

# Dilating dangerous pupils

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**SUMMARY** Altogether 85 eyes from patients at risk to the development of closed-angle glaucoma were dilated with either parasympatholytic or sympathomimetic drugs. Of 21 eyes dilated with cyclopentolate  $\frac{1}{2}\%$ , 9 developed angle closure and a significantly raised pressure at some stage during dilatation and subsequent miosis. Of 58 eyes dilated with tropicamide  $\frac{1}{2}\%$ , 19 developed angle closure and a significantly raised pressure during dilatation. Treatment with intravenous acetazolamide and pilocarpine rapidly returned pressure to normal levels. Six eyes that had previously had a positive provocative test with simultaneous pilocarpine and phenylephrine were safely dilated with phenylephrine alone. Subsequent miosis with pilocarpine produced closed-angle glaucoma in all eyes.

The significance of these observations is explained and discussed, and it is suggested that high-risk eyes should never be dilated with cyclopentolate. Tropicamide is safe if elementary precautions are observed. Safest of all, however, is phenylephrine-induced mydriasis and subsequent miosis with thymoxamine drops  $\frac{1}{2}\%$ .

Pupillary dilatation is potentially dangerous, since a variable proportion of eyes at risk to closed-angle glaucoma develop a rise in pressure of 8 mmHg or more. A much smaller percentage of narrow-angle eyes with no relevant history will respond similarly. Given a *particular* eye with a narrow angle, how can the dangers be minimised if the pupil must be dilated?

Gonioscopy is of no help, since it gives a subjective assessment of grades of narrowness. While it is intuitively obvious that the narrower the angle the greater is the probability of closure, there is no published evidence to show that angle appearance is a reliable indicator of future behaviour on dilatation. The most that can be known before dilating a *particular* pupil is that there exists a certain probability that that eye will develop closed-angle glaucoma. Anyone who dilates pupils therefore is taking a chance.

Given this situation, the clinician has two options. Firstly, he can accept that a risk is present, explain it, measure it, and devise a scheme for treating the eye that develops closed-angle glaucoma so that any possible damage is reduced to a minimum. Secondly, he can refuse to accept the risk and devise a method whereby *any* pupil can be safely dilated. Both options are explored in this paper.

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## Material and methods

(1) Twenty-one eyes at risk to the development of closed-angle glaucoma (because the contralateral eye had had an episode of acute closed-angle glaucoma) were on no treatment. All had been previously provoked with simultaneous pilocarpine and phenylephrine, and 17 had positive provocative tests (that is, a pressure increase of greater than 8 mmHg).

They were reprovoked as follows: At zero hours an anterior segment photograph was taken, intraocular pressure measured, and one drop of cyclopentolate  $\frac{1}{2}\%$  instilled. Thereafter at approximately  $\frac{3}{4}$ -hourly intervals pressure was recorded and an anterior segment photograph taken. If after 2 hours had elapsed pressure had not increased significantly, pilocarpine drops 2% were instilled at approximately  $\frac{3}{4}$ -hourly intervals for at least 3 hours, up to a maximum of 6. As soon as intraocular pressure began to increase significantly pilocarpine 2% was instilled and, after a variable period, intravenous acetazolamide 500 mg too. Thereafter the test was continued until pressure was normal or until it was decided to do a peripheral iridectomy with pressures recorded and anterior segment photographs taken at approximately  $\frac{3}{4}$ -hourly intervals. Subsequently, slides were projected and P/C ratios (P = pupillary, C = corneal diameters) calculated in the horizontal meridian.

