

## Provocative tests in closed-angle glaucoma

R. MAPSTONE

From St Paul's Eye Hospital, Liverpool

The absence of a provocative test with proved predictive value, in eyes at risk of developing closed-angle glaucoma, creates many problems—for example, a patient presents with a family history of acute closed-angle glaucoma and has narrow angles. What is the probability of his developing an acute attack?

Gonioscopy is of no help in answering this question since an assessment of the narrowness of an angle is a subjective one. If—on the basis of gonioscopy findings—an angle is thought to be capable of closure then three options are open to the ophthalmologist:

1. All such eyes require prophylactic iridectomy
2. Some such eyes require iridectomy
3. Gonioscopy provides insufficient evidence on which to base a decision and therefore other criteria must be invoked.

The first option is rarely, if ever, adopted. The second option is logically inconsistent, and the third a reasonable inference. It is perhaps relevant to mention that it is unnecessary to perform gonioscopy to determine the narrowness of an angle. Van Herrick and Shaffer (1969) showed that moving the slit beam to the corneal side of the limbus is—with practice—just as informative on this point.

Again, no prospective studies are available to show which narrow angle will close—indeed, there would be no point in such a study because one would merely be left with one group of (gonioscopically) narrow angles that occluded and another group that did not, but with insufficient quantitative data on which to base a decision in a particular eye.

A more useful approach would be to devise a provocative test scheme from which it could be inferred with a high degree of probability that a particular eye would (or would not) develop angle closure. Such a scheme would have the following characteristics:

1. A sound theoretical and experimental basis
2. Simplicity
3. Speed (not time-consuming)
4. Reproducibility

5. No false positives
6. No false negatives
7. No danger to the patient
8. It would be within the limits of normal experience, that is, physiological.

It is probable that these criteria will prove difficult to meet. The purpose of this paper is to describe and illustrate a scheme which goes some way towards that goal.

### Material and methods

Altogether 119 eyes from 100 patients were selected for provocative testing on the basis of the following criteria:

1. Acute closed-angle glaucoma in the contralateral eye
2. Chronic closed-angle glaucoma in the contralateral eye
3. A history of intermittent closed-angle glaucoma in one or both eyes
4. A central retinal vein occlusion in the contralateral eye associated with narrow angles.

Each eye was provoked as follows:

At zero hours a photograph of the anterior segment was taken. Pilocarpine drops 2 per cent and phenylephrine drops 10 per cent were instilled alternately three times at 1 min intervals, and the intraocular pressure was recorded. Subsequently, at approximately half-hourly intervals, phenylephrine 10 per cent was instilled, an anterior segment photograph was taken, and the intraocular pressure recorded. As soon as the intraocular pressure had increased significantly (more than 8 mmHg) intravenous acetazolamide 500 mg, thymoxamine drops 0.5 per cent, and pilocarpine drops 2 per cent were instilled. Pressures were measured and anterior segment photographs were taken thereafter at approximately hourly intervals. The slides were subsequently projected and P/C\* ratios calculated in the horizontal meridian.

If, after 2 h, the above test was negative then a further dose of pilocarpine 2 per cent was instilled, together with 10 per cent phenylephrine, and the test continued as described above. If, 1½ h later, the intraocular pressure had not increased, thymoxamine drops 0.5 per cent were instilled to terminate the test.

On another day, eyes that were negative to the pilocarpine and phenylephrine test were re-provoked as follows:

At zero hours an anterior segment photograph was

\*P/C = Pupillary and corneal diameters

taken, tropicamide drops 0.5 per cent three times at 1 min intervals were instilled, and the intraocular pressure was recorded. Subsequently, at approximately half-hourly intervals, an anterior segment photograph was taken and the intraocular pressure recorded. As soon as the intraocular pressure had increased significantly, with evidence of angle closure, intravenous acetazolamide 500 mg was given and pilocarpine 2 per cent instilled. If after 2 h the pressure increase was less than 8 mmHg, pilocarpine 2 per cent was instilled and the test terminated.

Gonioscopy was not routinely done; the presence of partial or complete angle closure can be quickly and adequately determined by moving the slit beam to the corneal side of the limbus in the four quadrants.

