Mechanisms in ocular hypertension

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SUMMARY This paper investigates the hypothesis that intermittent partial angle closure is one of the causes of ocular hypertension. 139 eyes from 76 patients with ocular hypertension were provoked with pilocarpine and phenylephrine. Four distinct responses appeared. Firstly, in 39 eyes (from 24 patients, 32%) gonioscopic closure of part or all of the angle appeared. Secondly, in 30 eyes (from 19 patients, 25%) no angle closure occurred but there was a substantial pigment release into the aqueous. Thirdly, in 9 eyes (from 8 patients, 11%) both angle closure and pigment release occurred. Finally, in 61 eyes (from 36 patients, 59%) neither angle closure nor pigment release appeared. (Since the 2 eyes of a patient did not always behave in the same way, for example, 1 eye might develop angle closure and the other not, 1 patient may appear in 2 groups.) From the first group 1 eye from each patient was randomly chosen for iridectomy. A repeat provocative test at least 1 year later produced a significantly different result. It is considered that the evidence obtained in this study supports the hypothesis that intermittent partial angle closure is one of the causes of ocular hypertension.

There is no reason to suppose that ocular hypertension has one unique cause, and a clinically indistinguishable picture has been shown to occur in some eyes at risk to the development of closed-angle glaucoma (Mapstone, 1979a). This paper investigates the hypothesis that one of the causes of ocular hypertension is intermittent partial angle closure.

Material and methods

One hundred and thirty-nine eyes from 76 patients were studied. They were selected on the following criteria: (1) No story suggestive of intermittent closed-angle glaucoma; (2) no glaucomatous field defect; (3) a gonioscopically open angle with no peripheral anterior synechiae; (4) a mean applanation pressure on 3 consecutive occasions of 21 mmHg or more; (5) no anterior segment exfoliation; (6) no venous occlusive disease; (7) no family history of glaucoma.

The eyes were provoked as follows: At zero hour intraocular pressure was measured, facility of outflow recorded, and pilocarpine drops 2% plus phenylephrine drops 10% instilled. Approximately 1½ hours from the start of the test the intraocular pressure

was recorded, tonography was repeated, and another dose of pilocarpine and phenylephrine instilled. Finally, after another 1½ hours (that is 2½ hours from the start of the test) pressure was recorded and tonography repeated.

Gonioscopy was done on every patient at the start and termination of the test. Thirty-three patients developed partial or complete gonioscopic closure of the angle in 1 or both eyes. One eye from each of these patients was then randomly selected for a peripheral iridectomy. The result of a provocative test before and at least 1 year after iridectomy are recorded (this represents 19 patients; in 14 cases 1 year has not yet elapsed since an iridectomy was done).

The critical measurement at the inception of angle closure is the distance between iris and cornea just internal to the limbus (Mapstone, 1979b). Angles were therefore divided into 3 groups: (1) Iridocorneal distance less than one-quarter of corneal thickness; (2) iridocorneal distance about one-quarter of corneal thickness; and (3) iridocorneal distance greater than one-quarter of corneal thickness. The gap was estimated in the temporal quadrant.

During each provocative test attention was also directed to the amount of pigment released into the aqueous and was subjectively classified as follows: (1) Pigment absent; (2) pigment present, but the

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Fig. 1 Response of 139 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded

Fig. 2 Response of 39 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded

number of pigment granules present in a slit beam of 3 mm length could, if necessary, be counted; and (3) pigment present, but to such a degree that a count would be impossible.

Results

Provocative test result in 139 eyes from 76 patients

Fig. 1 records the mean response and shows that the first dose of phenylephrine and pilocarpine decreased pressure from a mean of 22.9 to 20.7 mmHg and increased outflow from a mean of 0.15 to 0.20 μ l/mmHg per min. The second dose increased pressure from a mean of 20.7 to 21.3 mmHg, outflow remained at 0.20.

The 4 patterns of outflow response described previously (Mapstone, 1977a, b, 1978) were also shown by this group. However, for the purpose of this paper the responses are analysed as follows.

(1) Response of 39 eyes (from 27 patients) that developed gonioscopic angle closure only. Fig. 2 records the result and shows that the first dose of pilocarpine and phenylephrine reduced pressure from a mean of 22.7 to 21.1 mmHg and increased

outflow from a mean of 0.15 to 0.19. The second dose increased pressure from a mean of 21.1 to 24.7 mmHg and outflow decreased from a mean of 0.19 to 0.17.

