

Provocative tests and chronic simple glaucoma

- I. Effect of atropine on the water-drinking test: intimations of central regulatory control
- II. Fluorescein angiography provocative test: a new approach to separation of the normal from the pathological

GEORGE L. SPAETH AND NIBONDH VACHARAT

Glaucoma Service, Wills Eye Hospital, Philadelphia

To distinguish between the severely affected and the entirely normal presents little difficulty. However, when findings are at the outer limits of "normal",* or when the presence of one "abnormal" sign conflicts with other "normal" characteristics, then diagnosis becomes a subtle art necessitating a combination of knowledge, observation, imagination, and intuition. The aim of provocative tests is to establish the diagnosis before damage gives rise to manifest symptoms.

For example, the diagnosis "glaucoma" may be made with relative certainty in patients stamped with the three hallmarks of the disease: intraocular pressure above 21 mm.Hg; glaucomatous cupping of the optic disc; and glaucomatous visual field loss. But where on the probability scale extending from normal to diseased is an individual to be placed who has only one of these findings, perhaps elevated intraocular pressure? *To treat* patients when they have no glaucomatous disease does them a great disservice, and a few may be significantly incapacitated thereby. *To fail to treat* those who have early glaucomatous disease will lead to loss of sight. The physician caring for the glaucoma suspect, or the "ocular hypertensive", is thus goaded by both horns of his dilemma. It is no wonder that so many attempts have been made to predict the future for this type of patient.

A provocative test introduces stress upon the eye, the response of which is appropriately recorded. Experience has suggested that the intraocular pressure of the eye with glaucomatous disease, especially in an untreated state, usually reacts to stress in a more exaggerated manner than does that of the normal eye. The understandable, but illogical, next step is to assume that an eye that reacts to stress in an exaggerated fashion has glaucomatous disease. Were this always true, it *would* be possible to diagnose glaucomatous disease reliably, even in the absence of evidence of optic disc cupping or visual field loss.

*Normal has been used here as it is customarily employed. It is, however, an incorrect usage. "Normal" correctly means the absence of pathology; it does not indicate an "average" condition, which is a statistically determined attribute unconcerned with pathology. For example, average weight in a large population of males is about 160 lb. Average weight for a group of entirely healthy 7' males, on the other hand, is about 230 lb. If a 5' 10" man weighed 160 lb., his weight would be both *normal* and *average*. If a 7' man weighed 160 lb., his weight would be *abnormal* but *average*. And if a 5' 10" individual weighed 230 lb. his weight would be neither *normal* nor *average*.

Such a goal may be as unattainable as the alchemist's dream. And if the inclusion of explicit pathology in the definition of disease is demanded, then it will never become possible to diagnose *a priori* illness before damage has been done. Provocative tests are said to help to distinguish the earliest divergence from the normal.

The scope of this paper is limited to procedures designed to discover the presence of chronic simple glaucoma.

As the method of performance and the interpretation of provocative tests have become more accurately defined, their predictive value may also have increased. Drance (1958), for example, has shown that "false" negative water-drinking tests can be eliminated by measuring the changes that occur in the blood concentration during the test; those not showing significant haemodilution have not a false negative test, but rather one from which no conclusion can be drawn.

An unpleasant fact still confronts the ophthalmologist struggling to diagnose chronic simple open-angle glaucoma; namely, the presently available tests do not concern themselves directly with the primary question: "what is the likelihood of this patient's losing vision?"

Of the various provocative tests which have evolved, most have important limitations. The response to caffeine or nicotine varies in relation to the individual's use of these agents before testing; furthermore, the tests themselves are not well standardized, and the variable results are hard to interpret (Graeber, 1968). The subconjunctival injection of priscoline is unpleasant for patients and, though apparently of fair reliability, is of limited value because of the physician's reluctance to use it (Leydhecker, 1955; Nørskov, 1966a). The "lability tests" (cold-pressor, venous congestion, etc.) are also unpleasant for the patient and do not yield data that justify the distress (Leydhecker, 1950a). The change in intraocular pressure induced by altering the posture has not been studied closely enough to allow valid conclusions about its reliability (Tomemori, 1969), a criticism that may also be made of the reaction to various cycloplegic agents (Harris and Galin, 1969b). Even if the normal limits of response to these tests were better defined, their use as predictive indicators of pathology is clearly limited, because the degree of correlation between a positive response and the subsequent development of glaucomatous visual loss has not been determined.