**Results**

Fig. 1 shows that 66 (55.5 per cent) were positive with simultaneous pilocarpine and phenylephrine alone. This figure is increased by eight to 74 (62 per cent) if additional pilocarpine was instilled after 2 h, in the patients who were initially negative with simultaneous pilocarpine and phenylephrine. Of the remaining 45 patients nine (8 per cent of the total) were subsequently positive on re-provocation with tropicamide. Thus, of the 119 eyes, 83 (70 per cent) responded to provocative testing with a positive result; 36 or 30 per cent were negative.

The eyes provoked, therefore, fell into four groups:

1. Simultaneous pilocarpine and phenylephrine produced a positive result (66 or 55 per cent)
2. Additional pilocarpine was necessary to provoke angle closure (8 or 6.7 per cent)
3. Pilocarpine and phenylephrine were negative but tropicamide was positive (9 or 7.6 per cent)
4. Neither test was positive (36 or 30 per cent).

The mean statistics relating to these four groups are shown in the Table under the following headings:

1. Number of eyes
2. Time interval (min) between start of provocative test and rise in intraocular pressure
3. Time between second dose of pilocarpine and rise in pressure
4. Rate of rise in intraocular pressure
5. Increase in intraocular pressure
6. Total time taken
7. P/C ratio at onset of rise in pressure
8. P/C ratio at second instillation of pilocarpine

	Pilocarpine and Phenylephrine		Add Pilocarpine		Tropicamide
Positive	66	2 hours	8	Days or weeks	9
Negative	53		45		36

FIG. 1 Results of provocative tests with pilocarpine, phenylephrine, and tropicamide

9. P/C ratio at termination of provocative test
10. Maximum P/C ratio with pilocarpine and phenylephrine
11. Maximum P/C ratio with tropicamide.

The results for the simultaneous pilocarpine and phenylephrine group are summarized in Fig. 2. After 63 min the intraocular pressure began to increase at a P/C ratio of 0.37. The increase in pressure was 21.5 mmHg; 79 min after intravenous acetazolamide, the intraocular pressure had resumed a normal level and the P/C ratio fallen to 0.23. The total time taken was 2 h 22 min.

The results for the eight patients in the simultaneous pilocarpine and phenylephrine group in whom additional pilocarpine was necessary to provoke angle closure are summarized in Fig. 3. All times were at least doubled—after 3 h 5 min the intraocular pressure began to rise (on average 34 mmHg) at a P/C ratio of 0.40 (having decreased from 0.43). After intravenous acetazolamide the

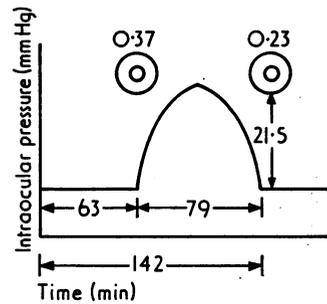


FIG. 2 Mean statistics of eyes provoked to angle closure by simultaneous instillation of pilocarpine and phenylephrine. P/C ratios at angle closure and termination of test are shown

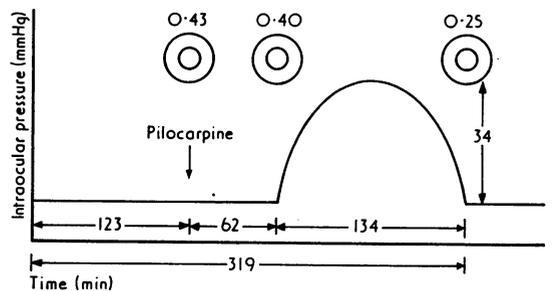


FIG. 3 Mean statistics of eyes provoked to angle closure by simultaneous instillation of pilocarpine and phenylephrine, in which additional pilocarpine was necessary. P/C ratios at instillation of pilocarpine, angle closure, and termination of test are shown

pressure resumed a normal level 2 h 14 min later and the P/C ratio had fallen to 0.25. The total time taken was 5 h 19 min.

