

Pigment release

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SUMMARY Guttae phenylephrine 10% produced a significant decrease in intraocular pressure and increase in facility of outflow in eyes with untreated ocular hypertension. If at the same time pigment was released into the aqueous, the pressure and outflow effect was nullified. Guttae pilocarpine 2% also reduced pressure and increased outflow, but if phenylephrine was added to the pilocarpine 2 responses appeared. If no pigment was released, pressure decreased and outflow increased; if pigment was released, there was no significant change in either. An identical response was shown by eyes with treated open-angle glaucoma. In eyes with treated exfoliation glaucoma pilocarpine and phenylephrine combined produced a significant increase in pressure and decrease in outflow because of pigment release. Finally, 18 eyes are described in which pigment release produced a mean increase in intraocular pressure of 14 mmHg. An acute release of pigment has an outflow-blocking effect that can be readily demonstrated. It provides an explanation for some of the paradoxical responses that occur after the instillation of autonomic drugs. It also provides a sufficient explanation for glaucoma associated with pigment dispersion.

A sudden release of many pigment granules into the aqueous might be expected to produce a measurable increase in intraocular pressure and a decrease in facility of outflow. Experiments designed to test this have been published^{1,2} and confirm a notion that seems entirely reasonable. However, when phenylephrine-induced pigment release is used as an experimental model in human eyes, no consistent response pattern develops. Kristensen³ recorded a pressure increase in patients with pigmentary and exfoliation glaucoma, but Aggarwal and Beveridge⁴ and Epstein *et al*⁵ found this rarely. There are several reasons why a pressure increase may not occur.

Firstly, pigment release will take time to have an effect. The granules have to pass from posterior to anterior chambers, negotiate the convection current, arrive at the meshwork, produce a mechanical blockage and then (maybe) a pressure and outflow change. Consequently acute experiments completed within 1½ hours may miss a maximum effect and explain the generally noted lack of response.

Secondly, pigment may mechanically block one component of trabecular meshwork that in normal circumstances offers little resistance to flow. For example, if low-resistance uveal meshwork allows a free passage of aqueous to meshwork downstream,

and if pigment is trapped at the uveal level, then the effect would be of little consequence. Consequently eyes with a normal outflow system may be unable to demonstrate a pigment-induced pressure increase.

Thirdly, intraocular pressure is inversely proportional to facility of outflow. Therefore, for a given absolute decrease in facility of outflow the resulting increase in intraocular pressure will be greater if the initial facility of outflow is low. This means that if an eye already has outflow damage it is more likely to demonstrate a pigment-release effect.

This paper describes the result of experiments designed to test these aspects of pigment release.

Material and methods

The basic experiment was divided into 3 stages. *Stage 1.* At the start intraocular pressure, facility of outflow, and pupil diameter were measured. Gonioscopy was done and iridocorneal contact sought in the 4 quadrants. One drop of the drug (or drugs) was instilled into the right eye or, if the ocular hypertension or glaucoma was left-sided, then into that eye. Finally, the presence or absence of pigment granules in the aqueous was noted. *Stage 2.* Approximately 1¼ hours later the measurements and observations made at the start of stage 1 (with the exception of gonioscopy) were repeated. Another

drop of the drug or drugs was instilled. *Stage 3.* After the lapse of another 1½ hours the measurements and observations were recorded again and the experiment was terminated—that is, 2½ to 3 hours from the start.

If at any stage during the experiment an eye developed iridocorneal contact, it was not included in this paper.

Meticulous attention was directed towards pigment present in the aqueous. Either no or very little pigment appeared, or the aqueous contained innumerable granules. In addition the time at which pigment appeared was taken into account. For example, if very little pigment was present at the beginning of stage 2 but much pigment was present at the start of stage 3, there is a priori reason to suppose that the effect would not be the same as when much pigment was present at the beginning of both stage 2 and stage 3. Consequently the only patients included in this paper were: (1) those in whom very little pigment appeared at any stage during the test; (2) those in whom much pigment was present throughout stages 2 and 3.

The following experiments were done:

(1) Thirty right eyes from 30 patients with untreated ocular hypertension were submitted to a dummy provocative test. The procedure described above was followed but at no stage was any drug other than benoxinate hydrochloride instilled.

