COMMUNICATIONS

SOME OBSERVATIONS ON THE WATER-DRINKING TEST IN GLAUCOMATOUS AND NON- GLAUCOMATOUS SUBJECTS*

BY

D. A. CAMPBELL, J. GLOSTER, AND E. L. TONKS

From the Research Department, Birmingham and Midland Eye Hospital

THE imbibition of water is known to cause a rise in intra-ocular pressure in glaucomatous subjects, particularly in those in whom the intra-ocular pressure is raised initially (Léydecker and Niesel, 1954). Although the test in its present form is of limited diagnostic value in cases of suspected glaucoma, it is of some academic interest in respect of the relationship of intra-ocular pressure to accompanying changes in the extracellular fluid of the body. This paper is a preliminary study of the nature of diuresis and of the alterations in diffusible and non-diffusible constituents of the blood in relation to intra-ocular pressure.

The most noticeable effect of the imbibition of a large volume of water is a considerable diuresis, yet there is no gross dilution of the plasma (Haldane and Priestley, 1916). In glaucomatous subjects, Marx (1925), de Decker (1929), Wegner (1930 a, b), and Schmidt (1931) observed that the rise in intra-ocular pressure coincided with an initial dilution of the plasma, and that the latter was followed by phasic variations (as shewn by the haemoglobin content) which appeared to be due in sequence to (a) loss of water by diuresis and (b) migration of fluid from the plasma into and out of the tissues. These variations bore no relationship to the actual volume of water taken, nor to the diuresis (de Decker, 1929). There is no doubt that fluid interchanges in the body, as well as excretion, account for such conflicting evidence as that of Marx (1926a), who found an initial fall of 12 per cent. in the plasma proteins with a return to normal level after 1½ hours, and of Verney (1929), who later observed that there was no change in the plasma protein concentration even at the height of diuresis.

The accumulated physiological evidence shews that in normal subjects (Best and Taylor, 1950) after water imbibition, the great bulk of ingested fluid leaves the vessels and is followed or accompanied by salt which serves to preserve the isotonicity of the tissue fluids :

The load is subsequently discharged from the tissues in a slow but steady stream and transported to the kidneys (p. 457).

Further, the diuresis which follows is largely due to the inactivation of the antidiuretic factor (Verney, 1929) through a fall in the osmotic pressure

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*Received for publication December 1, 1954.

of the blood, and particularly through a fall in the concentration of sodium chloride. The factor is unaffected by variations in colloidal osmotic pressure.

The variation in electrolytes is therefore of some significance; Priestley (1916) found in normal subjects that the imbibition of water caused the electrical conductivity of the serum to diminish by 2.5 per cent., and Marx (1926b) also found a temporary decrease in serum chloride. Leydhecker (1950), in 42 glaucomatous patients, observed changes in the electrical resistance of the serum in most cases directly related to changes in intra-ocular pressure, indicating an initial fall in the plasma electrolytes.

Sodium as an electrolyte exerts a considerable osmotic effect, and in certain subjects, *e.g.* those who suffer from migraine, an abnormality of sodium excretion has been observed in the water imbibition test. The diuresis which occurs is of normal amount and course, but the amount of sodium excreted is very much greater than in the normal subject (Campbell, Hay, and Tonks, 1951).

Experimental Work

It will be appreciated that the carrying out of a water imbibition test, with coincident records of intra-ocular pressure and the frequent collection of blood and urine for analysis, is time-consuming, and requires a team of research workers. Thus in the present series of tests we have investigated only eleven glaucomatous subjects, eight of whom were of the congestive type, while the other three had glaucoma simplex, according to Miller's classification, but we have been able to compare our results with those from 74 non-glaucomatous subjects.

Having had the experience of one subject who developed acute glaucoma and required an emergency operation after a water imbibition test, we selected known glaucomatous cases who had comparatively low initial tensions or who had already had an adequate filtration operation before the test. This explains the comparatively low rises in tension obtained during the test—but does not invalidate our results—since all subjects were subjected to precisely the same conditions of experiment and our main interest was directed to the changes which might occur in the plasma and urine.

