

Response of the human eye to laser irradiation of the iris

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SUMMARY Irradiation of the iris of glaucoma patients with either a ruby or an argon laser caused no obvious disruption of the blood-aqueous barrier (as visualised by fluorescein angiography), in contrast to a sudden and pronounced effect in the rabbit eye. Only a low and variable increase in intraocular pressure occurred in the human subjects after the laser irradiation in comparison with a consistently high rise of ocular tension in the rabbit. This investigation indicates that the human eye is much less responsive to injury.

Since the rabbit is the experimental animal most frequently used in investigative ophthalmology, it is important to establish the extent to which the acute inflammatory response of the rabbit eye to noxious stimulation is representative of that in man. There are notable anatomical differences between the structure of the anterior uvea in primates and rabbits which most probably account for the significant differences in the pattern of changes and the sensitivity of the respective eyes to trauma (Prince, 1964; Hogan *et al.*, 1971). Anterior chamber paracentesis, for example, in the monkey causes only a slight infiltration of a blood plasma protein marker, which appears to enter the chamber by a retrograde passage through the outflow channels (Raviola, 1975), whereas in the rabbit eye a sudden and pronounced influx of protein occurs primarily across the ciliary processes (Unger *et al.*, 1975).

Ruby laser irradiation of the rabbit iris, like mechanical or chemical irritation, provokes a rapid ocular response consisting of immediate vasodilatation of the anterior uveal vessels, constriction of the pupil, and an increase in the intraocular pressure (IOP). Perhaps the most striking and least easily prevented change in the rabbit is a sudden breakdown of the blood-aqueous barrier (Larsson, 1930; Duke-Elder and Duke-Elder, 1931; Davson and Huber, 1950; Sears, 1960; Ambache *et al.*, 1965; Fontenberry *et al.*, 1969; Bethal and Eakins, 1972; Cole and Unger, 1973; Unger *et al.*, 1974).

The clinical use of the laser in treating glaucoma due to angle closure afforded a unique opportunity to study the reaction of the human eye to a moderate form of trauma. In the following report fluorescein

angiography of the iris performed shortly after the application of the argon or the ruby laser to the iris of such patients demonstrated the relative stability of the blood-aqueous barrier in the human eye after laser irradiation of sufficient energy to elicit a decided effect in the rabbit.

Materials and methods

Patients selected for the present study had glaucoma for which laser treatment was clinically indicated (Perkins and Brown, 1974). Most of the subjects were being treated with one or more of the following drugs: 1 to 4% pilocarpine, 0.5% eserine, 0.1 or 1% neutral adrenaline, acetazolamide 250 mg tablets, or 0.3% prednisolone (see Table 1). Generally, the last administration of any drug occurred 3 to 4 hours before laser irradiation.

LASER TREATMENT

Since exposure of a pigmented iris to the argon laser destroys stromal tissue and induces melanocyte infiltration into the site of the lesion, argon laser irradiation is routinely used to effect shrinkage of the anterior surface of the iris proximal to the angle and to prepare a target-site of deep pigmentation for subsequent ruby laser irradiation. Consequently, the ruby and/or the argon laser may have been used on several occasions to treat the same iris in an effort to achieve a full thickness iridotomy. Many of the patients, therefore, had received previous laser treatment (see Table 1).

Ruby laser irradiation. A single emission of the ruby laser consists of a 0.6 ms pulse train, having an integrated energy of 550 to 650 mJ, which was focused on an area of iris of about 1 mm diameter

Table 1 Fluorescein photography of the anterior segment following irradiation of the iris in patient volunteers

Subject	Diagnosis ¹	Previous ²		Laser dose ³			Medication ⁴	IOP rise ⁵		Fluores. ⁵ Leakage	Differences ⁷
		Age	Sex	Argon	Ruby	µm		mW	X		
<i>(Argon laser irradiation)</i>											
50	Male CAG	—	—	200	100	81	2% P	15	0.5	0.5	
69	Female CAG, small synechiae	1 (90)	—	200	250	90	4% P 0.1% A	2	1.0	ND	
66	Female CAG, diabetic, rubeosis?	1 (31)	—	100	500	22	4% P 25OD	1	0.5	0.5	
64	Female SG, bombe iris	—	—	50	500	28	0.3% Pred 25OD	8	<0.5	ND	
73	Male CAG, iridectomy fellow eye	—	—	100	200	32	4% P 1% A	20	0.5	less	
60	Female CAG	—	—	100	300	63	0.25% E	5	<0.5	ND	
<i>(Ruby laser irradiation)</i>											
71	Female CAG	2 (78)	1 (1)	(mJ X)			1% P 0.3% Pred	14	<0.5	ND	
76	Female CAG	2 (184)	—	550	2	—	2% P 0.3% Pred	2	<0.5	ND	
60	Male CSG	1 (3)	1 (3)	550	2	—	—	6	<0.5	less	
51	Female CAG	1 (26)	—	650	2	—	2% P	7	<0.5	less	
66	Female CAG, diabetic, rubeosis?	2 (127)	—	650	3	—	4% P 25OD	5	0.5	0.5	
60	Male CAG	—	—	650	3	—	2% P	3	<0.5	ND	

