COMMUNICATIONS

PRISCOL PROVOCATIVE TEST*

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THE use of Priscol (2-benzyl 4:5-imidazoline) as a provocative test in chronic glaucoma and the method employed (10 mg. by subconjunctival injection) have already been reported (Leydhecker, 1954, 1955; Kronfeld, 1955; Sugar and Santos, 1955; Primrose, 1958). The present communication is a further assessment of the test and its relation to certain other tests.

Healthy Non-glaucomatous Eyes

A series of eleven male and thirteen female non-glaucomatous persons aged 35 to 74 years (average 56.5) was considered as controls. In three instances both eyes were tested and for these three the average result from the two eyes was used in order to maintain the statistical value of the series. The average initial tension was 19 mm. Hg (Schiotz) (S.D. 4.12) and the average rise in tension with the Priscol test was 6.2 mm. Hg (S.D. 1.9). No rise was greater than 10 mm. Hg and the maximum tension reached was 32 mm. Hg. If we accept the criterion of Sugar and Santos (1955), that a rise of 9 mm. Hg or more is positive, there are three positive cases in this series. The occasional weakly positive reading at the upper end of normality is to be expected and need not invalidate the above criterion which is probably a practical basis for differentiating the usual normal from the abnormal case. These few suspicious cases had no other sign of glaucoma, nor did they develop any while under observation for upwards of 2 years, the outflow and water-drinking tests remaining satisfactory.

Glaucomatous Eyes

Chronic Simple Glaucoma (C.S.G.)—This series consisted of thirty male and twenty-two female patients (average age 62.3 years). They all had open angles and had been diagnosed as cases of definite chronic simple glaucoma before being subjected to the Priscol test (except one patient in whom cupping and field loss were absent but who had been referred because the ocular tension habitually lay between 28 and 35 mm. Hg; 2½ years later she developed some cupping and field loss, thus confirming the suspected diagnosis). None of the eyes in this series had been operated on. The mean rise with the Priscol test was 11.8 mm. Hg (S.D. 3.9)—this being a significant difference ($t=2.074$. $0.05 > p > 0.01$) from the normal series. There were positive results

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in 75 per cent. (rise of 9 mm. Hg or more). The maximum rise in tension was 23 mm. Hg and the minimum 5 mm. Hg.

In 38 of these eyes a comparison may be made between the results of the Priscot test and the water-drinking test and tonography which had already been done. The Priscot test was positive in 29 (79 per cent.) (a rise of 9 mm. Hg or more being considered positive). According to Leydhecker (1954) a rise of 11 mm. Hg or more should be accepted as positive, and if we accept this criterion there are 23 (60.5 per cent.) positive cases in this series. The water-drinking test was positive in 22 (58 per cent.), accepting a rise of 8 mm. Hg or more as positive. The facility of outflow (values calculated on the 1955 scale of Friedenwald) was reduced to $C=0.17$ or less in 21 cases (53 per cent.). There was a considerable overlap of positive findings in these three tests but no definite relationship between them; in seven eyes the Priscot test alone was positive when the other two were satisfactory, in three the water-drinking test alone was positive, and again in three a reduced facility of outflow was the only significant finding. In no case were all three tests negative. It would thus seem that these three tests provoke different facets of the glaucomatous tendency. It is also interesting that sixteen of these eyes had a good outflow in spite of the presence of chronic simple glaucoma, C being 0.20 or more, a finding in agreement with that of Becker and Christensen (1956). A further comparison with their work was also available to us—the calculation of the ratio of the initial tension to the facility of outflow. This is accepted as a very reliable test of simple glaucoma. The value of P_0/C was 100 or more in 25 of our series (66 per cent.).

For a comparison with the 24 normal cases, the first 24 simple cases have been analysed further. The mean initial tension was 25.9 mm. Hg (S.D. 4.32) and the mean rise was 11.25 mm. Hg (S.D. 3.39). The chart (Fig. 1) shows the rises in tension for both groups.

FIG. 1.—Rises in ocular tension in normal subjects and cases of chronic simple glaucoma after the Priscot test.

Although there is a considerable overlap between normal and affected eyes in the cases with an initial ocular tension of 20–25 mm. Hg, even here the affected eyes showed a considerably higher rise than the normal eyes; and this is clinically the important level at which differentiation is required. The graph (Fig. 2) shows the average rises at 15, 30, 60, and 90-minute readings for the two groups. It shows that the rise in tension starts quickly, is maintained for about an hour and then subsides. It also shows that the timing of the rise and fall is similar in both groups, though the rise in tension is very much greater in degree in the glaucoma group than in the normal eyes.