Methods

(1) **Water-Drinking Test.**—The patient was admitted on the day before the test. Nothing was given by mouth after 10 p.m. on the night before the test until 7.30 a.m., when two small portions of toast and butter and 5 oz. of water were taken in order to guard against dehydration before the test. The patient remained in bed and smoking was not permitted. At 9.30 a.m. urine was collected, a specimen of blood was taken, and the tensions were measured. Immediately afterwards, the patient drank a quantity of slightly warmed tap-water as rapidly as possible. The volume of water given was either 1,000 or 1,500 ml., but occasionally patients were unable to take the intended amount. In the majority of tests, further measurements of tension and collections of blood were made at intervals of half an hour, 2 hours, and 4 hours after drinking the water, but, when possible, more frequent readings were taken. Urine was collected every half-hour and the volume and specific gravity of each specimen were recorded. The patient remained in bed at rest throughout the test which was continued for 4 hours from the time of drinking water. Blood was taken from the lobe of the ear if serum sodium only was to be estimated, but if plasma proteins were also estimated a venepuncture was done.

(2) **Tensions.**—Miotics had been discontinued for at least 24 hours before the beginning of the test. All tensions were measured by the same observer, using an earlier model of the Schiötz tonometer, having a plunger with a concave surface. 4 per cent. butocaine was instilled before tonometry. The illumination in the patient's room was kept as constant as possible during the test.

(3) **Serum Sodium.**—In the earlier experiments in this series, serum sodium was estimated by Eisenman's modification of Kramer and Gittleman's method (Wakeman, Eisenman, and Peters, 1927; Kramer and Gittleman, 1924). Later estimations were done using a flame photometer.

(4) **Serum Proteins.**—These were estimated by a modification of the method of King, Haslewood, and Delory (1937).

Results

(A) Course of Diuresis

(1) *Incidence of 'High' and of 'Delayed' Diuresis.*—Leydhecker (1950) classified diuresis as 'high' or as 'delayed' by the following criteria. In 'high' diuresis, more than nine-tenths of the ingested water was excreted within the first 2 hours, or more than the total amount ingested was excreted within 3 hours. In 'delayed' diuresis, the corresponding figures were less than six-tenths within 2 hours or less than eight-tenths within 3 hours. He established that, in 67 tests on patients suffering from glaucoma, twelve (18 per cent.) shewed a 'delayed' diuresis, and thirty-five (52 per cent.) a 'high' diuresis, the figures for simple and congestive glaucoma showing no substantial difference from one another, but his control tests were few.

We compared the incidence of 'high' and 'delayed' diuresis in:

- (a) Eleven glaucoma patients
- (b) Twenty normal healthy subjects
- (c) Forty migraine patients.

Table I shows that our results for glaucoma are in general agreement with those of Leydhecker, and *that the incidence of 'high' and 'delayed' diuresis in glaucoma does not differ significantly from that in healthy subjects or in migraine patients.*

TABLE I
INCIDENCE OF "DELAYED" AND "HIGH" DIURESIS IN WATER-
DRINKING TESTS

Clinical Condition	Source of Data	Number of Tests	Incidence of "Delayed" Diuresis (per cent.)	Incidence of "High" Diuresis (per cent.)
Glaucoma	Leydhecker (1950)	67	18	52
Glaucoma	Present Series of Tests	11	18	55
Controls		20	20	50
Migraine		40	25	50

(2) *Rate of Excretion and Variations in Specific Gravity of Urine.*—The change in the rate of excretion of urine and the variations in the specific gravity were compared in glaucoma patients and in control subjects after drinking 1,000 or 1,500 ml. of water (Fig. 1). Each curve is constructed from the average for eight individuals; the volume of water taken varies from person to person, the two groups being closely matched in this respect. *There were no gross differences between the rates of excretion of urine and the specific gravity changes in glaucoma patients as compared with control subjects.*

Fig. 1.—Rate of excretion of urine and specific gravity of urine after drinking 1,000-1,500 ml. water.

the test; one had vomited after drinking, but there was no obvious explanation for the behaviour of the serum sodium in the other.