I. WATER-DRINKING TEST

The water-drinking test has been the most widely used, and has had the most standard technique determined. It is relatively easy and safe to perform, causes the patient little distress, and gives results that are fairly simply interpreted (Heegaard and Larsen, 1931; Leydhecker, 1950b; Kronfeld, 1955; Becker and Christensen, 1956; Suzuki, Takeuchi, and Kitazawa, 1966; Spaeth, 1967; Nørskov, 1967b; Armaly, 1970a). Furthermore, when the test is performed properly, the majority of patients with elevated intraocular pressure react positively and those with normal intraocular pressure react negatively. Water-drinking tonometry is usually to be preferred over water-drinking tonography for several reasons:

(1) The time at which intraocular pressure reaches a peak after a water load cannot be predicted accurately in any given individual. While in most cases maximum pressure is reached about 25 minutes after water has been drunk, it may occur as early as 10 minutes or as late as 90 minutes after drinking, and any technique that limits itself to one measurement is certain to miss a large percentage of peak rises in pressure. In one study, had the pressure been determined one hour after ingestion of water, only 3 per cent. of the highest pressures would have been detected (Spaeth, 1967).

Since tonography cannot be repeated at short intervals without undue risk to the eye, tonometry is preferable in this respect.

- (2) Both tonometry and the water-drinking test are sufficiently complicated in themselves; using the two together only compounds the complexity.
- (3) Tonography is beyond the reach of many ophthalmologists, but water-drinking tonometry can be performed by all.
- (4) Requiring more equipment and personnel, tonography is more expensive and more time-consuming, for both patient and physician.
- (5) Lastly, a rise in intraocular pressure may be a more valid indicator of the glaucomatous condition than a decrease in the coefficient of aqueous outflow (Becker and Christensen, 1956). The change in outflow often noted after water-drinking may not be a direct response to the water load itself, but rather a change secondary to the increased intraocular pressure that is itself the primary characteristic aspect of this test (Sugar and Fainstein, 1955; Galin, Aizawa, and McLean, 1965; Casey, 1965).

The proper technique for performing water-drinking tonometry is as follows:

The patient should fast for 8 hours before the test; no sedative or stimulant medications should be taken; drugs designed to lower intraocular pressure should be stopped long enough before the test to ensure that their effect has worn off; baseline intraocular pressure is determined with an applanation tonometer; stability of the pressure should be ascertained; tap water (cooler than room temperature, but not icy cold) 14 ml./kg. body weight (that is, one litre for a 70 kg. adult) is drunk within a span of 5 minutes; intraocular pressures are determined at 15-minute intervals for 1 hour or until the pressure stops rising.

A rise in intraocular pressure of more than 7 mm.Hg exceeds the response of two standard deviations from the average, and thus suggests that the individual being tested is outside of the "normal" population. A rise greater than 9 mm.Hg is characteristic of the pathological response seen in patients with chronic simple open-angle glaucoma (Leydhecker and Niesel, 1954).

The absolute level of pressure should not be considered as a measure of positivity. However, the degree of elevation at the start of the test does influence the likelihood of a positive reaction. Leydhecker (1950b) and Drance (1958) have both shown that patients with chronic simple glaucoma who have higher intraocular pressures will have greater rises in pressure after water drinking. Patients with glaucoma but with normal initial pressures will show an increase of 8 mm.Hg only in 17 per cent. of cases (Leydhecker and Niesel, 1954). When the intraocular pressure is below 30 mm.Hg at the start of the test, the frequency of a positive response is 33 per cent. (Leydhecker and Niesel, 1954) or 54 per cent. (Drance, 1958; "false negatives" excluded); when the pressure is above 30 mm.Hg the frequency is 70 per cent. (Leydhecker and Niesel, 1954) or 100 per cent. (Drance, 1958; "false negatives" excluded). Furthermore, Nørskov (1967b) noted that 9 per cent. of "normal" eyes with intraocular pressure below 20 mm.Hg develop an increase in intraocular pressure greater than 7 mm.Hg, whereas 17 per cent. of eyes with pressures between 20 and 25 mm.Hg and 48 per cent. of eyes with pressures above 25 mm.Hg manifest a rise greater than 7 mm.Hg. This is a very distressing finding, for it suggests that *positivity of the water-provocative test is a function of initial intraocular pressure and is not a function of presence or absence of glaucomatous disease itself.*

It follows, then, that since patients with elevated intraocular pressures respond to water loading with a large rise in pressure, and since patients with glaucomatous disease usually have elevated intraocular pressures, patients with glaucoma will usually also show large

increases in intraocular pressure after water drinking, NOT, however, because they have glaucoma, but because they have elevated intraocular pressures. In this respect it is interesting to note that apparently normal individuals who develop a significant corticosteroid-induced rise in pressure also develop positive water-drinking tests (Spiers, 1965; Spaeth, 1966; Kitazawa, 1966). This has been interpreted as an indication that these individuals are heterozygous for the gene ('g') that Becker and Hahn (1964) have proposed as responsible for glaucoma and steroid hypertension. Another interpretation is that they are homo- or heterozygous for the gene ('P') that Armaly (1967a) has proposed as accounting directly for sensitivity to the hypertensive effect of corticosteroids and contributing to the polygenetically determined disease, glaucoma. Still a third reading could be that the positive water-drinking response is unrelated to either the 'g' or the 'P' gene, and is solely a function of the height of the initial intraocular pressure.