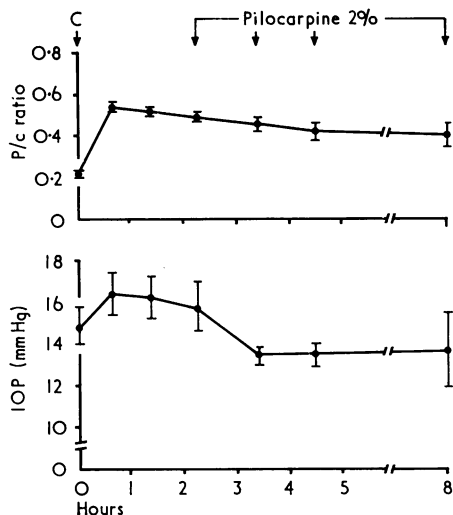


Fig. 1 Response of 12 eyes to dilatation with cyclopentolate drops  $\frac{1}{2}\%$ , no significant increase in pressure developed. C = cyclopentolate, P/C ratio = pupillary and corneal diameters in horizontal meridian. Mean and standard error recorded

(2) Fifty-eight eyes from 49 patients with either primary closed-angle glaucoma in the contralateral eye (40) or intermittent closed-angle glaucoma in one or both eyes (9) had provocative tests with pilocarpine and phenylephrine; 70% were positive. At a later date they were provoked as follows: At zero hours an anterior segment photograph was taken and tropicamide drops  $\frac{1}{2}\%$  were instilled. At approximately  $\frac{1}{2}$ -hourly intervals thereafter pressure was recorded and an anterior segment photograph taken. If after 2 hours intraocular pressure had not increased, pilocarpine 2% was instilled and the test terminated. In eyes that developed a significant rise in pressure intravenous acetazolamide 500 mg and pilocarpine drops 2%  $\times 1$  were instilled; pressure recordings and anterior segment photographs were taken until pressure was back to normal levels.

(3) Six eyes from 6 patients with closed-angle glaucoma in the contralateral eye had positive provocative tests with simultaneous pilocarpine and phenylephrine. Subsequently they were dilated with phenylephrine, and the pupil was returned to miosis by the instillation of thymoxamine drops  $\frac{1}{2}\%$  without the development of a significant pressure increase (see Mapstone, 1974b). The same 6 eyes were then provoked as follows: At zero hours pressure was recorded, an anterior segment photograph taken, and phenylephrine drops 10% were instilled. One hour later this was repeated. Two hours after the start of the test an anterior segment photograph was taken, pressure recorded, and

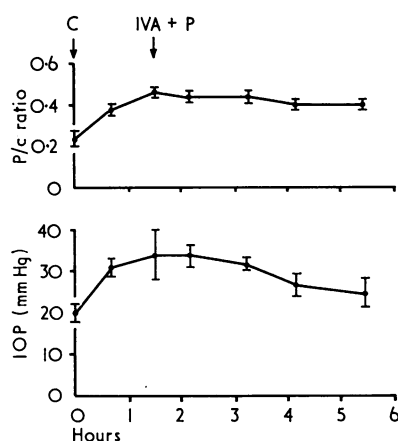


Fig. 2 Response of 4 eyes to dilatation with cyclopentolate drops  $\frac{1}{2}\%$ , a significant pressure increase occurred within  $\frac{1}{2}$  hour—as the pupil moved up to mid-dilatation. C = cyclopentolate, IVA = intravenous acetazolamide, P = pilocarpine. Mean and standard error recorded

pilocarpine drops 2% were instilled. As soon as pressure had increased significantly intravenous acetazolamide 500 mg, pilocarpine drops 2%, and thymoxamine drops  $\frac{1}{2}\%$  were instilled. The test was continued until pressures had returned to normal levels.

## Results

### 21 EYES DILATED WITH CYCLOPENTOLATE

Twelve eyes developed no significant increase in pressure measured over an 8-hour period. Fig. 1 records the results and shows that repeated doses of pilocarpine 2% had little effect on pupil diameter. All 12 were seen 24 hours later, and none had developed a significant rise in pressure.

Nine eyes developed a significant increase in pressure but there were three distinct patterns of response:

(a) In 4 eyes (Fig. 2) pressure had increased significantly after 36 minutes (from a mean of 19.3 to a mean of 30.5 mmHg);  $1\frac{1}{2}$  hours from the start intravenous acetazolamide and pilocarpine were given, but even after  $5\frac{1}{2}$  hours the mean pressure was still 25.3 mmHg. In addition pupil diameter was little affected.

(b) In 2 eyes the pupil moved rapidly up to wide dilatation and there remained for 3 hours with no change in pressure. As the pupil moved down to mid-dilatation pressure increased significantly. An example is shown in Fig. 3.