¹CAG—closed-angle glaucoma; SG—secondary glaucoma; CSG—chronic simple glaucoma.

²Number of laser sessions (total number of applications).

³For the argon: µm—micron spot size diameter; mW—milliwatts; X—number of applications.

For the ruby: mJ—millijoules; X—number of applications.

⁴P—pilocarpine; A—neutral adrenaline; D—Diamox (acetazolamide); Pred—prednisolone; E—eserine.

⁵Fluorescence of aqueous humour scored from 0 (nil) to 10 (completely filled; cf. Unger *et al.*, 1975). IOP—intraocular pressure.

⁶Rise of IOP at 40 min after laser irradiation.

⁷Difference in leakage between irradiated and fellow eye at 15 min after injection.

using a modified slit-lamp apparatus described by Perkins and Brown (1973). In the present study the laser was usually applied 2 or 3 times to the iris of each subject.

Argon laser irradiation. Argon laser light was generated by a Coherent 800 Argon-Laser Photo-coagulator (Coherent Radiation; Palo Alto, California), which emits a continuous beam of variable diameter and intensity. Treatment consisted of multiple applications (up to 150) of a laser beam, usually of 50, 100, or 200 µm diameter, each for a duration of about 0.2 s with an energy of 100 to 1000 mW (specific conditions have been summarised in Table 1).

Fluorescein angiography. To demonstrate any breakdown in the blood-aqueous barrier a 20% solution of sodium fluorescein (0.1 ml/kg body weight) was injected rapidly into the brachial vein 10 to 15 minutes after treatment with the laser. Photographs of the anterior segment were taken at desired intervals over a 15-minute period using a 35-mm motorised Nikon camera. Illumination was provided by xenon flash tube and an arrangement of appropriate filters to ensure that only the fluorescence of the dye was recorded. The procedure has been described more fully by Cole (1974), Unger *et al.* (1974), and Edwards (1975).

IOP changes after laser irradiation. The IOP was measured by applanation tonometry before and at intervals over a 75-minute period after irradiation. The response was usually maximal at 40 minutes. Subjects included only those in whom the last administration of pilocarpine (and, in a few cases, acetazolamide or adrenaline with pilocarpine) had

been not less than 3 hours prior to laser application.

Laser irradiation of the rabbit iris. To simulate conditions encountered in the patients Dutch rabbits were pretreated with either topically applied pilocarpine and eserine or neutral adrenaline and/or intramuscularly or intravenously injected acetazolamide (see Table 2). Animals weighing 2 to 2.5 kg

Table 2 Response of the rabbit eye to laser irradiation of the iris

Type	No.	Medication ¹	Laser dose ²		IOP rise ³		Fluorescein ⁴ leakage
			(µm)	(mW X)	10 min	30 min	
<i>(Ruby laser irradiation)</i>							
Dutch	1	1	550	2	30	28	5
	1	1	550	3	25	20	7
	1	2	550	2	24	22	6
	1	3	550	2	25	20	6
	1	4	550	2	28	26	7
	1	5	550	2	26	22	5
	1	—	550	1	—	—	5
	1	—	550	2	25	20	6
	1	—	650	2	—	—	6
	3	—	550	3	—	—	6-8
10	—	550	4	31 + 1	28 + 1		
New Zealand	1	—	550	2	—	—	—
	1	—	550	6	—	—	—
<i>(Argon laser irradiation)</i>							
Dutch	16	—	500	750	5	—	—
	4	—	500	750	5	—	4-7
New Zealand	2	—	500	750	5	—	—
	2	—	500	750	5	—	—

¹Numbers refer to drugs outlined in the text.