(2) Twenty-two eyes from 22 patients with untreated ocular hypertension were given guttae pilocarpine 2% at stages 1 and 2.

(3) Thirty-five eyes from 35 patients with untreated ocular hypertension were given guttae phenylephrine 10% at stages 1 and 2.

(4) Two groups of eyes were given guttae pilocarpine 2% and guttae phenylephrine 10% at stages 1 and 2: (a) 66 eyes from 66 patients with untreated ocular hypertension; (b) 51 eyes from 51 patients with treated open-angle glaucoma. Before the experiment they were instructed to continue treatment as was their habit.

(5) Nineteen eyes from 19 patients with treated exfoliation glaucoma were given guttae pilocarpine 2% and guttae phenylephrine 10% at stages 1 and 2. Before the experiment they were instructed to continue treatment as was their habit.

Finally, 18 patients are described who during a provocative test with pilocarpine and phenylephrine developed a pressure rise of greater than 10 mmHg. At the same time much pigment was released into the aqueous and none developed angle closure of any degree. All patients had open-angle glaucoma and were first seen during the past 10 years.

The statistical test used was Student's *t* test. The level of significance was set at 0.01.

Results

Experiment 1: no drug instilled (30 eyes)

During the 2½-hour interval intraocular pressure changed from a mean of 23.0 (stage 1) to 21.9 (stage 2) to 21.7 mmHg (stage 3). At the same time facility of outflow changed from a mean 0.15 (stage 1) to 0.14 (stage 2) to 0.16 μ l/mmHg/min (stage 3). Neither change is statistically significant (for pressure $t=1.34$, for outflow $t=0.74$).

Experiment 2: pilocarpine 2% instilled (22 eyes)

Intraocular pressure decreased from a mean of 20.8 (stage 1) to 18.8 (stage 2) to 17.1 mmHg (stage 3). At the same time facility of outflow increased from a mean of 0.15 to 0.19 to 0.23 μ l/mmHg/min. Both changes are significant (for pressure $t=6.9$, $p<0.001$; for outflow $t=5.18$, $p<0.001$).

Experiment 3: phenylephrine 10% instilled (35 eyes)

(i) No pigment released—22 eyes (Fig. 1). After the first dose of phenylephrine pressure decreased from a mean of 22.8 to a mean of 19.7 mmHg ($t=4.11$, $p<0.001$); outflow increased from a mean of 0.16 to a mean of 0.19 μ l/mmHg/min ($t=2.7$, not significant). After the second dose pressure increased from a mean of 19.7 to a mean of 20.5 mmHg ($t=1.73$, not significant) and outflow increased from a mean of 0.19 to a mean of 0.2 ($t=0.75$, not significant). Overall, pressure decreased and outflow increased by a significant amount (for pressure $t=3.15$, $p<0.001$; for outflow $t=2.96$, $p<0.001$).

(ii) Pigment released—13 eyes (Fig. 1). After the

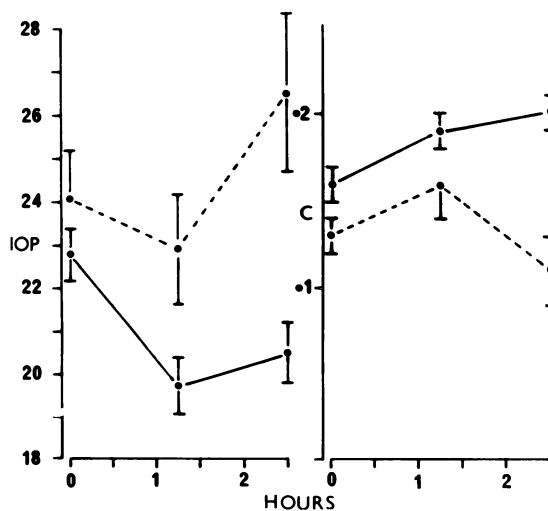


Fig. 1 Response of eyes with ocular hypertension to the instillation of phenylephrine. Solid line, no pigment released; interrupted line pigment released.