Low-Tension Glaucoma (L.T.G.).—

A series of twenty cases of this heterogeneous diagnostic group was already available to us by courtesy of Mr. J. Winstanley (1959). They all had cupping, field loss, maximum P_0 not over 28 mm. Hg, and a negative water-drinking test. Fifteen cases (average age 65.7 years) of Winstanley's series were subjected to the Priscol test, in five cases on both eyes. When one eye was positive the other was usually found to be positive or borderline, and likewise when one was negative its fellow tended also to be negative. It is for this reason that bilateral cases are a statistical snare and why each case is considered as a unit even if both eyes are tested. There were five cases with a rise of 9 mm. Hg or more. In addition there were four cases in which the tension was raised to 30 mm. Hg or more; although the rise itself was not as much as 9 mm. Hg, this was considered sufficient evidence in this dubious group for removing them from the low-tension category and for assuming that they were in reality cases of a low-grade form of chronic simple glaucoma. It is of interest that, of the remaining six cases, two were high myopes, three had wide physiological cups with a glaucomatous spread in the eye tested, and one was considered

FIG. 2.—Average rises in ocular tension in the two groups shown individually in Fig. 1.

to be a case of low-grade chronic simple glaucoma. The ratio P_0/C was 100 or more in eleven cases. The facility of outflow was poor in eleven of the fifteen cases, and became poor after water-drinking in one more case. In two cases the Priscol test was the only test to give a positive result. In one other case the resting tension of 17 mm. Hg rose by 9 mm. to 26 mm. Hg, and the only other positive finding was a rather poor facility of outflow which water-drinking failed to impair further.

Narrow-angle Glaucoma.—From the previous series of clear-cut angle-closure cases (Primrose, 1958), the results were so variable that the test was not considered to be very reliable or informative. The rise in tension seemed to vary with the level of the initial tension and with the degree of control by miotics, but not consistently so. This is in contrast to the findings in the cases of chronic simple glaucoma, in which miotic therapy had little effect on the result and even those with a low initial tension showed a good rise. No acute attacks, however, were precipitated in thirty tests carried out on 28 patients. [The average age in this group was 53.6 years and there were seven males to 21 females. The mean rise was 7.5 mm. Hg (S.D. 3.66) with positive results in ten cases (33 per cent.)]. The general assumption still holds good that, if the angle is not in the closed state, the eye reacts as a normal eye, but if the angle is in the closed or partially-closed state, large rises in ocular tension are to be expected. This may be seen from the wide range of the rise with Priscol, the minimum being 3 and the maximum 20 mm. Hg.

Further Investigations

Consistency of the Test.—Some cases were subjected to a repeat of the test on the same eye and under similar conditions; as Table I shows, the tension levels and the degrees of rise in tension were remarkably consistent. Two cases of narrow-angle glaucoma in which the test was repeated, however, showed quite different results (not charted).

TABLE I
RESULTS OF REPEAT TESTS ON SAME EYES

	Test	First			Second		
		P_0	P_{max}	Rise (mm. Hg)	P_0	P_{max}	Rise (mm. Hg)
Group	Normal	20	25	5	20	22	2
		14	23	9	17	26	9
	Low-Tension Glaucoma	17	30	13	18	30	12
		25	33	8	22	34	12
	Chronic Simple Glaucoma	28	45	17	28	42	14
		22	37	15	21	36	15
		17	30	13	18	30	14
		27	35	8	24	33	9

Use of Control Solution.—Five patients with a positive Priscol test were given a subconjunctival injection of an inert solution, which was equivalent in pH, osmotic pressure, and molecular size to the Priscol solution. There was a slight and very transient rise in tension in three of the cases and a fall in the other two. The manipulation and anaesthesia were therefore considered to have no appreciable effect on the test.

Other Effects of Priscol.—After the administration of Priscol some chemosis and a marked vasodilatation of the episcleral blood vessels were the rule. The redness persisted for 24 hours or so, even after adrenaline was given at the end of the test. There was no pain from this *per se*, but one patient developed a subconjunctival haematoma which took some days to absorb. The vasodilatation could be seen to affect the vessels of the iris in cases in which this tissue was not heavily pigmented, the major arterial circle, where visible by gonioscopy, and presumably also the vessels from it supplying the ciliary body. The retinal vessels were seen to be unaltered. No change in the width of the angle was noticed, and the size of the pupil showed little change.