²mJ—millijoules; µm—spot size in microns; mW—milliwatts.

X—number of applications of the laser.

³IOP increase in mmHg at 10 and 30 min after irradiation.

⁴Fluorescence of the anterior chamber at 10 min after injection scored according to an arbitrary scale from 0 (nil) to 10.

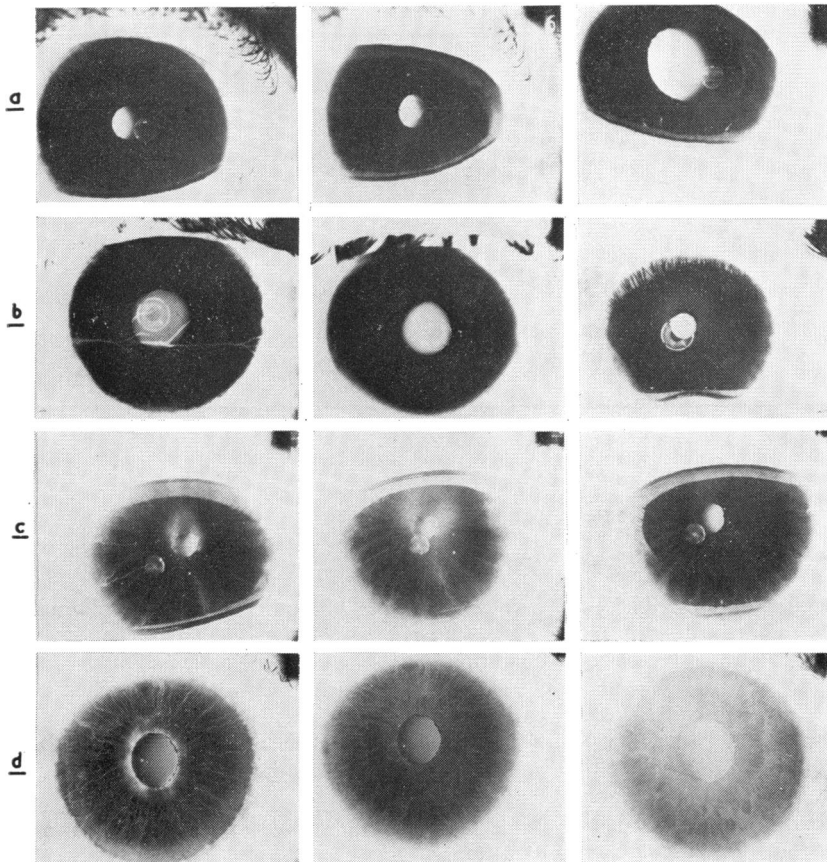


Fig. 1 Fluorescein angiography of the anterior segment of the human eye following laser irradiation of the iris. The appearance of fluorescein is shown at 2 and 10 min in the irradiated eye and at 10 min in the untreated contralateral eye (from left to right) in (a) a 76-year-old female after 2 ruby laser applications; (b) a 60-year-old female after 63 argon laser applications; (c) a 66-year-old female after 3 ruby laser applications; and (d) a 60-year-old male after 2 ruby laser applications

were placed in a holding tray and anaesthetised by an initial intravenous injection of 30 mg/kg sodium pentobarbitone. Ten to 15 minutes after irradiation a fluorescein angiogram was carried out. In other experiments the IOP was determined by applanation tonometry before and at desired times up to 60 minutes after application of the argon or ruby laser.

Results

Fluorescein angiography after ruby laser irradiation in humans. A fluorescein angiography was carried out in 6 subjects 10 to 15 minutes after irradiation at 2 to 3 sites on the upper half of the iris. All but 1 subject had had prior argon and 2 had prior ruby laser treatment. Only 1 patient had had no previous medication (summarised in Table 1).

Virtually no influx of fluorescein into the anterior chamber was visible over the 15-minute period of photography in either the test or the contralateral eye in 5 subjects (see Fig. 1a). Some fluorescence was apparent over the pupil, but this was due to the natural fluorescence of the lens itself.

In one diabetic subject a local fluorescence was seen at the pupil margin (from permeable, possibly rubeotic vascular loops) (see Fig. 1c). Another subject exhibited a similar leakage, but by 10 minutes after injection the fluorescence was greater in the contralateral eye (see Fig. 1d).