Another consideration relates to the definition of the positive test. Armaly (1970a) and other workers (Nørskov, 1967b; Leydhecker and Niesel, 1954) have stressed the importance of using change in pressure as the measure of reactivity. Spaeth (1966) has suggested, however, that change, measured in terms of mm.Hg intraocular pressure, may not be a physiologically accurate representation, and that change expressed as a percentage may give more valid results. Spaeth found that normal volunteers rarely developed a pressure change exceeding 22 per cent. This is in good agreement with Armaly's data (when recalculated in terms of percentage) that 95 per cent. of normals will show a change of less than 20 per cent. and 99 per cent. a change of less than 35 per cent. In contrast, glaucoma patients infrequently show a change less than 20 per cent. Conceivably, a more valid indicator of the positivity of the water-drinking test may thus be obtained by using percentage change rather than absolute change in mm.Hg. Retrospective examination of previous data indicates that an increase of more than 20 per cent. suggests that the individual under consideration differs significantly from the normal population, and an increase of more than 30 per cent. should exclude at least 95 per cent. of the normal population. This is shown clearly in Table I.

Table I *Positivity of water-drinking test expressed as absolute (mm.Hg) and relative percentage change in intraocular pressure*

<i>Baseline intraocular pressure (mm.Hg)</i>	15	20	25	30
Probable pathological rise (mm.Hg)	4	5	6	8
(per cent.)	27	25	24	27
More certain pathological rise (mm.Hg)	5	7	8	10
(per cent.)	33	35	32	33

The rise in intraocular pressure induced by drinking water is supposedly due to the transfer of water from haemodiluted blood into the more concentrated aqueous humour (Drance, 1958; Leydhecker, 1950b; Hertel, 1914; Galin, Aizawa, and Baras, 1961). This rapid inflow is apparently able to be handled by the normal eye, but the glaucomatous eye cannot readjust its already reduced resistance to aqueous outflow, and a rise in intraocular pressure results. A relationship between rise in intraocular pressure and change in blood osmolality has been well documented (Galin and others, 1965). However, the magnitude of the two responses is not always in good agreement (Campbell, Gloster, and Tonks, 1955). Moreover, after water-drinking approximately 20 per cent. of individuals develop an

increase in intraocular pressure before any change in serum osmolality is detectable, which strongly suggests that there are other factors at work (Spaeth, 1967). Casey (1965) noted in monkeys that the rise in pressure induced by water could be diminished by previous administration of atropine and hexamethonium. In order to test this in humans the following study was designed.

Method of study

Patients were selected from the Glaucoma Service of the Wills Eye Hospital. Age, race, and sex are indicated in Table II. Six patients were classified as chronic open-angle glaucoma suspects, signifying that the intraocular pressure was consistently above 20 mm.Hg, but that signs of glaucomatous cupping of the optic nerve or glaucomatous visual field loss were not present; most of these patients also had a decreased coefficient of aqueous outflow. Definite chronic open-angle glaucoma was present in ten cases, this diagnosis being limited to those with intraocular pressure above 20 mm.Hg, normal open angles, coefficient of aqueous outflow below 0.15/ml./min./mm.Hg, glaucomatous cupping of the optic disc, and visual field defects characteristic of glaucoma. Those patients receiving therapy were being treated with either pilocarpine or epinephrine; none was receiving echthiophate or acetazolamide.