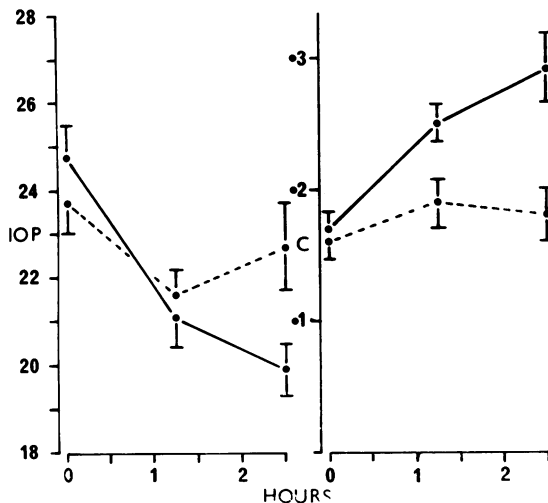


Fig. 2 Response of eyes with ocular hypertension to the simultaneous instillation of pilocarpine and phenylephrine. Solid line, no pigment released; interrupted line, pigment released.

first dose of phenylephrine pressure decreased from a mean of 24.1 to a mean of 22.9 mmHg ($t=1.49$, not significant); outflow increased from a mean of 0.13 to a mean of 0.16 ($t=1.28$, not significant). After the second dose pressure increased from a mean of 22.9 to a mean of 26.5 mmHg ($t=1.87$, not significant); outflow decreased from a mean of 0.16 to a mean of 0.11 ($t=2.43$, not significant). Overall there was no significant change in either pressure or outflow (for pressure $t=1.3$; for outflow $t=1.56$).

Experiment 4: Pilocarpine 2% and phenylephrine 10% instilled

(a) Sixty-six eyes with untreated ocular hypertension. (i) No pigment released—40 eyes (Fig. 2). After the first dose pressure decreased from a mean of 24.8 to a mean of 21.1 mmHg ($t=7.7$, $p<0.001$); outflow increased from a mean of 0.17 to a mean of 0.25 ($t=7.35$, $p<0.001$). After the second dose pressure decreased from a mean of 21.1 to a mean of 19.9 mmHg ($t=2.89$, $p<0.01$); outflow increased from a mean of 0.25 to a mean of 0.29 ($t=3.15$, $p<0.01$). Overall, pressure decreased and outflow increased by a significant amount (for pressure $t=8.65$, $p<0.001$; for outflow $t=8.59$, $p<0.001$).

(ii) Pigment released—26 eyes (Fig. 2). After the first dose pressure decreased from a mean of 23.7 to a mean of 21.6 mmHg ($t=3.9$, $p<0.001$); outflow increased from a mean of 0.16 to a mean of 0.19 ($t=1.8$, not significant). After the second dose pressure increased from a mean of 21.6 to a mean of 22.7 mmHg ($t=1.31$, not significant); outflow

decreased from a mean of 0.19 to a mean of 0.18 ($t=0.79$, not significant). Overall there was no significant change in either pressure or outflow (for pressure $t=0.94$; for outflow $t=1.11$).

(b) Fifty-one eyes with treated open-angle glaucoma. (i) No pigment released—21 eyes (Fig. 3). After the first dose pressure decreased from a mean of 24.6 to a mean of 18.7 mmHg ($t=4.8$, $p<0.001$); outflow increased from a mean of 0.15 to a mean of 0.21 ($t=4.96$, $p<0.001$). After the second dose pressure decreased from a mean of 18.7 to a mean of 17.4 mmHg ($t=1.62$, not significant); outflow increased from a mean of 0.21 to a mean of 0.23 ($t=1.4$, not significant). Overall, pressure decreased and outflow increased by a significant amount (for pressure $t=5.18$, $p<0.001$; for outflow $t=4.47$, $p<0.001$).

(ii) Pigment released—30 eyes (Fig. 3). After the first dose pressure decreased from a mean of 23.5 to a mean of 22.8 mmHg ($t=0.87$, not significant); outflow remained unchanged at 0.13. After the second dose pressure increased from a mean of 22.8 to a mean of 25.2 mmHg ($t=3.26$, $p<0.001$); outflow was again unchanged at a mean of 0.13. Overall there was no significant change in either pressure or outflow (for pressure $t=1.62$; for outflow $t=0.56$).