(c) In 3 eyes the pattern of response was a combination of a and b. As the pupil moved up to

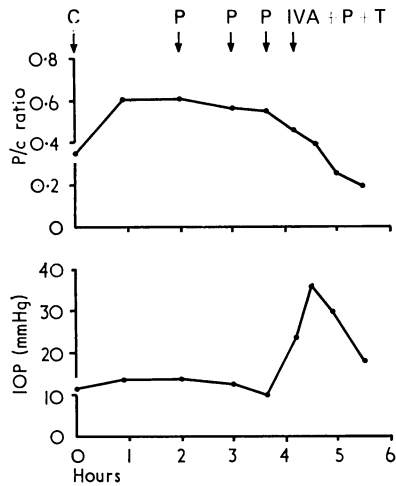


Fig. 3 Response of 1 eye to dilatation with cyclopentolate drops  $\frac{1}{2}\%$ . As the pupil moved to wide dilatation no significant change in pressure occurred. After 4 hours as the pupil moved down to mid-dilatation pressure increased. C = cyclopentolate, P = pilocarpine, T = thymoxamine, IVA = intravenous acetazolamide

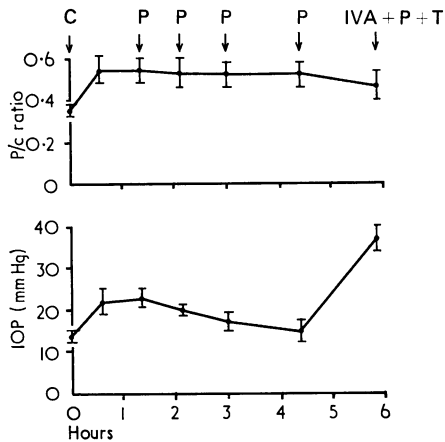


Fig. 4 Response of 3 eyes to dilatation with cyclopentolate drops  $\frac{1}{2}\%$ . A significant pressure increase occurs as the pupil moves up to wide dilatation. In that position pressure falls to normal levels, rising again as the pupil moves down towards mid-dilatation. C = cyclopentolate, P = pilocarpine, T = thymoxamine, IVA = intravenous acetazolamide

wide dilatation a significant increase in pressure occurred (from a mean of 14.3 to a mean of 23 mmHg—Fig. 4). At wide dilatation pressure fell to normal, and as the pupil moved down towards mid-dilatation pressure again increased. One patient is described in detail:

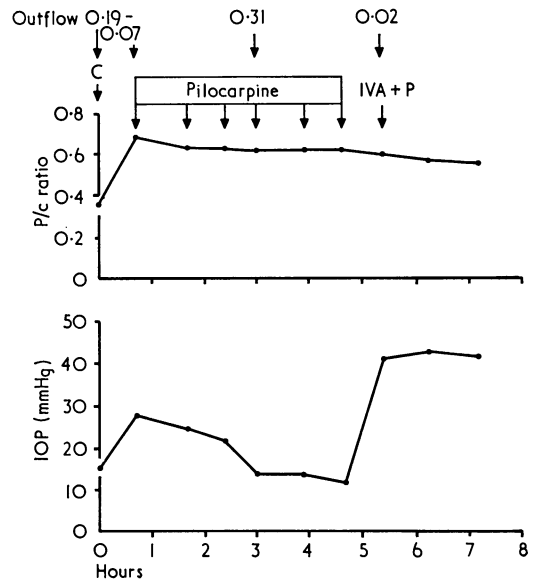


Fig. 5 Response of 1 eye to dilatation with cyclopentolate drops  $\frac{1}{2}\%$  (see text)

Female age 56, no symptoms, but her mother had closed-angle glaucoma. Provocative tests in this patient with pilocarpine and phenylephrine were negative but with tropicamide positive (see Mapstone, 1976b). She was reprovoked with cyclopentolate, with the result shown in Fig. 5. As the pupil moved up to wide dilatation outflow fell from 0.19 to 0.07;  $2\frac{1}{2}$  hours later pressure was 14 mmHg and the corneal diameter had increased to 0.31. However,  $5\frac{1}{2}$  hours after the start of the test the corneal diameter had decreased to 0.02 and pressure increased to 42 mmHg.