Table II Changes in intraocular pressure after water-drinking test in sixteen patients, 29 eyes

Case no.	Age (yrs)	Race	Sex	Diagnosis	Eye	Intraocular pressure (mm.Hg)				IOP (mm.Hg) after atropine†					
						Before water	After water (min.)				Before water	After water (min.)			
							15	30	45	60		15	30	45	60
1	59	B	F	COA	R	24	28	30	31	31	20	24	24	23	23
					L	24	28	30	32	31	22	25	25	24	24
2	66	B	M	COA	R	32	38	42	45	40	29	32	36	35	34
3	54	B	M	COA	R	25	26	28	29	32	27	31	32	31	29
					L	26	28	30	30	34	29	32	33	32	30
4	49	B	F	COA	R	34	38	38	39	41	30	30	31	32	32
					L	30	34	36	38	39	26	26	26	27	27
5	83	W	M	COA	R	21	26	27	29	30	34	34	36	36	37
					L	22	26	28	29	32	26	27	32	33	33
6	63	W	M	COA	R	26	35	36	37	37	24	32	35	34	33
					L	23	28	30	30	32	24	32	34	28	29
7	60	B	F	COA	R	30	35	37	38	36	27	26	30	29	28
8	76	B	F	COA	R	23	30	31	28	28	26	29	28	28	28
9	59	B	F	COA	R	26	27	30	31	30	26	28	29	30	30
					L	23	26	30	28	25	20	23	23	24	24
10	76	B	M	COA	R	18	22	25	29	29	15	22	24	23	23
					L	21	23	27	32	34	17	23	24	24	24
11	60	B	F	COAS*	R	18	24	26	26	24	23	28	27	25	24
					L	21	29	29	29	28	24	30	30	30	29
12	30	B	M	COAS	R	24	30	26	26	25	27	24	24	25	24
					L	18	21	21	23	18	23	22	21	20	18
13	60	W	F	COAS	R	24	24	28	30	29	20	24	26	24	25
					L	30	32	36	39	37	21	27	29	30	28
14	65	W	F	COAS	R	15	18	20	20	19	16	17	15	14	15
					L	15	17	20	21	18	16	19	16	12	14
15	58	W	F	COAS	R	26	29	30	30	30	24	25	27	27	27
					L	25	28	29	29	30	22	22	25	25	26
16	47	B	F	COAS	R	28	30	32	34	39	29	32	34	34	28
					L	22	24	26	29	32	22	23	30	32	27

*COAS—Chronic open-angle glaucoma suspect

†Atropine 0.4 mg./70 kg. given intramuscularly 30 min. before water-drinking test

The plan of the study was explained to the patient. All medications were stopped for 2 days before the first water-drinking test; a second test was repeated the following day at exactly the same time. No food or drink was taken for at least 8 hours before testing. After determination of the baseline intraocular pressure with a Goldmann applantation tonometer, the patient drank cooled water, 14 ml./kg., within 5 minutes. Intraocular pressure was then determined at 15-minute intervals for 1 hour. The second test was performed in exactly the same manner, except that atropine 0.4 mg. was administered intramuscularly 30 minutes before drinking water.

The data were analysed in standard statistical fashion. All tests were performed by one individual.

Results

The intraocular pressures in all subjects tested are shown in Table II. The maximum rise during the standard water-drinking test averaged 8.03 mm.Hg (Table III). There was no difference between the magnitude of increase in patients with chronic open-angle glaucoma and those in whom this diagnosis was suspected but not proven (Table IV). The "total rise" in intraocular pressure induced by water was determined by summing the differences between the baseline intraocular pressure and the pressure 15, 30, 45, and 60 minutes after water ingestion. This value (23 mm.Hg) is also shown in Table III. After the administration of atropine, the mean rise in intraocular pressure was 4.69 mm.Hg, and the average total increase in pressure 13.24 (Table III). Mean intraocular pressure before the standard water-drinking test was 23.9 mm.Hg, a value not significantly different from the mean of 23.4 mm.Hg before the atropine water-drinking test.

Table III Rise in IOP induced by water-drinking test in 29 eyes

Intraocular pressure (mm.Hg)	Standard test		Atropine, intramuscularly before standard test
Peak rise	8.03 ± 2.37		4.69 ± 3.16
Total increase for four readings	23.00 ± 7.69		13.24 ± 12.02

Table IV Magnitude of rise in IOP induced by water-drinking

Diagnosis	No. of eyes	Maximum rise (mm.Hg)	
		Standard test	Atropine test
Chronic simple glaucoma	17	8	4
Chronic simple glaucoma suspect	12	8	54

The mean maximum rise in intraocular pressure after atropine was significantly less than the mean rise noted in the standard water-drinking test (as determined by the student's t-test; $P \leq 0.001$). The difference between the means of the total change in intraocular pressure induced by water-drinking before and after atropine was also significant ($P \leq 0.01$).

Examination of paired data shows that 83 per cent. of eyes had a larger rise in intraocular pressure when the water-drinking test was performed without the previous administration of atropine; 14 per cent. showed no change in magnitude of the response; in 3 per cent. the rise was larger after atropine.