Fluorescein angiography after argon laser irradiation. Six patients, 2 of whom had had previous argon laser treatment, were irradiated according to schedules summarised in Table 1. In 4 of them no noticeable difference was seen between the treated and the fellow eye in the extent of fluorescein infiltration into the anterior chamber (see Fig. 1b). A moderate but diffuse fluorescence appeared in the anterior chambers of both eyes of a fifth patient, apparently coming from the anterior surface of the irides (see Fig. 2a). The contralateral eye of a sixth patient, which had experienced a surgical iridectomy 17 years earlier, exhibited some fluorescein leakage exceeding that seen in the irradiated eye (see Fig. 2b). In 2 patients, 1 with a possible rubeosis, a slight vascular leakage near the pupil margin of the irradiated iris was evident (see Figs. 3a and b).

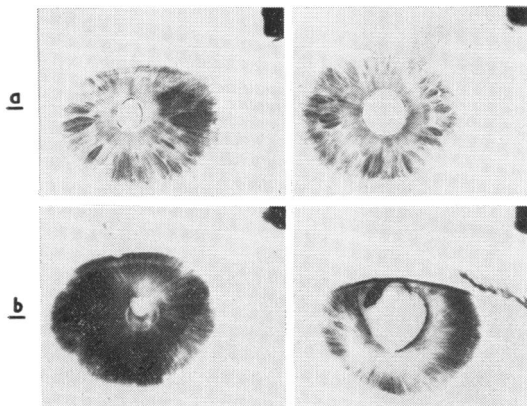


Fig. 2 Fluorescein angiography following argon laser irradiation. The appearance of the fluorescein is seen at 10 min after injection in the irradiated (left) and fellow eye (right) in (a) a 69-year-old female given 90 applications and (b) a 73-year-old male receiving 32 applications and presenting a contralateral eye with a surgical iridectomy

Breakdown of the blood-aqueous barrier in the rabbit following laser irradiation. By contrast with the human subjects, an obvious and pronounced laser-induced disruption of the blood-aqueous barrier was demonstrated in the rabbit using the fluorescein procedure. The extent of fluorescein infiltration into the aqueous humour of an eye receiving 1 to 3 laser lesions was considerably greater at 10 to 15 minutes after injection than in man (scored 4 to 9 compared to 0.5 or less in man on an arbitrary scale from 0 to 10, *c.f.*, Unger *et al.*, 1975; see Table 2 and Fig. 4). It was obvious in the rabbit that the bulk of the fluorescein entered the anterior chamber via the pupil and was apparently associated with a plasmoid

aqueous of greater density than normal aqueous since it settled by gravity into the lower half of the chamber.

A similar effect was observed in 4 rabbits receiving argon laser irradiation (200 or 500 μm , 750 mW, 5 times at 0.5 s each application; see Fig. 4d). It was of some interest that neither ruby nor argon laser irradiation of the non-pigmented rabbit iris (New Zealand variety) produced a breakdown of the blood-aqueous barrier (see Table 2 and Figs. 4e and f).

In order to compare more closely the results found in patients with that of the rabbit, rabbits were treated with the following drugs over a given period immediately before irradiation at a single site on the iris: (1) 2% pilocarpine and 0.5% eserine administered topically as 1 drop/5 min over 60 minutes; (2) 2 drops of 0.1% neutral adrenaline 60 minutes previously; (3) 25 mg/kg acetazolamide injected intramuscularly 4 hours previously; (4) 25 mg/kg acetazolamide injected intravenously 15 minutes prior; and (5) a combination of that given in (1) and (4). In every case a sudden influx of fluorescein was visualised (a score of 4 to 7; see Table 2 and Fig. 4c) on angiography.

Comparison of the IOP rise following laser irradiation in man and the rabbit. In the 12 additional patients, the IOP was followed up to 75 minutes after irradiation. A slow rise in pressure with a broad peak between 40 and 60 minutes occurred in all patients, but the maximum rise only exceeded 10 mmHg in 3. The height of the response did not seem to be related to the type of laser, the energy level, or previous medication.