58 EYES DILATED WITH TROPICAMIDE

Thirty-nine eyes developed no significant increase in pressure measured over a 2-hour period (Fig. 6). The instillation of pilocarpine 2% at this point produced a fall in pupil diameter over the next hour.

Nineteen eyes developed a significant increase in pressure. Fig. 7 records the results and shows that after 45 minutes pressure increased from a mean of 17.9 to a mean of 30.4 mmHg. These eyes were left untreated for an average of 30 minutes. Intravenous acetazolamide 500 mg and pilocarpine 2% returned the pressure of all eyes to normal within  $1\frac{1}{2}$  hours.

In 9 eyes outflow facility was measured at the start of the test and at the first recorded significant increase in pressure. The results are recorded in Table 1. They show that when a significant pressure increase had occurred substantial outflow facilities remained.

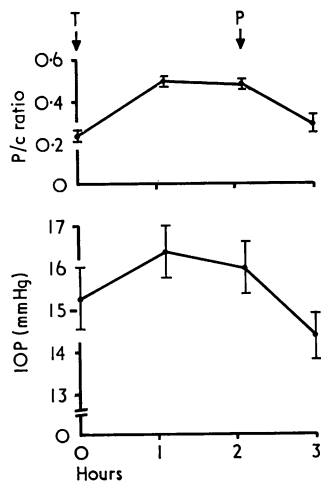


Fig. 6. Response of 39 eyes to dilatation with tropicamide drops  $\frac{1}{2}\%$ . No significant pressure increase developed. Mean and standard error recorded. T = tropicamide, P = pilocarpine

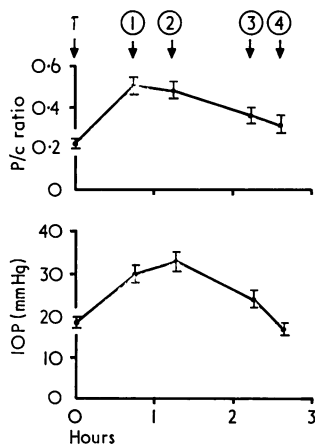


Fig. 7. Response of 19 eyes to dilatation with tropicamide drops  $\frac{1}{2}\%$ . 1 = mean time interval for a significant pressure increase to occur. 2 = mean time interval at which intravenous acetazolamide and pilocarpine drops were given. 3 = mean pressure 1 hour after treatment given. 4 = mean time interval for pressure to return to normal. T = tropicamide

#### 6 EYES DILATED WITH PHENYLEPHRINE AND MIOSED WITH PILOCARPINE

Fig. 8 records the results and shows that pressure remained little affected by phenylephrine mydriasis as long as the pupil was kept widely dilated. As soon as pilocarpine-induced miosis occurred, pressure increased from a mean of 14.2 to a mean of 35.3 mmHg. Treatment rapidly returned the eyes to a normal state.

Table 1 Outflow values in 9 eyes dilated with tropicamide.  $C_1$  = outflow at start of test.  $C_2$  = outflow at first recorded significant increase in pressure

$C_1$	$C_2$	At time (minutes)	Increase in IOP (mmHg)
0.20	0.07	40	15
0.09	0.06	40	10
0.19	0.11	37	10
0.20	0.10	57	18
0.18	0.10	48	8
0.23	0.11	40	9
0.19	0.10	30	14
0.21	0.22	32	16
0.18	0.05	45	12
Mean	0.19	0.10	41
s.e.m.	0.01	0.02	4.2

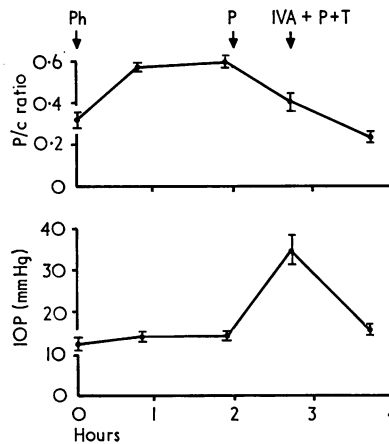


Fig. 8 Response of 6 eyes to dilatation with phenylephrine drops 10% and subsequent miosis with pilocarpine drops 2%. Pressure increased as the pupil moved down from wide to mid-dilatation. Mean and standard error recorded. Ph = phenylephrine, P = pilocarpine, T = thymoxamine, IVA = intravenous acetazolamide

