. Dr. R. Kempthorne and Dr. D. Ferriman kindly collaborated in the methonium experiments.

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