The statistics of this group are, however, biased by the fact that 8 eyes from 6 patients developed acute closed-angle glaucoma (gonioscopic closure with an increase in pressure of at least 8 mmHg) during the test. In 8 eyes reductions in pressure and substantial increases in outflow occurred in spite of extensive gonioscopic closure. This fact is obscured by the analysis.

(2) Response of 30 eyes (from 19 patients) that developed no gonioscopic angle closure but released much pigment into the aqueous. Fig. 3 records the result and shows that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 22.9 to 21.2 mmHg and increased outflow from a mean of 0.16 to 0.17. The second dose increased pressure from a mean of 21.1 to 21.9 mmHg and outflow decreased from a mean of 0.17 to 0.16.

(3) Response of 9 eyes (from 8 patients) that developed both gonioscopic angle closure and much pigment release. Fig. 4 records the result and shows

Fig. 3 Response of 30 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded

Fig. 4 Response of 9 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded

Fig. 5 Response of 61 eyes to provocative testing with pilocarpine (P) and phenylephrine (F). Mean and standard error recorded

that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 21.6 to 20.8 mmHg and increased outflow from a mean of 0.14 to 0.16. The second dose decreased pressure from a mean of 20.8 to 20.2 mmHg and increased outflow from a mean of 0.16 to 0.17. No patient developed acute closed-angle glaucoma.

(4) Response of 61 eyes (from 36 patients) that developed neither gonioscopic angle closure nor

pigment release. Fig. 5 records the results and shows that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 23.3 to 20 mmHg and increased outflow from a mean of 0.15 to 0.22. The second dose decreased pressure from 20 to 19.1 mmHg and increased outflow from 0.22 to 0.25.

An analysis of the overall change in pressure and facility of outflow produced by a provocative test in the different groups is shown in Table 1. It can

Fig. 6 Response of 19 eyes to provocative testing with pilocarpine (P) and phenylephrine (F), before (solid line) and after (interrupted line) a peripheral iridectomy. Mean and standard error recorded

Table 1 Significance of the changes in pressure and outflow in various groups of eyes during a provocative test

	ΔP		ΔC	
	t	P	t	P
AC only	1.06	NS	1.45	NS
PR only	1.02	NS	0.36	NS
AC + PR	1.31	NS	1.63	NS
Neither	6.16	<0.001	7.91	<0.001
All eyes	2.52	<0.02	6.09	<0.001

AC = angle closure. PR = pigment release. *t* = Student's *t* statistic. *P* = probability value. ΔP = total change in pressure. ΔC = total change in outflow. NS = not significant

be seen that in eyes showing angle closure, pigment release, or both no significant change in pressure or outflow occurred. In the 61 eyes that showed neither there was in contrast a very significant decrease in pressure and increase in outflow.

Provocative test result in 19 eyes before and after a peripheral iridectomy

Before iridectomy: Fig. 6 records the mean response and shows that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 21.8 to 20.1 mmHg and increased outflow from a mean of 0.15 to 0.18. The second dose increased pressure from a mean of 20.1 to 23.8 mmHg, and decreased outflow from a mean of 0.18 to 0.15. Neither the overall change in pressure nor outflow was statistically significant.

After iridectomy: Fig. 6 records the mean response and shows that the first dose of pilocarpine and phenylephrine decreased pressure from a mean of 21.4 to 16.9 mmHg and increased outflow from a mean of 0.14 to 0.21. The second dose increased pressure from a mean of 16.9 to 17.1 mmHg and

increased outflow from 0.21 to 0.24. Both the overall decrease in pressure and increase in outflow are statistically significant ($P < 0.001$). None developed angle closure of any degree.

Incidence of angle closure in eyes graded according to iridocorneal distance

Table 2 records the result and shows that there is a significant association between iridocorneal distance and the subsequent development of angle closure.