The results for the nine patients in whom provocation with pilocarpine and phenylephrine was negative, but re-provocation with tropicamide was positive, are summarized in Fig. 4. After 47 min intraocular pressure began to increase (on average 22.7 mmHg) at a P/C ratio of 0.52. After intravenous acetazolamide, 77 min later, the pressure had fallen to normal at a P/C ratio of 0.3. The total time taken was 2 h 4 min.

Application of Student's *t* test to any P/C ratio (Table) from pilocarpine and phenylephrine provocative tests (positive or negative), in any combination taken two at a time, shows no significant difference. Similarly there is no significant difference between positive and negative tropicamide P/C ratios. There is however a significant difference between any pilocarpine and phenylephrine ratio and any tropicamide ratio (at the 1 per cent level).

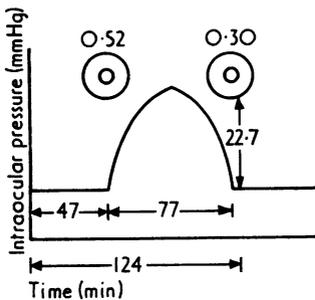


FIG. 4 Mean statistics of eyes provoked to angle closure by tropicamide. P/C ratios at angle closure and termination of test are shown

The mean age of the patients in the simultaneous pilocarpine and phenylephrine positive group was 62.8 years (range 34 to 80). For the group in whom all provocative tests were negative the mean age was 65.6 years (range 48 to 84). Application of Student's *t* test to these two means showed no significant difference.

## Discussion

The theoretical and experimental basis for this approach to provocative testing has been discussed in previous papers (Mapstone, 1974a, b, c, 1976) and depends on the following considerations:

- The pupil blocking force—and therefore pupil block—is due mainly to the sphincter muscle.
- Angle closure most commonly occurs at around mid-dilatation.
- Hence to provoke angle closure the ideal situation would be a mid-dilated pupil in the presence of increased sphincter activity. This is achieved by instilling phenylephrine and pilocarpine simultaneously. The former produces just sufficient dilatation to allow enhanced sphincter activity—produced by pilocarpine—to increase pupil block. The pressure of aqueous in the posterior chamber then 'pushes' a lax iris on to the cornea and closes the angle.
- It has also been shown that additional pilocarpine—after the simultaneous instillation of pilocarpine and phenylephrine—can precipitate angle closure by a mechanism independent of a significant change in sphincter

Table Mean statistics obtained during provocative testing

Test	Pilocarpine and phenylephrine positive	Pilocarpine and phenylephrine pilocarpine positive	Pilocarpine and phenylephrine negative tropicamide positive	Pilocarpine and phenylephrine negative tropicamide negative
Number of eyes	66	8	9	36
Time between start of test and rise in pressure (min)	63	185	47	—
Time between second pilocarpine instillation and rise in pressure	—	62	—	—
Rate of rise in pressure (mmHg/min)	1 in 3.7	1 in 1.8	1 in 4.5	—
Increase in pressure (mmHg)	21.5	34	22.7	—
Total time taken (min)	142	319	175	—
P/C ratio at angle closure	0.37	0.40	0.52	—
P/C ratio at second pilocarpine instillation	—	0.43	—	—
P/C ratio at end	0.23	0.25	0.3	—
Maximum P/C ratio with pilocarpine and phenylephrine	0.37	0.43	0.37	0.38
Maximum P/C ratio with tropicamide	—	—	0.52	0.51

activity. It was suggested that the additional mechanism was an increase in trabecular meshwork outflow 'pulling' the iris on to the cornea.

- e. Finally, it was shown that in some eyes too much parasympathetic activity precludes the development of angle closure, but that, with a mid-dilated pupil obtained by parasympathetic inhibition (tropicamide), pupil block was sufficient to allow the pressure in the posterior chamber to 'push' the iris on to the cornea.

The remaining criteria for an ideal provocative scheme mentioned in the introduction are not completely fulfilled:

By no yardstick can the tests be considered difficult and 90 per cent are complete within 2½ h. There remain, however, 10 per cent (the simultaneous pilocarpine, phenylephrine, and additional pilocarpine group) in whom the test takes approximately 5 h—although basic ophthalmic care is necessary only after 3 h. No doubt these times could be shortened by measuring pressures more frequently. There has to date been one false negative (see below) and false positives are by their very nature impossible to prove—since a positive provocative test cannot be ignored. The question whether these tests are 'physiological'—that is, within the limits of the possible autonomic stress to which an eye may be exposed—must also be considered.