#### Discussion

Given a suitably predisposed anterior segment two main variables determine the development of angle closure—namely, pupil diameter and the size of the pupil block force. The variation of the sphincter pupil block force during normal pupillary activity is shown in Fig. 9 (Mapstone, 1974c). It is apparent that a pupil can attain three main positions:

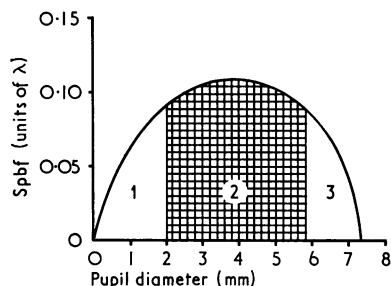


Fig. 9 Variation of sphincter pupil block force during the pupillary play of the light reflex. Spbf = sphincter pupil block force.  $\lambda$  = modulus of elasticity of iris stroma. 1 = miosis, 2 = mid-dilatation, 3 = wide dilatation

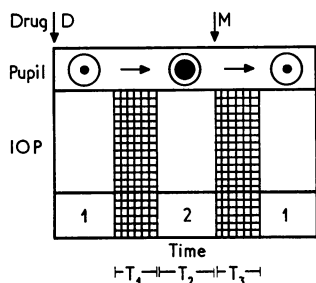


Fig. 10 Diagram illustrating the pupillary response to a weak mydriatic (D) and subsequent miosis (M). 1 = miosis, 2 = mid-dilatation. Cross-hatched areas represent intermediate states with the pupil moving from one main position to another. T = time intervals (see text)

(1) Miosis with a taut iris and small pupil block force; (2) mid-dilatation with a lax iris and large pupil block force; (3) wide dilatation with a compressed iris and small pupil block force.

Experimentally, (1) and (3) are not associated with angle closure, while (2) is the position of greatest risk (Mapstone, 1974a, b, c).

Figs. 10 and 11 illustrate events that can happen during pupillary dilatation and subsequent miosis. If a weak dilator drug is used (Fig. 10) the pupil moves from miosis (1) to mid-dilatation (2); a miotic then moves the pupil back to (1). There are therefore two situations in which angle closure can occur, during interval  $T_1$  as the pupil moves up to mid-dilatation and during interval  $T_2$  while the pupil is actually at mid-dilatation. Conversely there are two situations in which the angle can open, during interval  $T_3$  as the pupil moves down to miosis or while the pupil is back in position (1) miosed.

With a strong dilator drug (Fig. 11) the pupil moves from miosis (1) to mid-dilatation (2) to wide dilatation (3); the instillation of a miotic then moves the pupil back down to (1) again. In this instance

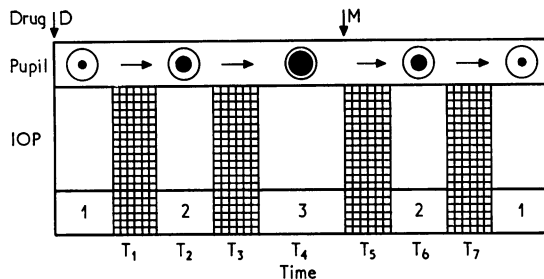


Fig. 11 Diagram illustrating the pupillary response to a strong mydriatic (D) and subsequent miosis (M). 1 = miosis, 2 = mid-dilatation, 3 = wide dilatation. T = time intervals (see text)

there are four situations in which angle closure can occur: during interval  $T_1$ , as the pupil moves up to mid-dilatation; during interval  $T_2$ , while the pupil is mid-dilated moving up; during  $T_5$  as the pupil moves down to mid-dilatation; and during  $T_6$  while at mid-dilatation moving down. Conversely there are four situations in which the angle can open: during  $T_3$  as the pupil moves from mid to wide dilatation; during  $T_4$  at wide dilatation; during  $T_7$  as the pupil moves down to miosis and finally at miosis.

