

Closed-angle glaucoma. Experimental results

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If the event of angle closure (AC)—and hence closed-angle glaucoma (CAG)—is related to the size of the pupil-blocking force (pbf), then variations in the latter produced by autonomic drugs would have predictable results. Theoretical conclusions are described in a previous communication (Mapstone, 1974); the purpose of this paper is to submit these to experimental test.

Material and methods

(1) 27 patients who had acute CAG in one eye, and three patients with subacute CAG (in one bilateral) were treated prophylactically with thymoxamine drops 0.5 per cent. twice daily (Mapstone, 1970). Both eyes in the subacute group were treated, and the 27 eyes in the acute group that had not had an acute attack, *i.e.* 33 eyes in total. The period of treatment varied from 1 to 3 years.

(2) In ten patients with acute CAG in one eye, the effect of 2 per cent. pilocarpine in the contralateral eye was measured over a 2-hr period. Intraocular pressure was measured at $\frac{1}{2}$ -hr intervals and gonioscopy performed at 1 hr.

(3) The same ten eyes were provoked using a combination of 2 per cent. pilocarpine and 10 per cent. phenylephrine. At zero hours intraocular pressure was measured, a photograph taken of the anterior segment, and pilocarpine 2 per cent. plus phenylephrine 10 per cent. instilled at 1 min. intervals $\times 3$. Intraocular pressure was measured at approximately $\frac{1}{2}$ -hr intervals thereafter, an anterior segment photograph taken and phenylephrine instilled. If, after 2 hrs, pressure had not increased additional pilocarpine 2 per cent. $\times 3$ at 1-min. intervals was instilled. As soon as intraocular pressure increased the patient was treated with intravenous Diamox 500 mg., pilocarpine drops 2 per cent. and thymoxamine drops 0.5 per cent. stat, and at $\frac{1}{4}$ -hrly intervals. Subsequently the slides were projected and pupil diameter/corneal diameter ratios calculated (P/C ratio).

(4) On another day, after pilocarpine had been stopped for 1 week, the same ten eyes were dilated with cyclopentolate drops 1 per cent. and thymoxamine drops 0.5 per cent. at 1-min. intervals $\times 3$. Intraocular pressure was measured and anterior segment photographs were taken—again at $\frac{1}{2}$ -hr intervals. The pupils were kept dilated for at least 2 hrs. Slides were subsequently projected and P/C ratios calculated.

(5) The same ten eyes—again after no treatment for 1 week—were dilated with 10 per cent. phenylephrine at 1-min. intervals $\times 3$. Dilatation was maintained with phenylephrine at $\frac{1}{2}$ -hr intervals. Intraocular pressure was measured and anterior segment photographs taken at approximately $\frac{1}{2}$ -hr intervals. The pupils were kept dilated for at least 2 hrs. Slides were subsequently projected and P/C ratios calculated.

Results

(1) PROPHYLACTIC THYMOXAMINE

All patients had a relative miosis with a mobile pupil.

(a) *Subacute group*

Episodes of subacute CAG were not controlled and all six eyes have now had prophylactic peripheral iridectomies.

(b) *Acute group*

Three patients developed acute closed-angle glaucoma, one 18 months, one 7 months, and one 4 months after treatment was started. 21 of the 27 eyes have now had peripheral iridectomies. Six patients have so far refused.

In addition five patients developed a contact dermatitis.

(2) PILOCARPINE

The intraocular pressures of the ten eyes after the instillation of pilocarpine were all within normal limits throughout the 2-hr period and no angle closed on gonioscopy.

(3) PILOCARPINE AND PHENYLEPHRINE

A typical sequence of events is illustrated in Fig. 1. In eight patients intraocular pressure had risen significantly and was back to normal within 1½ hrs. In one intraocular pressure was not back to within normal levels after 3½ hrs and an iridectomy was done. One other patient required further pilocarpine after 2 hrs before intraocular pressure became raised.

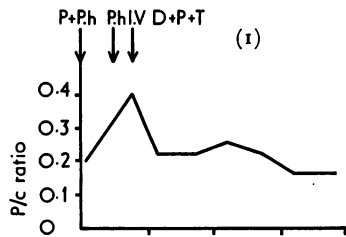


FIG. 1 *Precipitation of angle closure by simultaneous instillation of pilocarpine and phenylephrine*