Data on the response of the IOP to laser treatment was available for an additional 27 patients and also showed a variable rise in pressure from 0 to 24 mmHg

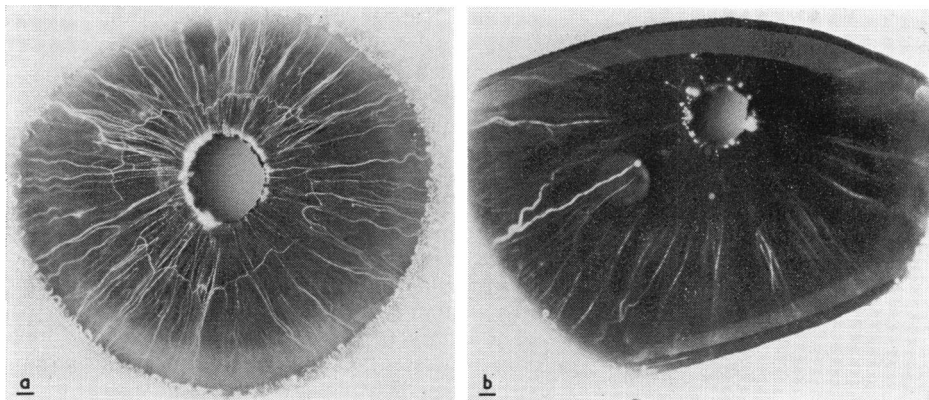


Fig. 3 Fluorescein angiography following ruby laser irradiation. Fluorescein is seen to leak from permeable iris vessels near the pupil margin (a) 30 s after dye injection in a 60-year-old male receiving 3 laser applications and (b) at 18 s in a 66-year-old female having 3 laser applications

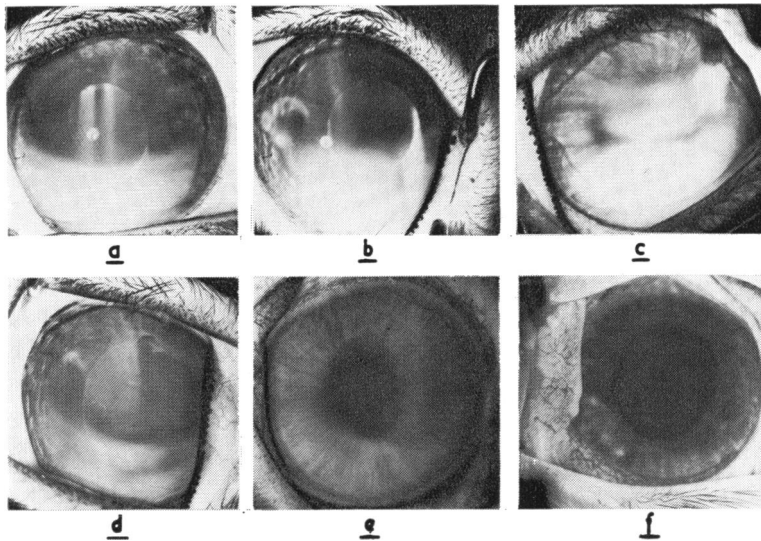


Fig. 4 The sudden breakdown of the blood-aqueous barrier is indicated by the influx of intravenously injected fluorescein following laser irradiation of the pigmented rabbit iris with (a) 1 and (b) 2 ruby laser applications and (c) 2 applications in an eye pretreated with pilocarpine, but not (f) in an albino rabbit eye receiving 6 applications. A similar appearance of fluorescein occurred (d) in the pigmented eye but not (e) the albino eye receiving 5 applications of argon laser light (0.5 s; 500 μm). All photographs were taken 10 min after injection of fluorescein

after ruby laser treatment and 0 to 20 mmHg after argon laser irradiation. Again there was no obvious correlation between the rise in IOP and the number of applications, the energy level, or the medication.

By contrast, the response in the rabbit to either laser reached a peak at about 15 to 20 minutes and declined to 50% at about 40 minutes (argon) and 50 minutes (ruby) after irradiation (see Fig. 5). The peak IOP rise after ruby laser irradiation (4 applications; 550 to 600 mJ) was 31 mmHg (\pm SE 1; 10 experiments) and after argon irradiation (5 applications of 500 μm , 750 mW, 0.5 s) was 18 mmHg (\pm SE 2; 14 experiments). Administration of drugs comparable to that used in the patients had essentially no effect on the IOP change (see Table 2).