Experiment 5: pilocarpine 2% and phenylephrine 10% instilled into 21 eyes with treated exfoliation glaucoma (Fig. 4)

After the first dose pressure increased from a mean

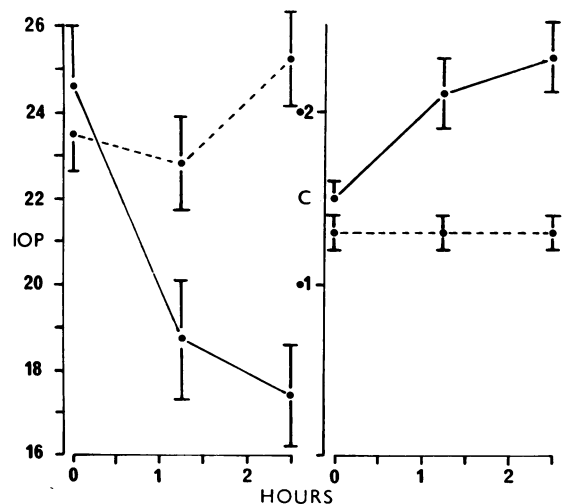


Fig. 3 Response of eyes with open-angle glaucoma to the simultaneous instillation of pilocarpine and phenylephrine. Solid line, no pigment released; interrupted line, pigment released.

of 19 to a mean of 20.6 mmHg ($t=1.31$, not significant); outflow decreased from a mean of 0.13 to a mean of 0.11 ($t=1.53$, not significant). After the second dose pressure increased from a mean of 20.6 to a mean of 23.5 mmHg ($t=3.14$, $p<0.01$); outflow decreased from a mean of 0.11 to a mean of 0.09 ($t=2.38$, not significant). Overall pressure increased and outflow decreased by a significant amount (for pressure $t=3.02$, $p<0.01$; for outflow $t=4.17$, $p<0.001$).

Fig. 5 records the response of 18 eyes from 18 patients with treated open-angle glaucoma. Pressure increased from a mean of 23 to 27.3 to 37 mmHg; at the same time outflow decreased from a mean of 0.11 to 0.07 to 0.06. No angle closure of any degree appeared, but much pigment was released into the aqueous.

Finally, the change in pupil diameter of eyes with untreated ocular hypertension from experiments 3 and 4 are recorded. Table 1 shows that when no pigment was released phenylephrine produced a significant change in pupil diameter, but pilocarpine and phenylephrine combined did not. When pigment was released (Table 2) both phenylephrine alone and pilocarpine and phenylephrine together produced significant changes in pupil diameter.

Discussion

These are acute experiments, unconcerned with the long-term consequences of autonomic drugs on aqueous inflow and outflow. Topical pilocarpine produces an increase in facility of aqueous outflow that is a direct consequence of ciliary muscle contraction^{6,7}; a fall in intraocular pressure follows.

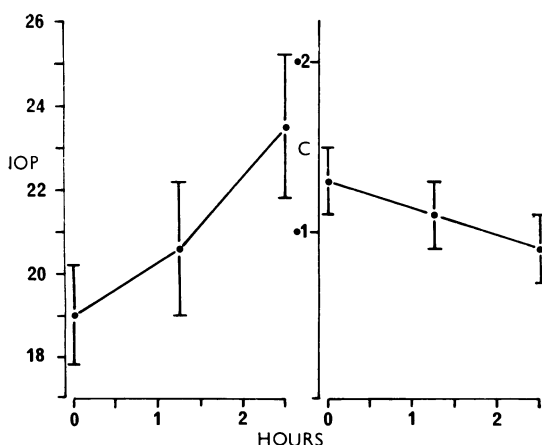


Fig. 4 Response of eyes with exfoliation glaucoma to the simultaneous instillation of pilocarpine and phenylephrine. Pigment released.