With this as a model the patterns of behaviour described in the results can be interpreted as follows: (1) The pupil moves from miosis to wide dilatation and back to miosis with no significant change in pressure. Twelve eyes dilated with cyclopentolate behaved in this manner (Fig. 1). It has also been shown that pupils at risk dilated with phenylephrine and then miosed with thymoxamine show a similar response (Mapstone, 1974b). Some pupils dilated with tropicamide behaved in a like manner, others moved to mid-dilatation and then back to miosis, with 67% of the total showing no significant increase in pressure (Fig. 6). At no stage, therefore, did these eyes develop sufficient angle closure for a sufficient period to produce a significant pressure rise.

(2) The pupil moves from miosis to mid-dilatation, during which sufficient of the angle closes to produce a significant pressure increase (Fig. 12). Four eyes dilated with cyclopentolate (Fig. 2) and 19 eyes dilated with tropicamide (Fig. 7) show this pattern. Miotic treatment with or without acetazolamide then returns the pupil rapidly (tropicamide-dilated) or slowly (cyclopentolate-dilated) back to miosis. Two points are worth mentioning. Firstly, the recorded outflow values (see Table 1) in tropicamide-positive tests indicate that much of the angle remains open (cf. eyes provoked with pilocarpine and phenylephrine—Mapstone, 1977). Secondly, the cyclopentolate-dilated pupils achieved a P/C ratio

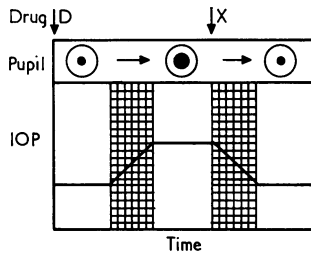


Fig. 12 Diagram illustrating pupillary and pressure responses in eyes that develop a significant increase in pressure as the pupil moves up to mid-dilatation. At X acetazolamide and pilocarpine are given, and pressure decreases as the pupil moves down to miosis. D = mydriatic

of 0.46—less than other pupils dilated with this drug (cf. Figs. 1, 2, 3, and 4).

The time taken for the pupil to move to mid-dilatation and develop a positive provocative test is clinically important. Fifty-eight eyes were dilated with tropicamide, and 19 (33%) developed a significant pressure increase (greater than 8 mmHg) within 45 minutes (standard deviation 9 minutes)—Fig. 7. Treatment brought the pressure back to normal within 2½ hours of the start of the test. In the 39 eyes that had no significant pressure increase within the first hour, keeping the pupil at mid-dilatation for an additional hour produced no more positive results (Fig. 6). The practical consequence is that if an eye at risk develops closed-angle glaucoma by dilatation with tropicamide it will do so within the first hour.

If after that time pressure has not increased significantly, it is safe to dismiss the patient with no treatment. Miotics are unnecessary and may even precipitate angle closure in mid-dilatation (the significance of angle closure precipitated by pilocarpine in this situation has been discussed elsewhere (Mapstone, 1974, 1976)).

(3) The pupil moves rapidly (within 1 hour) from miosis to wide dilatation with no increase in pressure. Movement of the pupil back to mid-dilatation with pilocarpine produces angle closure and a significant increase in pressure (Fig. 13). Further treatment then moves the pupil back to miosis, the angle opens, and pressure falls. This pattern occurred in two situations: (a) Two eyes dilated with cyclopentolate (Fig. 3) developed a raised pressure as the pupil moved down to mid-dilatation with pilocarpine. Further treatment brought pressure back to normal. (b) Six eyes dilated with phenylephrine moved rapidly from position (1) to (3) and were kept there for nearly 2 hours without developing a pressure increase (Fig. 8). Pilocarpine then moved the pupil