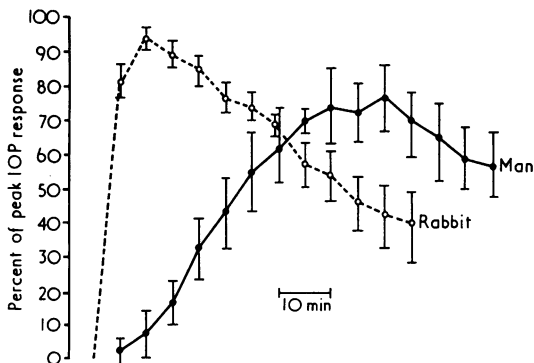


Fig. 5 Percentage of the maximal IOP rise following laser irradiation plotted against time. The curve for man includes only those exhibiting a peak response greater than 5 mmHg. The results obtained with both the argon and the ruby laser have been pooled. Each point shows the mean \pm SE

Discussion

Stimulation of the human iris with ruby or argon laser light caused very little obvious disturbance of the blood-aqueous barrier as assessed by fluorescein angiography. Unlike the rabbit eye, which suffers an immediate and marked breakdown, the extent of fluorescein infiltration into the anterior chamber was about the same in the treated as in the contralateral (control) eye. In several subjects some diffuse fluorescein was seen to enter the anterior chamber apparently from the anterior surface of the iris, in two cases near the pupil margin. In the rabbit, however, fluorescein entered via the pupil, associated with dense, presumably plasmoid, secondary aqueous after ruby or argon laser irradiation (see Unger and Bass, 1977). Thus in man what dye does enter the anterior chamber probably arrives from dilated iridial vessels, whereas in the rabbit there is an overt breach in the blood-aqueous barrier of the ciliary processes, ostensibly by a bulk flow of extravascular fluid across the ciliary epithelium (see Cole, 1974; Unger *et al.*, 1974, 1975). It is unlikely that the observed difference between man and the rabbit is due to the previous medication or to the clinical status of the patients. Instead, the greater sensitivity of the rabbit eye to trauma and the instability of the blood-aqueous barrier reflect gross anatomical differences.

The ciliary bodies of the rabbit eye have long iridial processes (as well as a more posterior group) extending radially along the posterior surface of the iris; in places the two structures share the same epithelial covering, and thus the stroma of the iris and ciliary processes are continuous (Prince, 1964;

Kozart, 1968). Thus injury to the rabbit iris and any concurrent release of a chemical mediator would be readily transmitted through the stroma to the ciliary processes. Indeed, after anterior chamber paracentesis, ruby laser irradiation of the iris, or intracameral instillation of various vasodilator drugs the blood vessels in the tips of the ciliary processes (but not the iris) are seen to take up intravenously injected colloidal carbon, an indication of increased permeability (Unger *et al.*, 1974; Cole, 1975). Consequently, oedema develops in the rabbit iridial processes followed by a breakdown in the blood-aqueous barrier of the ciliary epithelium (Kozart, 1968). In man by contrast the ciliary processes are more regular and are separated from the iris, so that they are less likely to be affected by the release of a chemical mediator from the iris.

A rapid and consistent elevation in IOP is a feature of the ocular response in the rabbit and is most likely to be due to vasodilatation as well as mechanical and osmotic effects caused by disruption of the blood-aqueous barrier. The rabbit response is mediated partly by E-type prostaglandin and by an apparent non-cholinergic neurogenic component (Neufeld *et al.*, 1973; Unger *et al.*, 1974, 1976). Although neither prostaglandin nor noxious stimuli appear to increase aqueous humour secretion (sodium transport), prostaglandin, at least, may stimulate fluid conductivity and solute permeability across (isolated) ciliary epithelia (Duke-Elder and Gloster, 1968; Green, 1974; Pederson and Green, 1975).

In man, the laser-induced IOP response seems less immediate, less intense, and very inconsistent from one individual to another; in over half of the subjects the IOP rise was less than 5 mmHg. Although the number of cases was limited, there was no apparent correlation between the rise in tension and age of the patient, the type of laser, or the number of laser applications. If an increase in aqueous formation (ultrafiltration) occurs in man after laser stimulation, then individual differences in outflow facility might possibly explain the wide variations as well as the delayed onset of IOP changes. Although an age-related increase in drainage resistance is uncertain, the tendency for an increase in the magnitude of variation between individuals seems greater in the elderly (Duke-Elder and Gloster, 1968) and the subjects in the present study were all over 50 years of age ($64 \pm SE 3$). The therapeutic use of prednisolone might be expected

to increase outflow resistance (Linnér, 1959; Armaly, 1963, 1964) whereas miotic agents would decrease the resistance (Krill and Newell, 1964; Linnér, 1958). However, in the present study there was no correlation between the size of the IOP change and treatment with prednisolone, pilocarpine, or acetazolamide (which would decrease aqueous formation).

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