Additionally, Macri and Cevario^{8,9} demonstrated that pilocarpine can (in cats) induce a constriction of the afferent blood supply to the ciliary body. If a similar mechanism operates in man, the result, because of a change in ultrafiltration, will be a pseudofacility, showing tonographically as an

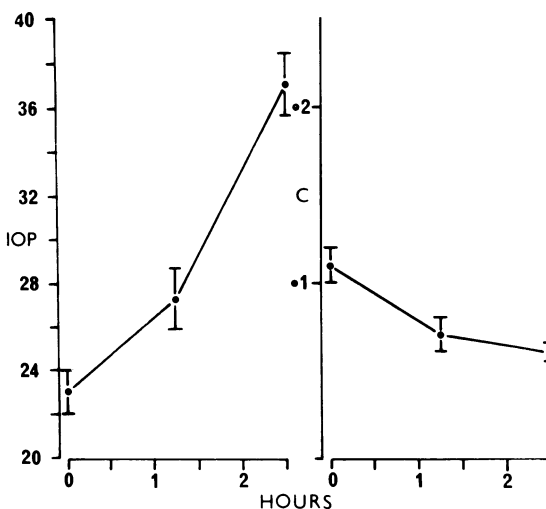


Fig. 5 Response of eyes with open-angle glaucoma to the simultaneous instillation of pilocarpine and phenylephrine. All eyes developed a pressure increase of at least 10 mmHg together with much pigment release.

Table 1 Pupil diameter changes in ocular hypertensive eyes following the instillation of phenylephrine or pilocarpine plus phenylephrine; no pigment was released

	Pd ₁	p	Pd ₂	p	Pd ₃	Total p
Phenylephrine	3.8	<0.001	7.1	NS	7.2	<0.001
Phenylephrine plus pilocarpine	3.9	NS	4.1	NS	3.8	NS

Pd₁ etc. = pupil diameter at stage 1 etc. p=Critical level. NS=not significant.

Table 2 Pupil diameter changes in ocular hypertensive eyes following the instillation of phenylephrine or pilocarpine plus phenylephrine; much pigment was released

	Pd ₁	p	Pd ₂	p	Pd ₃	Total p
Phenylephrine	3.6	<0.001	6.8	NS	7.0	<0.001
Phenylephrine plus pilocarpine	3.2	<0.001	4.3	<0.01	3.9	<0.001

Pd₁ etc. = Pupil diameter at stage 1 etc. p=Critical level. NS=Not significant.

increase in total facility of outflow. The net result of pilocarpine instillation during a 2½-hour period therefore is to produce an increase in total facility of outflow and a decrease in intraocular pressure.

Phenylephrine acts by direct stimulation of alpha adrenoreceptors.¹⁰ Clonidine—an alpha agonist—has no effect on facility of outflow in monkeys,¹¹ but in the isolated perfused cat eye it causes a decrease in aqueous production.¹² Adrenaline,¹³ salbutamol,¹⁴ and isoprenaline¹³ all increase facility of outflow—a consequence of beta agonist activity. Sears¹⁵ and Sears and Neufeld¹⁶ suggest that the effects of alpha agonist activity may be 2-fold. Firstly, receptor stimulation may constrict blood vessels supplying the ciliary body, reducing the quantity of ultrafiltrate presented to the ciliary epithelium. This will appear tonographically as an increase in C total—although in reality a pseudofacility. Secondly, effects on the external eye may cause arteriolar constriction, reduce episcleral venous pressure, and produce a slight increase in outflow. There is therefore no experimental evidence to suggest that pilocarpine and phenylephrine, singly or in combination, will have any effect in normal or ocular hypertensive eyes other than to increase total facility of outflow and decrease intraocular pressure.

The results show that, in a group of eyes with ocular hypertension, spontaneous change in outflow and pressure during a 2½-hour period was not statistically significant. Pilocarpine alone and phenylephrine alone (in the absence of pigment release) both produced a significant decrease in pressure and increase in facility of outflow. Similar results were obtained (in the absence of pigment release) after instilling pilocarpine and phenylephrine simultaneously into eyes with ocular hypertension or open-angle glaucoma.

However, if the instilled drugs also release much pigment into the aqueous, then in neither group of eyes does a significant change in outflow or pressure occur. The reasonable inference is therefore that pigment has mechanically blocked the outflow channels and prevented the pressure decrease and outflow increase that occur in the absence of pigment.

There is no reason to suppose that pigment release will have any direct effect on aqueous inflow, so that any pseudofacility effect will remain the same, whether or not pigment is released. It is concluded therefore that pigment release does cause a mechanical block and prevents the outflow increasing effect of autonomic drugs.