Parasympathetic inhibition and excitation present no problem since they have their clinical counterpart in the dark room and reading provocative tests. Combined maximal sympathetic and parasympathetic stimulation does however present difficulties. It is possible to conceive of situations in which this can happen—for example, reading a salacious novel—but does not constitute proof. Finally, there was no evidence to show that any eye lost vision or field as a result of a positive provocative test.

The significance of parasympathetic activity in precipitating angle closure is well illustrated by the results of provocative testing with simultaneous pilocarpine and phenylephrine. In the 66 eyes that developed closed-angle glaucoma, sphincter muscle activity was at a near maximum and the pupil mid-dilated, ideal conditions for developing 'push' closed-angle glaucoma. However, a further eight patients developed closed-angle glaucoma only after the instillation of a second dose of pilocarpine (Fig. 3). The change in pupil diameter (and hence pupil blocking force) was not statistically significant, so that an additional parasympathetic mechanism was necessary. It has already been suggested that an increase in trabecular meshwork outflow is the most probable result—in effect 'pulling' the iris on to the cornea.

That nine eyes developed a positive test with tropicamide but were negative with simultaneous pilocarpine and phenylephrine presents something of a paradox. There is a significant difference between the P/C ratios of eyes at angle closure induced by pilocarpine/phenylephrine and tropicamide. Furthermore, eyes that were positive with tropicamide had already responded negatively to pilocarpine/phenylephrine and, between the P/C ratios for (negative) pilocarpine/phenylephrine and (positive) tropicamide tests in the same eye, there was a significant difference. It is a necessary consequence, therefore, that in some anterior segments too much parasympathetic activity precludes the development of angle closure, the most probable explanation being that with a smaller pupil diameter the iris is too taut to become sufficiently *bombé* to close the angle. With tropicamide the pupil diameter is larger and the iris more lax, but pupil block significantly reduced. Nevertheless angle closure still occurs, and it must be concluded that in some eyes a minimal pupil blocking force is sufficient to produce angle closure—that is, this form of closed-angle glaucoma is precipitated by pupil block alone.

The 36 eyes in which all tests were negative form an interesting group. In five there was significant anisometropia with amblyopia although it was not always the more hypermetropic eye that developed an acute attack. As a group, however, there was no significant difference between the P/C ratios attained during provocative testing as compared with the positive groups; it is reasonable to conclude that autonomic drug delivery in all groups (positive and negative) was therefore the same. It could be argued that the anatomical peculiarities of these anterior segments were such that, no matter what the manipulation of the autonomic nervous system might be, angle closure would not develop. In particular, the shallowing of the anterior chamber with age that depends on lens growth is as yet insufficient. With the passage of time such a decrease will occur and then allow angle closure to develop. There is, however, no significant difference between the ages of positive and negative groups which, if present, would have supported the anatomical argument.

Finally, it could be asserted that there is no reason to suppose that these eyes will develop closed-angle glaucoma. Consequently, it was decided not to do prophylactic peripheral iridectomies nor to treat with miotics. The 36 eyes have been followed-up for a period of 1 to 7 years (mean follow-up 3 years), and to date, only one has developed acute closed-angle glaucoma 3 months after provocative tests were done. Throughout the period of follow-up each eye has been re-provoked, at roughly yearly intervals, with tropicamide and

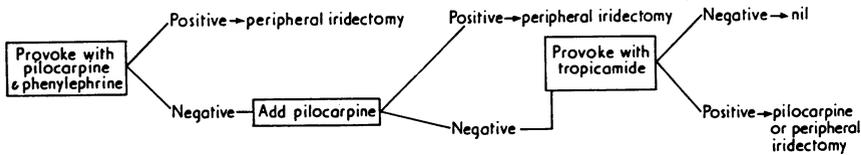


FIG. 5 Provocative test scheme

simultaneous pilocarpine/phenylephrine alternately. Data obtained from the series by Lowe (1962) indicate that at least 12 eyes should have developed acute attacks if they, as a group, did not differ from other contralateral eyes at risk. The evidence is by no means conclusive, but it seems reasonable to extend both the period of follow-up and the number of eyes.