The time at which intraocular pressure reached its highest level after ingestion of the water is indicated in Table V.

Table V *Time at which intraocular pressure reaches its peak after water-drinking*

Test	Minutes after ingestion of water (per cent.)			
	15	30	45	60
Standard water-drinking	5	15	40	40
Atropine, intramuscularly before water-drinking	20	31	29	20

No untoward effects were noted during this study.

Discussion

This preliminary study suggests very strongly that systemic atropine significantly diminishes the rise in intraocular pressure induced by water drinking in patients with chronic open-angle glaucoma or with ocular hypertension. The mechanism responsible for this difference is not clear. It is possible that absorption of water occurred more slowly in the atropine-treated group. This seems unlikely in view of the fact that intraocular pressure reached its peak level more rapidly in patients who had received atropine than in those who did not. It is also possible that water was less completely absorbed, with less haemodilution and consequently a small effect on the eye. Studies designed to investigate this are now in progress. Armaly (1970a) has shown that there is considerable variation in the same patient when tested repeatedly; however, the response to a second test tends to be larger rather than smaller. Anticholinergic agents given systemically in small doses produce little effect on the coefficient of aqueous outflow or intraocular pressure (Leopold and Comroe, 1948; Hiatt, Fuller, Smith, Swartz, and Risser, 1970; Lazenby, Reed, and Grant, 1970). There is evidence that, in larger doses or when applied topically, they reduce facility of outflow and increase intraocular pressure (Harris and Galin, 1969b; Makabe, 1970). Bill (1967, 1969), however, observed that intracameral atropine produced no change in "gross" outflow, enhanced uveoscleral flow, and reduced intraocular pressure slightly.

Perhaps more important than considerations regarding the local effects of anticholinergic agents on the eye are those relating to central neural control of intraocular pressure. That such a regulation exists is still a matter of controversy. Studies by von Sallmann, Fuortes, Macri, and Grimes (1958) suggest that changes in intraocular pressure may evoke afferent neural activity, indicating the presence of pressure-sensitive receptors in the eyeball (von Sallmann and Löwenstein, 1955). There has been no convincing histopathological evidence of such structures, though a rich nerve supply to the trabecular area representative of various types of fibres has been well demonstrated (Holland, von Sallmann, and Collins, 1956, 1957) and occasional reports have mentioned the presence of formations that could represent nerve endings (Kurus, 1958; Wolter, 1959; Rohen, 1970). The presence of efferent pathways has also been suggested by von Sallmann and Löwenstein (1955), who found that changes in intraocular pressure could be induced independently of blood pressure alterations by stimulating isolated areas in the diencephalon, an observation

confirmed by Gloster (1959). Perkins (1957) observed that elevation of intraocular pressure could be evoked by mechanical (though not electrical) stimulation of the fifth cranial nerve, and postulated the existence of a reflex pathway afferent and efferent antidromically in this nerve. Armaly (1959) noted changes in pressure regulation secondary to stimulation of the ciliary ganglion. On the other hand, Lele and Grimes (1960) were unable to demonstrate short-term control of intraocular pressure in the cat. Podos, Krupin, and Becker (1971) discovered that rapid intravenous administration of amounts of hyperosmotic agents (in doses so small as to produce only a transient, local change in blood osmolality without a detectable systemic alteration) failed to decrease intraocular pressure in the eyes of rabbits or monkeys in which the optic nerve had been transected, whereas they diminished markedly the pressure in the intact, sham-operated fellow eyes of the same animals. This led to the hypothesis that osmotic agents affect aqueous humour dynamics *via* efferent pathways in the optic nerve or sheath, possibly from the hypothalamus. It is conceivable that the fifth or third cranial nerves supply the efferent loop of the arc and that afferent fibres run within the optic nerve, which may explain some of the difficulties experienced by those looking for these fibres elsewhere. A related observation is the rather frequent occurrence of alterations in intraocular pressure that accompanies certain neurological abnormalities, especially those involving the region of the hypothalamus (Brand, 1967).

Atropine blocks the diurnal rise in plasma 17-hydroxycorticosteroids, an effect attributed to suppression of the hypothalamic-pituitary-adrenal axis (Krieger and Krieger, 1967). Adrenalectomized animals have low intraocular pressure primarily because of decreased aqueous production, and show little increase in pressure in response to water-loading (Linnér and Wistrand, 1963). It is feasible, then, that the systemic atropine given in the present study of the water-drinking test produces its effect *via* the central control of intraocular pressure, causing a lesser rate of aqueous humour production than usually follows water-loading. This component of aqueous inflow may account for the rise in intraocular pressure which is noted to occur before the development of haemodilution in about 20 per cent. of humans undergoing the water-drinking test (Spaeth, 1967).