The vasodilatation caused by Priscol primarily affects the arterioles. An increased pulsation on the tonometer is usually apparent (Fig. 3).

FIG. 3.—Tonography before and after subconjunctival Priscol.

The pulse travels further through the vascular bed in this state of arteriolar vasodilatation and can be seen even in the episcleral veins when measuring the episcleral venous pressure. These vessels are engorged and the episcleral venous pressure is appreciably raised (Stepanik, 1958a). This was kindly confirmed for me by Dr. Arthur Leith in two cases of chronic simple glaucoma in which the episcleral venous pressure rose from 11.5 to 18 mm. Hg and from 12.5 to 16 mm. Hg respectively with Priscol; in a normal eye it rose from 10.5 to 14 mm. Hg. Aqueous veins are difficult to find after administration of Priscol even where they were easily seen before; where lamination is seen the aqueous ribbon is greatly narrowed by the engorgement with blood, while other aqueous veins may no longer show any aqueous.

A comparison between the results of tonography performed about one hour after the injection of Priscol and the patient's ordinary tonography test suggests that the drainage of the aqueous is impaired (Table II).

TABLE II
TONOGRAPHY BEFORE AND AFTER PRISCOL

Group	Facility of Outflow C	Rise with Priscol (mm. Hg)	Facility of Outflow after Priscol
Normal	0.33	5	0.23
Chronic Simple Glaucoma	0.14	11	0.10
	0.13	13	0.06
	0.21	15	0.17
Low-Tension Glaucoma	0.32	6	0.21
	0.22	10	0.19
	0.20	8	0.14

The facility of outflow was reduced in all the cases tested. Stepanik (1958b) found this factor to be reduced by Priscol in cases of chronic simple glaucoma, and to be reduced to a greater extent in those showing a rise in tension of 11 mm. Hg or over than in those in whom the rise in tension was smaller. Swanljung and Blodi (1956) showed that the facility of outflow was reduced in thirteen out of 21 normal eyes, and in some cases of chronic simple glaucoma; they were of the opinion that the cases with a high initial facility of outflow responded with a marked diminution.

The Priscol test was done in three cases of glaucoma after 250 mg. Diamox had been taken by mouth. The essential action of Diamox is considered by most workers to depend on a reduction in the formation of aqueous. In these three cases the rise in tension following the injection of Priscol was considerably reduced in two (rise reduced from 15 to 6 mm. Hg and from 11 to 8 mm. Hg respectively) and was practically unchanged in the third. The inference might be drawn that Priscol acts to a certain extent by increasing the formation of aqueous. The action of Diamox, however, is not

sufficiently understood to justify this. Further experimental work is required here.

It was thought that the fluorescein permeability test of Amsler and Huber (1946) might be helpful in settling the question whether or not there was an increased formation of aqueous. Fluorescein was injected intravenously at times varying from 23 to 110 minutes after the subconjunctival injection of Priscol in seven cases. There was no consistent or appreciable difference (in the time of appearance of the fluorescein in the aqueous and in the minimum brightness of light required to show it) between the eye subjected to the Priscol test and its fellow. From this it may be deduced that the rate of diffusion of fluorescein across the blood-aqueous barrier is uninfluenced by the vaso-dilatation produced by Priscol. We know that the capillary permeability to fluorescein is increased in cases of active anterior uveitis (Cook and MacDonald, 1951; Miller and Swanljung, 1951). The vasodilatation produced by Priscol is not accompanied by increased capillary permeability and in no single case subjected to the Priscol test have I seen the production of a plasmoid aqueous. It is of interest that one of these patients, a case of simple glaucoma, had a freely-draining trephine operation on the left eye, the tension of which measured 6 mm. Hg only. The tension of the right eye after the instillation of pilocarpine 1 per cent. measured 21 mm. Hg. It was thought that the embarrassment of the outflow usually produced by Priscol might have been a factor hindering the increased production of aqueous, and by testing this freely-draining eye that factor could be ignored. A preliminary fluorescein permeability test was carried out in case some difference in flow was demonstrable between the two eyes at such differing tension levels; no such difference was found, as indeed Miller and Swanljung (1951) have previously shown in operated cases. The Priscol test on the left eye raised the tension to 9 mm. Hg (a Priscol test on that eye before its operation had raised the tension from 22 to 33 mm. Hg), yet still no appreciable difference in flow was found by carrying out a further fluorescein test while the eye was in the state of vasodilatation produced by the Priscol.