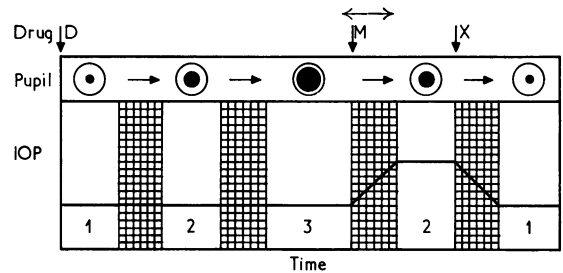


Fig. 13. Diagram illustrating pupillary and pressure responses in eyes that develop a significant increase in pressure as the pupil moves down from wide to mid-dilatation. At X acetazolamide and pilocarpine are given, and pressure decreases as the pupil moves down to miosis. No pressure increase occurs as the pupil moves from miosis to wide-dilatation. D = mydriatic, M = miotic

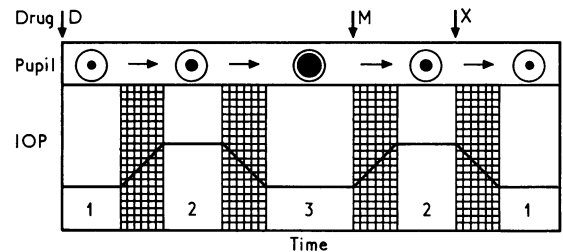


Fig. 14 Diagram illustrating pupillary and pressure responses in eyes that develop a significant increase in pressure as the pupil moves up from miosis to mid-dilatation and again as the pupil moves down from wide to mid-dilatation. During movement from 2 to 3 (going up) and from 2 to 1 (going down) pressure decreased to normal levels. D = mydriatic, M = miotic

down to mid-dilatation, the angle closed, and pressure increased. Subsequent treatment miosed the pupil and pressure fell to normal levels. It is relevant that all 6 eyes had been dilated with phenylephrine and miosed with thymoxamine without a significant increase in pressure. Pilocarpine-induced miosis of a phenylephrine-dilated pupil is therefore dangerous: it is simply a pilocarpine/phenylephrine provocative test in reverse (Mapstone, 1976a).

(4) The final pattern is shown in Fig. 14. The pupil moves from (1) to (2) and develops a significant pressure increase. Further dilatation to position (3) opens the angle and pressure falls to normal. Subsequent miosis moves the pupil back down from (3) to (2) and pressure increases again. Three eyes dilated with cyclopentolate behaved in this manner, the second increase in pressure occurring after the lapse of nearly 6 hours. This proved to be a difficult glaucoma to treat. A combination of ischaemia and drug-induced pupillary inertia left the pupil at mid-

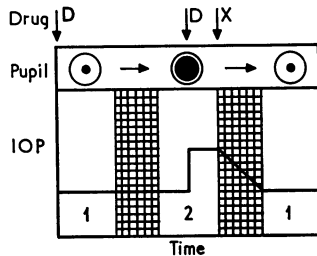


Fig. 15 Diagram illustrating pupillary and pressure responses in eyes that develop a significant increase in pressure at mid-dilatation. At zero time pilocarpine and phenylephrine (D) are instilled, the pupil moves to mid-dilatation with no increase in pressure. At mid-dilatation a second dose of pilocarpine and phenylephrine produces a pressure increase. Treatment (X) moves the pupil down to miosis and pressure returns to normal levels

dilatation, and, while mannitol temporarily reduced pressure, it rapidly rose again. All three needed iridectomies within 24 hours.

Three other patterns deserve mention: (5) Pilocarpine and phenylephrine instilled simultaneously may move the pupil from (1) to (2) without developing a pressure increase (Fig. 15). If at this point more pilocarpine and phenylephrine are instilled then in some eyes closed-angle glaucoma develops. Treatment moves the pupil back to position (1) and pressure returns to normal. This is the pilocarpine/phenylephrine provocative test and has been discussed elsewhere (Mapstone, 1974, 1976).

(6) Becker and Thompson (1958) showed that some angles can occlude on pupillary dilatation, yet no pressure increase is demonstrated. They suggested that this was because insufficient time had elapsed for pressure to increase. In a previous paper (Mapstone, 1977) it was shown that significant reductions in outflow can precede a rise in pressure. If the test is continued, almost complete angle closure and rise in pressure then occur. An extreme example is shown in Fig. 16, where complete (gonioscopic) angle closure preceded a rise in pressure by 2 hours. No pressure increase is therefore compatible with angle closure and can occur as the pupil moves from (Fig. 11) position (1) to (2), at (2), and as the pupil moves from (3) to (2).