Table II (opposite) compares variations in serum sodium after 1,000-1,500 ml. water had been ingested by ten glaucoma patients and ten non-glaucomatous subjects. It will be seen that in glaucoma there is a much wider range and a slower return of the serum sodium to its original level.

(2) *Changes in Colloid Osmotic Pressure of the Blood.*—The serum proteins

(3) *Volume of Diuresis.*

—We found that after the 1,000-ml. test the average diuresis in glaucomatous subjects (1,189 ml.), was slightly less than for normal subjects (1,286 ml.).

(B) *Changes in Composition of the Blood after drinking Water*

(1) *Changes in Serum Sodium.*—An initial fall in sodium was found in 33 out of forty water-drinking tests carried out on various subjects, the serum sodium being on an average, 3.5 per cent. below its initial level, half an hour after drinking water. Five subjects showed a small rise of serum sodium 30 min. after drinking, followed by a fall 1½ hours later. In two subjects, the serum sodium after drinking water remained above its original level throughout

TABLE II
VARIATION IN SERUM SODIUM IN WATER-DRINKING TEST

Series	Subject No.	Type of Glaucoma	Serum Sodium (mg/100 ml.)			
			Before Water	$\frac{1}{2}$ hr After	2 hrs After	4 hrs After
(A) Glaucoma Patients	1	Congestive ...	348	366	328	333
	2	Congestive ...	343	318	328	348
	3	Simple ...	340	345	357	345
	4	Congestive ...	365	355	324	340
	5	Congestive ...	340	315	328	343
	6	Simple ...	334	328	324	330
	7	Congestive ...	346	334	348	346
	8	Congestive ...	342	335	330	328
	9	Congestive ...	335	312	312	315
	10	Simple ...	325	318	324	330
Mean			342	333	330	336
(B) Subjects without Glaucoma	11		338	332	332	342
	12		335	340	320	340
	13		326	325	325	330
	14		330	320	324	338
	15		328	320	328	330
	16		330	320	326	326
	17		328	326	318	326
	18		322	320	318	322
	19		328	317	318	325
	20		335	322	328	344
Mean			330	324	324	332

were estimated in six glaucoma patients and the colloid osmotic pressure of the blood was calculated from the values of serum albumin and globulin according to the formula of Govaerts (1925). The average value was higher than for six normal patients. Both shewed a slight initial fall in total protein, although this did not occur in every individual case. Serum albumin was higher in glaucoma patients (Table III) but not significantly so.

TABLE III
VARIATION IN SERUM PROTEINS IN WATER-DRINKING TEST

Protein*	Before	After $\frac{1}{2}$ hr	After 1 hr	After 2 hrs	Series
Total (mg. per cent.)	6.66 6.51	6.50 6.36	6.75 6.46	6.88 6.48	Glaucoma Normal
Serum Albumin	4.31 3.85	4.26 3.80	4.43 3.96	4.65 3.88	Glaucoma Normal
Serum Globulin	2.65 2.65	2.30 2.57	2.32 2.51	2.27 2.60	Glaucoma Normal
Colloid Osmotic Pressure (mm. Hg.)	27.1 24.9	26.5 24.5	27.8 25.3	28.2 24.8	Glaucoma Normal

* Average values for six glaucomatous and six normal subjects.

It is appropriate to state here that the colloid osmotic pressure of the serum is unlikely to influence intra-ocular pressure, since the osmotic effect of sodium is so much greater. Robertson (1938) observed in patients suffering from nephrosis that the intra-ocular pressure remained normal despite a fall in serum colloid osmotic pressure from the usual 25 mm. Hg to values as low as 7 mm. Hg.

(C) Relationship of Changes in Ocular Tension to Type of Diuresis and to Changes in Composition of the Blood.—Although a 'delayed' type of diuresis might be taken as an indication of retention of water in the tissues, we found no unusual rise of ocular tension in association with this type of diuresis. An analysis of our results (Table IV) shews that we obtained no evidence of any relationship between the rise in tension and the type of diuresis.