II. FLUORESCEIN ANGIOGRAPHIC PROVOCATIVE TEST

Hoping to eliminate as completely as possible false negative provocative tests, some investigators have combined two or more standard tests. Leighton, Phillips, and Gibbs (1970) found that the frequency of positive tests in glaucoma suspects was low when homatropine alone was used, higher with water-drinking tonography, and highest with homatropine given topically before the water test. Groeschel and Müller (1969) noted that the combination of cyclopentolate, confinement in the dark for 60 minutes, and water-loading produced a rise in intraocular pressure in normal subjects of 4.8 ± 3.0 mm.Hg, while the rise was only 3.6 ± 2.8 mm.Hg when water-drinking was not included.

It would be expected that combining different provocative tests would increase the magnitude of the intraocular pressure response. Whether this enhances the tests' usefulness, however, is less clear. For *the clinical value of a provocative test lies solely in its ability to distinguish between the normal and the pathological*. Merely magnifying the size of the response without increasing the discriminatory capacity serves only to complicate matters. Since a 10 mm.Hg increase lies within the normal range of responses in the combined cycloplegic-dark-water test of Groeschel and Müller (1969), a sizeable number of normal individuals will react positively (that is, will be considered glaucomatous) unless the lower limit considered to be pathological is revised upwards. This accomplished, the high rate

of positives, true and false, falls and the method becomes of no greater diagnostic value than the standard water-drinking test. Since current data do not indicate that combined provocative tests improve diagnostic or prognostic accuracy by enlarging the gap between normal and pathological, they offer the physician little assistance.

There is one possible way in which the increased magnitude of response to combined stress may be of use. This relates to a preliminary but promising method of diagnosing glaucomatous disease, specifically, by means of fluorescein angiography. Patients with glaucomatous damage *and* elevated intraocular pressure almost invariably show a delayed entry of dye into the choroidal vessel system, in contrast to the normal person in whom fluorescein usually lights up the choroid first and the central retinal vasculature afterwards. The reliability of this finding is indicated in Table VI. The arm-to-retina circulation time of glaucoma patients with elevated pressures is also prolonged, as is the retinal transit time (Spaeth, 1971; Rosen and Boyd, 1970). Decrease in papillary fluorescence (Hayreh and Walker, 1967; Oosterhuis and Gortzak-Moorstein, 1970), splotchy areas of peripapillary choroidal hypofluorescence (Raitta and Sarmela, 1970; Blumenthal, Best, Galin, and Toyofuku, 1971b), and a diffuse rather intensely fluorescent peripapillary halo (Oosterhuis and Gortzak-Moorstein, 1970) have also been noted with sufficient regularity to indicate that they are reliable signs of glaucomatous pathology.

Table VI Mean circulation time in patients with glaucoma

Type of glaucoma	Intraocular pressure (mm.Hg)	Circulation time (sec.)		Arm-retina circulation time 2 sec. less than arm-choroid circulation time (percentage)
		Arm-retina	Arm-choroid	
(1) Chronic simple*	Above 30	17.3	32.0	100
	Less than 31	15.6	15.9	29
	Less than 21	15.0	14.8	0
(2) "Low tension"		14.8	16.2	40
(3) Not chronic simple†	Variable	12.8	13.7	8

*Does not include cases of "low tension" glaucoma.

†Includes secondary glaucomas and chronic simple glaucoma suspects. Based on Spaeth (1971).

The abnormal "reversed" pattern of dye entry that so typifies glaucoma patients with elevated intraocular pressure may revert to normal when the intraocular pressure is lowered (Spaeth, 1971; Rosen and Boyd, 1970). It has been suggested that this finding may permit determination of the intraocular pressure that any particular eye is able to tolerate (Spaeth, 1971); that is, what level of intraocular pressure will allow adequate vascular perfusion of the retina and optic nerve (Duke-Elder, 1962). Reversion to a normal pattern does not always occur, no matter how markedly the intraocular pressure is lowered, suggesting that in such cases glaucomatous disease will continue to progress regardless of therapy (Spaeth, 1971). In other cases a normal pattern returns only when the pressure has been lowered far more than is usually accomplished by medical or surgical therapy; this was documented in a woman with progressive visual loss associated with low-tension glaucoma whose angiogram was abnormal when her intraocular pressure was 20 mm.Hg but almost normal when the pressure had been lowered to 6 mm.Hg (Spaeth, 1971).