(7) The converse picture is provided by published reports (Lee, 1958; Hill, 1968; Haddad *et al.*, 1970; Mapstone, 1974b) that phenylephrine can produce a significant increase in pressure yet the angle is unequivocally open to gonioscopy. This can occur in two situations: (a) A pupil moves (Fig. 11) from (1) to (3), developing angle closure and a rise in pressure on the way. Having arrived at (3) the angle opens, and there is now the paradox of a

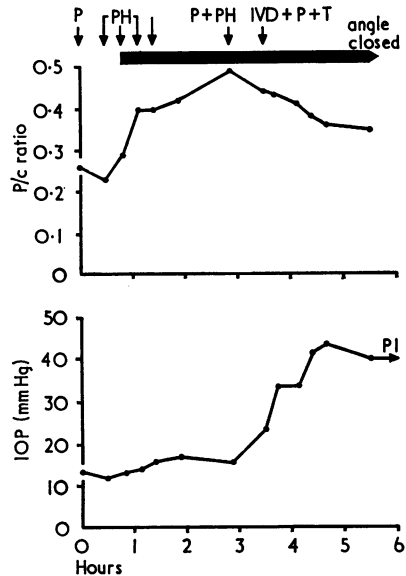


Fig. 16 Response of 1 eye to provocative testing with pilocarpine and phenylephrine. The angle was closed after  $\frac{3}{4}$  hour but a pressure increase did not occur until 3 hours had elapsed. P = pilocarpine, Ph = phenylephrine, T = thymoxamine, IVA = intravenous acetazolamide, PI = peripheral iridectomy

raised pressure and open angle. (b) Again a pupil can move (Fig. 13) from (3) down to (1), developing a raised pressure on the way. At (1) the angle is open and the paradox again present. A conventional gonioscopic interpretation would allow of no logical explanation. But by taking into account pupillary position and antecedent activity a ready interpretation is possible. The patient described by Mapstone (1974b) has had a peripheral iridectomy; reprovocation with phenylephrine subsequently produced no increase in pressure.

On the basis of the observations detailed above, therefore, it is suggested that the dilatation of narrow-angle eyes, for fundus inspection, be determined by the following considerations:

(1) Eyes at risk to the development of closed-angle glaucoma should never be dilated with cyclopentolate. If they are, then a minimum period of 24 hours' observation in hospital is necessary. Prescribing acetazolamide does not prevent angle closure (Mapstone, 1974).

(2) A pupil dilated to wide mydriasis by phenylephrine is in a safe position. Miosis with pilocarpine is highly dangerous, and a significant proportion of eyes at risk will develop closed-angle glaucoma. On the other hand miosis with thymoxamine is safe, since it is complete within  $\frac{1}{2}$  hour (Mapstone, 1970, 1974). This method has been used in more than

4000 eyes to date without the development of acute glaucoma.

(3) Tropicamide mydriasis is safe if the following procedure is adopted: (a) All eyes at risk can be dilated with tropicamide if the patient is observed for 1 hour after instillation of drops. (b) If pressure has not risen significantly within 1 hour, the probabilities of that event occurring are low indeed (not once in 58 eyes at risk). (c) As soon as pressure increases significantly intravenous acetazolamide 500 mg and pilocarpine 2% $\times$ 1 rapidly returns pressure to normal levels (usually in just over the hour, never longer than 1½ hours). This is so with tropicamide because angle closure is rarely complete, and significant outflow facilities remain in the presence of a raised pressure.

(4) Finally, a raised pressure caused by an angle-closing mechanism is quite compatible with a (gonioscopically) open angle. So, too, is a (gonioscopically) closed angle compatible with no pressure increase. What has happened and is happening to the pupil, and for how long, are the important considerations.

I thank colleagues who referred patients for study; Wm. Warner Ltd for supplies of thymoxamine; Mrs E. Tubb for secretarial help; and Mr R. McBride for preparing diagrams.

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