Discussion

The results described show that, analysed as a group, the 139 eyes responded to a provocative test in a way similar to normal eyes, showing a significant decrease in pressure and increase in outflow (Mapstone, 1977c). This result is due to the fact that 61 (44%) of the eyes developed neither angle closure nor pigment release (Fig. 5). In the 3 groups that did, a provocative test produced no significant change in either pressure or outflow, and the evidence suggests that this is a direct consequence of angle closure or pigment release. This is confirmed in 19 randomly chosen eyes that developed angle closure, since after a peripheral iridectomy a repeat provoca-

Table 2 Incidence of gonioscopic angle closure in eyes with varying iridocorneal distances

	Iridocorneal distance		
	< $\frac{1}{4}$	$\frac{1}{4}$	> $\frac{1}{4}$
Number of patients	8	32	36
Number with angle closure	7	22	4
	(88%)	(69%)	(11%)

$\frac{1}{4}$ = One-quarter of corneal thickness

tive test produced a highly significant pressure decrease and outflow increase (Fig. 6).

The results show that in 40 to 45% of patients with ocular hypertension gonioscopic closure of all or part of the angle can be seen on provocative testing. This may be merely an association signifying nothing in particular. However, gonioscopic angle closure is a rare event in nonglaucomatous eyes randomly selected for provocative testing (Mapstone, 1977c) but occurred in 53% of a group of normal eyes selected because of a gonioscopically narrow angle (Mapstone, in preparation). So the alternative explanation—that there is a causal relationship—is therefore worth examining.

In order to do this it is necessary to erect a hypothesis to explain the putative relationship and from this derive implications that can be submitted to experimental test. The first hypothesis is that ocular hypertension causes angle closure. This is, a priori, highly improbable and will not be discussed. The second hypothesis follows.

Angle closure is not an all-or-none phenomenon, but rather eyes exist in which some of the angle is closed for some of the time only. Eyes showing this progress through the following stages: *Stage 1* represents an eye that develops intermittent partial angle closure and, because of this, an intermittently raised pressure. After an (undetermined) interval the cumulative effect is *Stage 2*. An intermittently raised pressure then produces damage to the outflow system which shows as a reduced facility of outflow. The affected eye now has a permanently raised pressure and outflow damage—that is, ocular hypertension (Fig. 7).

A situation has been created which can evolve in one of several ways: (1) The trigger mechanism (intermittent angle closure) ceases to operate and the eye is left with ocular hypertension; (2) the mechanism continues to operate intermittently but at no point does a sufficient increase in pressure occur to produce a field defect—that is, ocular hypertension persists; (3) eventually pressure rises

Fig. 7 Postulated mechanism for the aetiology of ocular hypertension. Intermittent angle closure (AC) produces a raised pressure (RP) which, in turn, is the cause of outflow damage (OD)

Fig. 8 When pressure has increased sufficiently a field defect (FD) appears and the eye passes to the stage of open-angle glaucoma

Fig. 9 A stage is reached in some eyes where a trigger mechanism is no longer necessary. Here a raised pressure (RP) has produced outflow damage (OD) which raises pressure more, and a self-perpetuating mechanism is generated

sufficiently to produce a field defect and the eye passes to *stage 3*, the stage of open-angle glaucoma.

There are two ways in which this can be achieved. Firstly, intermittent angle closure increases an already raised pressure sufficiently to produce a field defect (Fig. 8). Secondly, an increased pressure (the result of intermittent partial angle closure) may damage the outflow system so much that that damage increases pressure still more. This in turn produces more outflow damage, and the self-perpetuating mechanism shown in Fig. 9 is generated. It no longer needs a trigger mechanism to sustain it and alone produces a field defect.

A number of implications can be derived from this hypothesis and submitted to experimental test. They are as follows:

(1) If the hypothesis is correct, then intermittent partial angle closure occurs and produces a raised pressure with no clinical symptoms. The evidence

for partial angle closure has been described in this paper and elsewhere (Mapstone, 1977a). That it may be intermittent can be inferred from the behaviour of contralateral eyes at risk to the development of closed-angle glaucoma that do not have a peripheral iridectomy (Mapstone, 1979a).

(2) A raised pressure produces permanent outflow damage. Evidence for this comes from several sources. It is a common clinical observation that after an episode of acute closed-angle glaucoma and subsequent iridectomy some eyes still need treatment to maintain a clinically acceptable pressure. Whatever the proximate causes of the underlying outflow damage may be, the remote cause is a raised pressure. Again, even in eyes that are normotensive after an acute attack, outflow damage can be demonstrated relative to the contralateral eye (which has not had a spontaneous acute attack) (Mapstone, 1977d).