Blumenthal, Best, Galin, and Gitter (1971a) have attempted to induce the abnormal vascular pattern of glaucoma by raising the intraocular pressure with suction apparatus,

hoping by this means to bring out defects otherwise not apparent. This valuable technique, however, is not without risk, especially in the glaucomatous eye in which the circulation is probably already impaired. Nor is it physiological or easily performed. On the other hand, to provoke a rise in intraocular pressure with water-drinking and then to determine if any change in flow has occurred is relatively easy, and this test mimicks the actual stresses to which a patient is subjected. Rosen and Boyd (1970) have already suggested this as a possible means to detect the vascular defects of early glaucoma. Our experience with *fluorescein angiographic provocative tests* is too limited for us to analyse our results, but the principle seems so sound, the procedure so straightforward, and the early results so promising that we feel its description is justified. The test is useful in patients suspected of having chronic simple glaucoma because of statistical abnormalities (elevated intraocular pressure, disc with larger than normal cup, etc.) but without definite evidence of glaucomatous disease.

A standard fluorescein angiogram is performed on the more involved eye; the patient should be receiving no glaucoma medications. The pupil is dilated with phenylephrine 10 per cent. or other similar sympathomimetic agent; cycloplegics should not be used. 5 ml. "Fluorescite" 10 per cent. are injected as rapidly as possible through a No. 20 needle into the antecubital vein. The timer is activated the instant the injection is started. Exposures are started 5 seconds later, at a frequency of at least one, and preferably two or three per second. These are continued for 10 seconds after the appearance of dye; 1- and 5-minute exposures complete the angiogram. Intraocular pressure is then measured and if it is significantly elevated, appropriate short-acting therapy is started.

On a succeeding occasion, at the time of day when the intraocular pressure is judged likely to be at its peak, a fluorescein angiographic provocative test is performed.

The cornea is anaesthetized with one drop of proparacaine. The minimum amount of fluorescein to allow applanation tonometry is instilled, and the pressure is determined with the eyes deviated slightly towards the direction of the eye being examined so that the central portion of the cornea is minimally disturbed. One drop of cyclopentolate 2 per cent. is placed in each eye and this is repeated at 5-minute intervals for four doses. After the final drop, the patient, who has been fasting for the previous 8 hours, drinks cooled tap water, 14 ml./kg. body weight, within 5 minutes and is then seated in a darkened room. Intraocular pressure is determined as described at 15-minute intervals until a rise of 25 per cent. occurs. A fluorescein angiogram is immediately performed, again on the more involved eye. Technical details of the two angiograms, including the method of development of the film, should be as nearly as identical as possible.

The negatives are examined for the following: arm-retina circulation time; arm-choroid circulation time; retinal transit time; intensity of choroidal and discal fluorescence; vascularity of the disc; peripapillary hypofluorescence; and peripapillary halo. The data from the two angiograms are compared; the interval between the time of dye appearance in the retina and the choroid is noted. If the dye enters the retinal vessels 2 or more seconds before the choroid, the angiogram is characteristic of chronic simple glaucoma.

If both angiograms show typical changes of glaucoma, not only is the diagnosis likely, but the need to lower the pressure is great; a repeat angiogram should then be performed after the administration of oral glycerol to determine the level of intraocular pressure which will allow adequate vascular perfusion. If the first angiogram is normal and the second abnormal, it may be concluded that the abnormality noted is due to the rise in pressure. This patient should be treated sufficiently vigorously to prevent rises in pressure. Conceivably any damage that has occurred may still be reversible at this stage, as best

demonstrated by Shaffer and Hetherington (1969) with theoretical and clinical confirmation by others (Spaeth, 1971; Enoch, Berger, and Birns, 1970). If both angiograms are normal and a significant rise in intraocular pressure is induced by the water-drinking combined with cycloplegia, the patient had best still be considered as a glaucoma suspect and appropriately followed.

The validity and reliability of this test await carefully designed clinical trials of sufficient size to allow standard deviations to be determined.

Summary

The clinical value of a provocative test lies in its ability to distinguish between the normal and the pathological. Tests presently employed in the diagnosis of chronic simple glaucoma are able to discriminate between normal and abnormal to a variable but small extent. No test can indicate infallibly which eyes will develop visual field defects.

The frequency of false negative provocative tests can be reduced by considering intraocular pressure rise in terms of percentages rather than in millimetres of mercury. A rise greater than 20 per cent. after water-loading is suggestive of the diagnosis of chronic simple glaucoma; an increase greater than 30 per cent. makes the diagnosis more likely.