TABLE IV
RANGE OF ALTERATIONS IN OCULAR TENSION IN DIFFERENT
TYPES OF DIURESIS

Type of Diuresis	Change in Tension (mm. Hg Schiötz) $\frac{1}{2}$ hr after Water Drinking		
	Non-Glaucomatous Subjects (14)	Glaucoma Patients (11)	
		Operated Eyes (9)	Unoperated Eyes (13)
High	-4 to +5	0 to +10	+3 to +15
Normal	-3 to +3	+2 to +5	+3 to +7
Delayed	0 to +3	+2 to +4	0 to +10

- = fall in ocular tension. + = rise in ocular tension.

Moreover, we were unable to demonstrate any obvious correlation between the *amount* by which the serum sodium fell after drinking water and the accompanying change in ocular tension (Table V).

TABLE V
RANGE OF ALTERATIONS IN OCULAR TENSION IN COMPARISON
WITH THE FALL IN SERUM SODIUM

Change in Serum Sodium (per cent.)	Change in Tension (mm. Hg Schiötz) $\frac{1}{2}$ hr after Water Drinking		
	Non-Glaucomatous Subjects (14)	Glaucoma Patients (10)	
		Operated Eyes (9)	Unoperated Eyes (11)
0 — 3 (fall)	-3 to +3	+2 to +9	+2 to +15
3 — 6 (fall)	-4 to +4	+4	+10
6 — 9		0 to +5	+3 to +6

- = fall in ocular tension. + = rise in ocular tension.

This lack of proportion between the extent of the fall in the serum sodium and the change in ocular tension was well illustrated by one case. This patient, who was 54 years old, had been diagnosed as suffering from simple glaucoma in 1947, and, in that year, a trephine operation was carried out on the left eye. She was kept under observation for a subsequent period of 6 years and the tension remained normal without the use of miotics. A water-drinking test was done in 1953 (Fig. 2a) and provoked a considerable rise of tension particularly in the right (unoperated eye) and she was advised to instil 1 per cent. pilocarpine drops into both eyes every night. Six months after the first test, a second water test was carried out (Fig. 2b).

Fig. 2 (a, b).—Water-drinking tests on a patient suffering from glaucoma simplex.

Whereas, in the first half-hour after drinking, the extent of the fall in serum sodium is almost the same in the two tests, yet the tensions increased much more in the first test than in the second, over the same period of time. From this, it is evident that the tension change is not solely dependent upon a change in blood composition. It appears likely that differences in local conditions in the eye (possibly attributable to the use of pilocarpine up to 48 hours before the second test) were of far greater importance

in determining the response of the intra-ocular pressure to drinking water than were alterations in the ionic content of the blood.

In 25 water tests on glaucoma patients and non-glaucomatous subjects, sixteen cases shewed an increase of tension over the period of time during which the sodium fell and *vice versa* (Fig. 3a, b, c, overleaf). Occasionally as in Fig. 3 (c), the highest tension was reached before the serum sodium had fallen to its lowest level. In three cases only, the reverse was found.

Discussion

Diuresis.—Our records shew that the diuresis induced in glaucomatous

Fig. 3 (a, b, c).—Relationship between ocular tension changes and serum sodium changes in water-drinking test.

subjects is normal in respect of rate, volume, changes in specific gravity, and in the incidence of “delayed” or of “high” diuresis. This would appear to indicate that there is no dysfunction of the posterior lobe of the hypophysis.

Our findings differ from those of Schmidt (1928, 1929, 1931) and of Wegner (1930 a, b), who after giving weak tea found a delayed diuresis and urine of low specific gravity in the majority of subjects suffering from glaucoma simplex. It should be noted that these workers do not state whether their subjects were kept at rest—an important precaution in experiments on diuresis (Netravisesesh, 1953).

Variations in Blood Constituents.—In exploring the possibility that the rise of intra-ocular pressure in this test is partly due to osmotic changes between the blood and the eye, we have the evidence that in the majority of cases the initial rise in pressure coincides with a fall in serum sodium and a fall in blood protein. Wegner (1930) and his school of observers obtained similar evidence of an immediate dilution of the plasma, as shewn by a fall in haemoglobin. They also found a few exceptional cases—as we did—in which the rise in intra-ocular pressure was accompanied by a rise in serum sodium.