A further check, by means of the fluorescein instillation test of Langley and MacDonald (1952), showed no appreciable difference in rate of flow of aqueous for the eye subjected to the Priscol test in three cases, but one case did show a definite increase. The limitations of the method and the small number of cases scarcely allow accurate deductions to be drawn, but in each case the fellow eye was used for control observations, and in the one definite case the fluorescein in the aqueous was reduced from a concentration of about 15 parts per million to 7.5 parts per million in $1\frac{1}{2}$ hours after the injection of Priscol, whilst the concentration in the fellow eye fell from 10.5 to 8.5 parts per million in the same time. This is a more definite test of flow than the fluorescein permeability test wherein permeability rather than flow is measured.

Discussion

The mechanism of the test is complex. There is no doubt that vascular engorgement of the anterior part of the eye occurs, both within the globe and in the episcleral plexus. The hydrostatic pressure within the capillary bed is raised and also that in the veins draining from the eyeball. The raised capillary pressure is transmitted to the intra-ocular structures and would immediately raise the intra-ocular pressure. Increased formation of aqueous might be expected to result from the increased pressure in the capillaries of the ciliary body, but this is counterbalanced by the raised intra-ocular pressure, hydrostatic equilibrium at a higher level being established between the capillary pressure and the intra-ocular pressure with no change in the osmotic forces as far as the action of Priscol is concerned. At this new level more aqueous might be expected to be forced out of the eye through the usual drainage channels, and, if this were so, there would be increased formation of aqueous to replace it and maintain the hydrostatic equilibrium. But the aqueous is hindered from draining into the episcleral veins at their raised pressure. The evidence for increased formation of aqueous is conflicting. Stepanik (1958b) calculated that the minute-flow of aqueous was unchanged or reduced; Swanljung and Blodi (1956) found that it was usually increased. Their calculations were based on the tension, facility of outflow, and episcleral venous pressure, all of which are greatly altered during the Priscol test and it is improbable that we can rely on calculations at such unusual values. The fluorescein tests reported in this paper have shown a definite increase in flow in only one case (although minor alterations may have been missed by the rather crude method of measurement employed).

Increased flow of aqueous does not appear to be an essential part of the causation of the rise in tension and would not account for the increased pulsation of the tonometer. Again, the raised episcleral venous pressure and the impaired outflow which regularly occur would not account for the increased pulsation and would scarcely account for such a rapid rise in tension as occurs. Miller (1953) produced vasodilatation by stellate ganglion block and found that the intra-ocular pressure rose immediately in cases of chronic simple glaucoma; but the pressure remained raised for about 10 minutes only, thereafter falling to somewhat below the original pressure. Miller attributed the rise to the increase in volume causing the dilated vessels to occupy more space within the eyeball and also to the impaired drainage characteristic of this disease preventing a corresponding volumetric displacement of aqueous through the drainage channels. The vasodilatation produced by subconjunctival Priscol and by stellate ganglion block are probably very similar. The outflow is embarrassed by the action of the Priscol. It may be that the loss of aqueous is not sufficient to compensate for the space taken up by the vascular engorgement and that this also is a

factor in maintaining the raised intra-ocular pressure, but it is the arteriolar vasodilatation which produces the engorgement and it alone can account for the increased pulsation.

Suffice it to say that the vascular engorgement raises the tension in both normal and glaucomatous eyes. The normal subjects can cope with the rise but the glaucomatous eyes fail to do so, because of impaired outflow, an excessive vascular reaction, increased aqueous production, or a combination of these factors.

Conclusions

The Priscol test is a valuable and reliable test for chronic simple glaucoma even of the low-tension type. It gives more definite results than the water-drinking test or tonography alone, and gives about the same proportion of positive results as the ratio P_0/C (as far as one can judge from those cases in this series in which the ratio was available). It is sometimes positive when other tests are negative. It is relatively easy to perform clinically, the important readings being those taken 30 and 60 minutes after injection (for general clinical use the 15- and 90-minute readings could well be omitted). In cases of chronic narrow-angle glaucoma, however, it is unreliable, the well-controlled cases behaving in much the same way as the normal subjects but the poorly-controlled cases showing a considerable rise.

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