Administration of atropine intramuscularly before the performance of standard water-drinking tonometry markedly reduces the pressure response in patients with definite or suspected chronic simple glaucoma (8 mm.Hg without atropine, 4 mm.Hg with atropine). This suggests that central neural control systems may be involved in the rise in pressure caused by water-drinking.

By combining water-drinking with repeated instillations of strong cycloplegic agents, the magnitude of pressure change can be increased. While this does not in itself enhance the sensitivity of the provocative test, it does provide a setting in which fluorescein angiography may be performed during periods of ocular hypertension. In this way the degree of vascular perfusion to the retina and choroid may be determined, allowing a more rational basis for diagnosis and therapy. The assessment of the value of the fluorescein angiographic provocative test awaits the completion of extensive clinical trials.

COMMENTARY

(1) VALUE OF FLUORESCEIN ANGIOGRAPHY IN THE DIAGNOSIS OF GLAUCOMA

The purpose of all the provocative tests is to separate three population groups; those who are normal and will never develop glaucoma, those who are now normal but who will later develop glaucoma, and those who have already developed glaucoma and have damage from this disease.

The standard provocative tests are of value in the last group, but the purpose of the fluorescein angiography test is to detect patients who show a change in their vascular dynamics early in the development of glaucoma. It is important that such an investigation should give very few false positive or false negative results. This procedure has not been evaluated for long enough to decide whether a patient requires treatment who has a slightly raised resting intraocular pressure with a normal fluorescein angiogram but who has an abnormal one when the pressure is artificially raised.

Older patients frequently have poorly dilated pupils and lens opacities. The timing of the flow of dye is notoriously difficult because of the variation in the arm-to-retina circulation time, particularly if the patient feels sick. Nevertheless, it was striking that most patients without field defects seemed to be able to maintain a normal fluorescein pattern with a raised intraocular pressure. One patient with a glaucomatocyclitic crisis and a pressure of 60 mm.Hg had a perfectly normal fluorescein pattern. On the other hand, patients with chronic open-angle glaucoma in the presence of field defects and cupping showed a great sensitivity to raised pressure.

Some of the technical difficulties could be overcome in the group of patients under 40 years old whose pressures were in the upper 20s and 30s but who had a normal disc. Dr. Spaeth had investigated about 500 cases and felt he had reasonable technical results in about one out of three of the patients with established glaucoma in the older age groups. He also felt that there should be at least a 2-second difference between the arm-to-retina circulation time and the arm-to-choroid circulation time for the phenomenon of reversal to be significant. However, Mr. S. S. Hayreh had seen filling of the choroidal circulation after the retinal circulation at longer intervals than this in perfectly normal eyes, and said that, so far, the method was unproven and required further investigation.

(2) PROGRESSION OF GLAUCOMA IN STEROID-INDUCED GLAUCOMA

Steroid-induced glaucoma is usually permanent but may regress, particularly in the early stages. Regression has been seen over several months and has been observed after a period of 10 years, but it is most unsafe to assume that the glaucoma has disappeared without very careful diurnal measurements, which must include a measurement of the pressure in the early morning with the patient *in bed*. The pressure may fall 5 mm.Hg within a few minutes of rising. Accurate diurnal curves are important in all patients with chronic glaucoma, both treated and untreated, but this is particularly true of cases of steroid glaucoma, in which the diurnal curve may remain abnormal for a prolonged period after the medication has been stopped.

(3) STEROID-INDUCED GLAUCOMA

An increasing number of children seem to have been treated with steroid drops, particularly for vernal conjunctivitis, and a large number of these have developed steroid glaucoma. Mr. Rice had two patients who were blind from steroid glaucoma which was irreversible. For the treatment of vernal conjunctivitis he now uses Intal which has no steroid-like effect and does not affect the intraocular pressure.

Diagnostic evaluation and therapeutic decision in the glaucomas

KENNETH T. RICHARDSON

Department of Ophthalmology, University of Pittsburgh School of Medicine, and Eye and Ear Hospital Pittsburgh, Pennsylvania 15213, U.S.A.

The glaucomas are multi-parameter medical problems that can cause confusion if the physician fails to organize his approach and his thinking. Once he becomes confused or insecure, the tendency is to look for precise measurement, a "magic number" that will eliminate his insecurity. Unfortunately, there are no magic numbers in the evaluation and therapy of the glaucomas. To determine whether a patient requires more or less intense therapy solely on the basis of a Po/C value, or to rest one's diagnosis of chronic open-angle glaucoma on the patient's response to water-drinking, suggests at best a superficial understanding of glaucoma as a disease. It further suggests a failure to understand that the disease, glaucoma, is not simply the inverse of random population statistics.

Three general guidelines are useful when evaluating a glaucoma patient.