P = pilocarpine

Ph = phenylephrine

T = thymoxamine

IVD = Intravenous Diamox

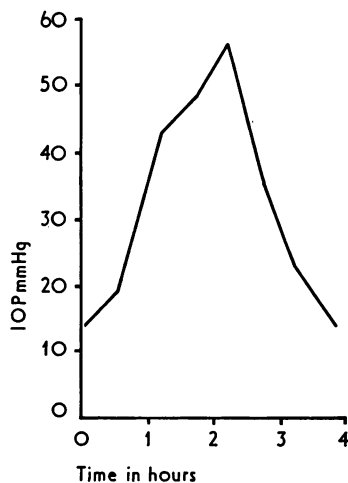
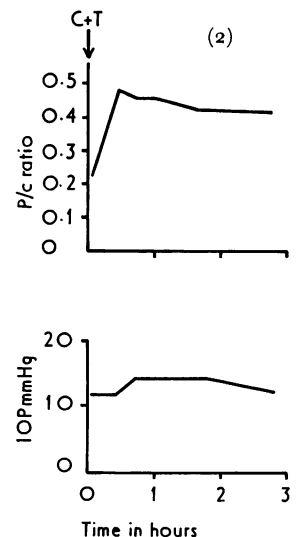


FIG. 2 *Effect of cyclopentolate and thymoxamine dilatation on intraocular pressure*

C = cyclopentolate

T = thymoxamine



(4) CYCLOPENTOLATE AND THYMOXAMINE

The intraocular pressure of all ten eyes remained within normal limits whilst the pupil was kept dilated. The behaviour of one eye is illustrated in Fig. 2.

(5) PHENYLEPHRINE

In nine eyes intraocular pressure remained within normal limits whilst the pupil was kept maximally dilated. One eye developed a significant rise in intraocular pressure (Fig. 3)—from 15 to 28 mm. Hg. This was not associated with angle closure and intraocular pressure slowly resumed a normal level although the P/C ratio remained 0.6.

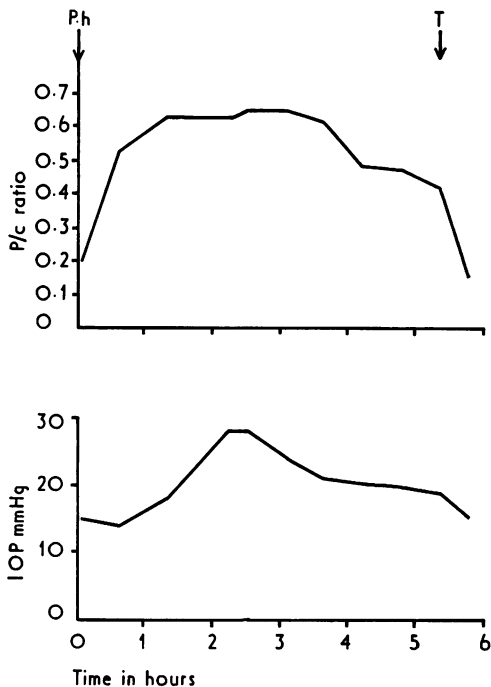


FIG. 3 Phenylephrine-induced mydriasis produced a significant rise in intraocular pressure in one patient. This was not associated with angle closure

Ph = phenylephrine

T = thymoxamine

Discussion

With the use of autonomic stimulators and inhibitors there are nine possible pupillary states that can be investigated (Table).

Table

	<i>S_o</i>	<i>S_n</i>	<i>S_m</i>	
<i>D_o</i>	Cyclopentolate Thymoxamine	Thymoxamine	Pilocarpine Thymoxamine	With autonomic drugs nine possible pupillary states can be investigated. <i>S_o</i> and <i>D_o</i> = S and D inhibited <i>S_n</i> and <i>D_n</i> = S and D contracting normally <i>S_m</i> and <i>D_m</i> = S and D contracting to a maximum
<i>D_n</i>	Cyclopentolate	Nil	Pilocarpine	
<i>D_m</i>	Cyclopentolate Phenylephrine	Phenylephrine	Pilocarpine Phenylephrine	

(1) *S_n D_n* represents the normal situation in which pupil size is governed largely by the light reflex. As the "normal state" is not associated with a closed angle there must be change in the anterior segment to produce AC. Effectively therefore autonomic activity changes.

(2) *S_m D_n* represents pilocarpine—parasympathetic—activity at a maximum in the presence of normal dilator tone. No angle closed and intraocular pressure fell, *i.e.* maximal parasympathetic activity in miosis was safe.

- (3) Sn Dm represents phenylephrine—sympathetic—activity at a maximum in the presence of normal sphincter tone. Excepting the eye with an atypical response, intraocular pressure remained within normal limits and no angle closed. Lee (1958), Hill (1968), and Haddad, Moyer, and Riley (1970) have also noted the pressure-elevating effect of phenylephrine in the presence of an open angle.
- (4) Sm Dm represents co-contraction of S and D, *i.e.* combined para- and sympathetic activity. In the ten patients included here, all developed a closed angle and rise in intraocular pressure. Their inclusion in this paper does not indicate the incidence of CAG in susceptible eyes provoked in this fashion, as they were taken from a larger group who had positive results. The conclusion is however the same, *viz.* co-contraction of S and D can provoke an acute attack.
- (5) Sn D_o represents thymoxamine, *i.e.* sympathetic inhibition in the presence of a normal parasympathetic. In this situation pbf is at a theoretical and experimental minimum. That three patients developed CAG, and subacute attacks were not prevented implies that AC can occur in the presence of a minimum pbf and sympathetic tone is not necessary.
- (6) S_oD_o represents cyclopentolate and thymoxamine, *i.e.* sympathetic and parasympathetic activity inhibited. Pbf is zero and no angles closed in the dilated position.
- (7) S_o Dn, Sm D_o, and S_o Dm represent similar situations to 6, 2, and 3 respectively and were not investigated.