(3) Partial angle closure produces ocular hypertension. Eyes at risk to closed-angle glaucoma (because the fellow eye had had an acute attack) may be treated with prophylactic pilocarpine drops. After a period of years a raised pressure and reduced facility of outflow may appear, although the angle is open, free of peripheral anterior synechiae, and there is no clinical evidence to suggest that acute chronic or intermittent closed-angle glaucoma has occurred. Since 90% of these eyes developed angle closure of some degree on provocative testing the reasonable inference is that intermittent partial angle closure has produced a picture clinically indistinguishable from ocular hypertension (Mapstone, 1979a). To say that this is a secondary change—which it is—and therefore not comparable to the change in 'primary' ocular hypertension begs the question.

(4) Another test implication is that if most instances of open-angle glaucoma are preceded for a variable period by ocular hypertension, then partial angle closure should be demonstrable in some eyes with open-angle glaucoma. Evidence for this has been published (Mapstone, 1978).

(5) Finally, if angle closure could be demonstrated in the ocular hypertension or open-angle glaucoma associated with venous occlusive disease, anterior segment exfoliation or diabetes then that would be additional supportive evidence for the hypothesis. There is evidence that this is so (Mapstone, in preparation).

The value of a hypothesis is directly proportional to the number of implications that can be derived from it and verified experimentally. It is suggested that there is now sufficient reason to suppose that an angle-closing mechanism is one of the causes of 'primary' ocular hypertension and open-angle glaucoma.

One other point is of interest. Published data (Armaly, 1969; Perkins, 1973; Wilensky *et al.*, 1974; Kitazawa *et al.*, 1977) suggest that 10% of patients with ocular hypertension proceed to open-angle glaucoma. It therefore necessarily follows that the majority of ocular hypertensives with partial angle closure will not develop field loss. There is therefore not sufficient reason for doing a peripheral iridectomy in all hypertensives with demonstrated angle closure, neither is there, at the moment, evidence to show which should be chosen. One thing is clear, ocular hypertension, partial angle closure, and a reduced outflow facility are quite compatible with normal visual health.

The results too have implications for gonioscopy as currently practised. It has already been shown that gonioscopic angle closure does not necessarily imply true angle closure (Mapstone, 1979b). It also follows from the results described above that from the coincidence of a raised pressure and open angle it cannot be asserted that the cause of the raised pressure (proximate or remote) is not angle closure. The fact that patients with non-narrow angles developed partial angle closure is also of significance. Finally, pigment release prevents (Fig. 3) the expected decrease in pressure and increase in outflow on provocative test and suggests that this may be another model of outflow damage. These points are explored in subsequent papers.

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References

- Armaly, M. F. (1969). Ocular pressure and visual fields. *Archives of Ophthalmology*, **81**, 25–40.
- Kitazawa, Y., Horie, T., Aoki, S., Suzuki, M., and Niskioka, K. (1977). *Archives of Ophthalmology*, **95**, 1180–1184.
- Mapstone, R. (1977a). Partial angle closure. *British Journal of Ophthalmology*, **61**, 525–530.
- Mapstone, R. (1977b). Outflow changes in positive provocative tests. *British Journal of Ophthalmology*, **61**, 634–636.
- Mapstone, R. (1977c). Normal response to pilocarpine and phenylephrine. *British Journal of Ophthalmology*, **61**, 510–511.
- Mapstone, R. (1977d). Outflow changes in normal eyes after closed-angle glaucoma. *British Journal of Ophthalmology*, **61**, 637–640.
- Mapstone, R. (1978). Mechanisms in open-angle glaucoma. *British Journal of Ophthalmology*, **62**, 275–282.
- Mapstone, R. (1979a). One model of outflow damage. *British Journal of Ophthalmology* (in press).
- Mapstone, R. (1979b). One gonioscopic fallacy. *British Journal of Ophthalmology* (in press).
- Perkins, E. S. (1973). The Bedford glaucoma survey: I. Long-term follow-up of border-line cases. *British Journal of Ophthalmology*, **57**, 179–187.
- Willensky, J. T., Podos, S. M., and Becker, B. (1974). Prognostic indicators in ocular hypertension. *Archives of Ophthalmology*, **91**, 200–202.