Schmidt (1931), Marx (1925), and Hertel (1914) ascribed the consecutive variations in dilution of the plasma (as judged by the haemoglobin content) to an *alteration* in the capillary endothelium affecting the fluid interchange between blood and tissues. Such a change should be more evident on the sodium figures, since we know (Wynn and Rob, 1954) that sodium is the factor which is responsible for 95 per cent. of the osmotic pressure of the extracellular fluid of the body.

Glaucomatous subjects shew an instability of plasma sodium even when resting in bed (Campbell, 1952) and in the present experiments have been found to have a higher initial value of blood sodium than normal subjects, and wider excursions of blood sodium levels during the test (Fig. 4).

Fig. 4 (a, b).—Serum sodium changes in water-drinking test in ten glaucoma patients and ten controls.

The fall in blood sodium which occurred during the first half hour, *i.e.* during the time when the intra-ocular pressure rose to a maximum was not however proportional to the amount of that rise. Indeed the difference in pressure which occurs between the two eyes of one individual is so well known that it is obvious that there must be some regulating mechanism within the eye itself which either has an independent influence on intra-ocular pressure or resists the effects which arise from osmotic changes in the blood.

The relationship of the intra-ocular pressure to diuresis is not yet fully known. Verney (1929) has shewn that diuresis is mainly due to the inactivation of the antidiuretic factor of the pituitary, which is brought about by the fall in osmotic pressure of the blood, which follows a drop in crystalloids especially of sodium chloride, but which is unaffected by alteration in the blood proteins.

Our results show that the average initial fall in blood sodium in both the glaucomatous subjects (4.1 per cent.) and in normal subjects (2.1 per cent.) might reasonably be expected to promote diuresis in both instances soon after drinking water.

It is interesting to find in some recent experiments (Thiel, 1952) that the rise of intra-ocular pressure caused by water imbibition can be increased by the injection of posterior pituitary lobe extract or by nicotine. The latter has an antidiuretic action, demonstrated by Burn and others (1945) in rats. Bietti and Cima (1954) found in rabbits that nicotine acting alone will cause an immediate rise in intra-ocular pressure of 4-7 mm. Hg and will enhance

the effect of water imbibition. Total hypophysectomy in the rabbit not only brings about a lasting fall in intra-ocular pressure but causes any subsequent test with water imbibition or with nicotine to have no effect on intra-ocular pressure.

Weinstein (1950) modified the imbibition test in human subjects by administering 1 litre tea and injecting an extract of posterior lobe of the pituitary. He obtained positive results in a number of cases in which the imbibition of water alone was without effect. The rise in intra-ocular tension was exacerbated by the smoking of cigarettes. It is unfortunate that the strength of the tea and the dose of pituitary are not stated. In contrast with his results, Leydhecker and Niesel (1954) report that the intramuscular injection of 6 Vogtlin units of pituitary hormone 15 to 25 min. before the water imbibition test produced no significant difference in the rise of intra-ocular pressure.

Marx (1926 a, b) suggested that there was a central nervous mechanism which controlled both diuresis and blood dilution. He based his theory on the fact that he was able to induce diuresis and a typical phasic dilution of the plasma in a subject under hypnosis by the suggestion of drinking.

It may be that the posterior lobe of the hypophysis has a direct effect on intra-ocular pressure, but it seems more probable that its action is an indirect one linked with the control of diuresis and with the resultant alteration in distribution and constitution of extracellular body fluid.

Summary

Experiments with the water-drinking test have enabled us to arrive at the following conclusions:

(1) Diuresis in the glaucomatous patient is normal in respect of volume of urine, specific gravity, and rate of excretion. The incidence of "high" and "delayed" types of diuresis is the same as among normal subjects.

(2) There is an initial fall in the blood sodium which coincides with the maximum rise in intra-ocular pressure but shows no proportional relationship to it. This applies to both normal and glaucomatous subjects with few exceptions.

(3) The blood sodium shows a higher initial level and wider variations during the test in the glaucomatous subject than in the normal subject.

The significance of these changes is discussed in relation to the effect of posterior pituitary hormone in controlling diuresis and causing a rise in intra-ocular pressure.

Our thanks are due to Miss Mary Howe and Miss W. Robbins for preparing the diagrams and typescript.

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