A comparison of experimental results with theoretical prediction (Mapstone, 1974) shows that most of the latter are fulfilled:

- (1) Increasing pbf to a maximum by combined para- and sympathetic activity produced CAG.
- (2) A dilated pupil obtained by inhibiting both para-sympathetic (cyclopentolate) and sympathetic (thymoxamine) did not produce AC, *i.e.* reducing pbf to a theoretical zero was safe in the dilated position.
- (3) A dilated pupil obtained by maximal sympathetic activity in the presence of a normal sphincter was also safe. Theoretically, this would not be so if *D* and *E* made a significant contribution to pbf. In this group therefore only sphincter block occurred (Mapstone, 1974). *D* and *E* make a contribution, but it is negative, pulling the iris away from the lens and tending to break the block.
- (4) Maximal parasympathetic activity (pilocarpine) in the presence of a normal dilator did not produce AC, pbf is at a maximum and so too is iris stromal stretch, iris *bombé* is therefore insufficient to close the angle.

However, if AC is a function of pbf, it is a necessary consequence that a reduction of pbf to below normal levels, *i.e.* those obtaining during the pupillary play of the light reflex, should prevent the occurrence of CAG. Thymoxamine reduces pbf to a minimum, but acute and subacute CAG still occurred. It could be argued that with an atonic dilator the iris will become *bombé* more readily and that therefore a smaller pbf is effective in producing AC. This is negated by the occasional post-operative “peripheral iridectomy” that leaves an intact pigment epithelium. The myoepithelium becomes *bombé* through the gap, indicating that the major factor preventing iris *bombé* is the iris stroma. An extreme example, is a “complete iridectomy”, in which sphincter and stroma are excised, leaving an intact myoepithelium; the pigment layer remains flat, *i.e.*, in the absence of a sphincter, iris *bombé* is not possible.

It could also be asserted that, as pbf is at a maximum in miosis, thymoxamine created a dangerous situation. By the same token pilocarpine should have an identical effect—but no angle closed as a result of its use.

Finally, it could be argued that the postulated relationship between AC and pbf is incorrect, *i.e.* while pupil block is necessary for the event of AC (otherwise a peripheral iridectomy would not prevent it), it is not sufficient to explain the occurrence of CAG. Hence it is not a necessary consequence that increasing pbf to a maximum will result in AC, neither will its reduction to below normal levels prevent its occurrence. The experiments described show that reducing pbf (with thymoxamine) did not prevent AC, but an increase to a maximum (with pilocarpine and phenylephrine) did. It is relevant, however, that, whilst thymoxamine alone affects primarily pbf, pilocarpine has—besides increasing pbf—other potent angle-closure effects.

On the evidence available, therefore, a model for pupil block is as follows:

Pbf is due mainly to sphincter (S) block which, during the pupillary play of the light reflex, has the form shown in Fig. 4. The graph represents a quadratic function with equation $S = 0.6d - 0.008d^2$, where S = sphincter pbf and d = pupil diameter. The results indicate that variations in pbf alone do not explain AC which later can occur in the absence of dilator tone. This model does not exclude sympathetic activity from involvement in the initiation of an acute attack since dilator contraction may pull a sphincter to mid-dilatation and so trigger an attack. It does suggest that CAG is primarily a result of parasympathetic activity since AC did not occur in its absence but did when the sympathetic was inhibited. However, parasympathetic anterior segment activity implies more than variations in S pbf. This is explored in subsequent papers.

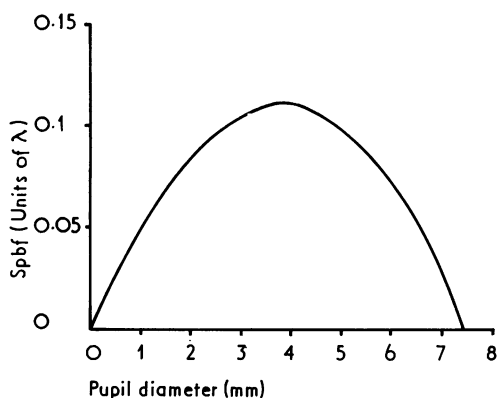


FIG. 4 Pbf is due mainly to the sphincter muscle, its variation during the pupillary play of the light reflex is shown

I should like to thank Miss E. Grogan for secretarial help and Mr. R. McBride for the preparation of the diagrams.

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