No one group showed a significant decrease in facility of outflow. To demonstrate that this can happen 2 groups of eyes were chosen. One, with exfoliation glaucoma, showed a significant increase in pressure and decrease in outflow. The other

showed a paradoxical response to a provocative test with pilocarpine and phenylephrine. In spite of open angles pressure increased by 14 mmHg, and outflow decreased. Both groups showed a large release of pigment.

One major determinant of these observations is to be found in the inverse relationship between pressure and outflow. The basic Goldman equation is $P_o = (F/C) + P_v$ where P_o = intraocular pressure (mmHg), F = aqueous inflow ($\mu\text{l}/\text{min}$), C = facility of outflow ($\mu\text{l}/\text{min}/\text{mmHg}$), P_v = episcleral venous pressure (mmHg).

Assume inflow constant at 1.5 $\mu\text{l}/\text{min}$ and episcleral venous pressure also constant at 10 mmHg. If an eye has a facility of outflow of 0.21, intraocular pressure is 17.1 mmHg. If outflow is decreased to 0.16, pressure increases to 19.4 mmHg.

On the other hand, if outflow is initially 0.11 and decreases to 0.06, then pressure increases to 35 mmHg. That is, a change in outflow when the initial facility is high will have a lesser effect on pressure than a numerically identical change at low facilities of outflow. This was the reason for studying patients with aging or damaged outflow systems in this paper.

CLINICAL IMPLICATIONS

The fact that phenylephrine alone, or in combination with pilocarpine, can release much pigment and produce large pressure increases is at first sight of little clinical significance. But there are various situations in which it is of significance.

Firstly, any statements concerning the effects of autonomic drugs on intraocular pressure and facility of outflow are of limited value unless the presence or absence of pigment release is also noted. This means that provocative tests involving pupil movement must take into account the effect of pigment, as also should reports of anomalous pressure changes after phenylephrine instillation.^{17 18}

Secondly, one drug combination used in the treatment of open-angle glaucoma, namely, pilocarpine and adrenaline, can cause a shower of pigment to appear and produce a paradoxical increase in pressure and decrease in outflow. For example, a man with exfoliation glaucoma was being treated with guttae pilocarpine 4% and guttae timolol maleate 0.5%. The effect of pilocarpine 2% and adrenaline 1% was to increase pressure from 20 to 28 mmHg and decrease outflow from 0.08 to 0.05. A shower of pigment was released and was, presumably, the cause of the change.

Thirdly, there is evidence that pigment can be released spontaneously in large quantities. Epstein *et al.*⁵ described 2 patients, in one of whom blurred vision and haloes appeared after exercise, Direct provocation (jogging for 2 hours) reproduced the

symptoms together with an increased pressure, decreased outflow, and much pigment release. In the other patient dim illumination and emotional crises produced symptoms. During a spontaneous attack, which occurred after working outside in dim illumination, intraocular pressure was 55 mmHg in the right eye together with much pigment in the aqueous.

Schenker *et al.*¹⁹ also described a patient in whom blurred vision and haloes appeared after exercise, emotional stress, and dim illumination. A darkroom provocative test and exercise both reproduced symptoms, together with an increased pressure and pigment release. They tried the effect of pilocarpine on the pigment-releasing effect of exercise and suggested that, because symptoms were no longer produced, it is possible to nullify the effect of pigment on pressure. However, the results described above suggest that this is not generally so.

From the association between stress or dim illumination and pigment release Schenker *et al.*¹⁹ infer that the cause is mechanical abrasion of pigment epithelium produced by pupillary movement. The results (Tables 1 and 2) show that while these conditions are necessary they are not sufficient, for the reason that phenylephrine produced a significant increase in pupil diameter in all eyes but pigment appeared in some only. When the effects of combined pilocarpine and phenylephrine are considered, it is apparent that pigment release is associated with significant changes in pupil diameter, whereas, if no change occurred, no pigment appeared. It therefore follows that, while pupillary movement and mechanical abrasion were necessary for pigment release to occur, their combined presence was not a sufficient condition.

Whatever the mechanism of pigment release may be, it is apparent that it can occur in sufficient quantities to produce a substantial increase in pressure. The outflow damage that is known to follow pigment release^{20 21} together with the observations described above provide a sufficient explanation for glaucoma associated with pigment release.

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