Published series indicate that not all eyes at risk subsequently develop closed-angle glaucoma—for example, Adams (1955) 46 per cent, Kronfeld (1956) 50 per cent, Winter (1955) 32 per cent, Bain (1957) 47 per cent, and Lowe (1962) 49 per cent. It would seem, however, that a follow-up period of 10 years is necessary before the true predictive value of a provocative test scheme can be determined. The negative results in the 36 patients described here indicate only that there is no pressing urgency for iridectomy, not that iridectomy is unnecessary. Indeed, it would be unwise to ignore evidence that routine iridectomy in contralateral eyes is—in general—the more prudent of the alternatives (Blaxter and Chatterjee, 1960; Douglas and Strachan, 1967). The intention is not to question that evidence, but to delineate a group of patients who have a high probability of developing closed-angle glaucoma yet do not develop positive provocative tests. The prospective study of these patients may eventually provide information of great relevance to the management of eyes with (gonioscopically) narrow angles.

Again, the patients who are tropicamide positive but phenylephrine/pilocarpine negative form an interesting group, in whom it is reasonable to suppose that too much parasympathetic activity

precludes the development of closed-angle glaucoma. Logically, therefore, the use of pilocarpine would be an effective prophylactic and an iridectomy would be unnecessary.

A suggested scheme for provocative testing is therefore as follows (Fig. 5):

1. All eyes at risk are provoked with simultaneous pilocarpine and phenylephrine. If the test is positive, a peripheral iridectomy is done.
2. If after 2 h the test is negative then additional pilocarpine is instilled. If the result is positive, a peripheral iridectomy is done.
3. If the result is negative, re-provoke with tropicamide. If this is negative no treatment is indicated but follow-up is required. If the result is positive an iridectomy should be done or pilocarpine prescribed.

### Summary

Altogether 119 eyes at risk of developing closed-angle glaucoma were provoked with simultaneous pilocarpine and phenylephrine; of these 74 developed closed-angle glaucoma. The remaining 45 eyes were re-provoked with tropicamide and a further nine developed closed-angle glaucoma.

The 36 eyes in which all tests were negative were given no treatment and have been observed for a period of 1 to 7 years (mean 3 years). One has developed closed-angle glaucoma.

A scheme for provoking eyes at risk of developing closed-angle glaucoma is described.

I should like to thank colleagues who referred patients, Mr R. McBride for preparing the diagrams, and Miss E. Grogan for secretarial help.

### References

- ADAMS, S. T. (1955) *Trans. Canad. ophthal. Soc.*, **7**, 227  
 BAIN, W. E. S. (1957) *Brit. J. Ophthal.*, **41**, 193  
 BLAXTER, P. L., and CHATTERJEE, S. (1960) *Ibid.*, **44**, 114  
 DOUGLAS, W. H. G., and STRACHAN, I. M. (1967) *Ibid.*, **51**, 459  
 KRONFELD, P. C. (1956) See R. N. Shaffer, A review of angle-closure glaucoma, p. 20, in 'Glaucoma' ed. F. W. Newell (Trans. 1st Conf. Glaucoma, Princeton, N.J., 1955)  
 LOWE, R. F. (1962) *Brit. J. Ophthal.*, **46**, 641  
 MAPSTONE, R. (1974a) *Ibid.*, **58**, 36  
 ——— (1974b) *Ibid.*, **58**, 41  
 ——— (1974c) *Ibid.*, **58**, 46  
 ——— (1976) *Ibid.*, **60**, 120  
 VAN HERRICK, W., and SHAFFER, R. N. (1969) In 'Proceedings of the 1st South African International Ophthalmological Symposium, 1968', ed. M. H. Luntz, p. 137. Butterworths, Durban  
 WINTER, F. C. (1955) *Amer. J. Ophthal.*, **40**, 557