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DIURETICS AND THE EYE*

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This lecture is given annually to honour the memory of Richard Middlemore, who was appointed surgeon to this hospital in 1828. In his day he was obviously a keen observer and a competent ophthalmic surgeon. In 1835 he published his *Treatise on the Diseases of the Eye*, which is a résumé of lectures he gave to members of the medical profession. That he was particularly aware of the importance of relating ocular disorders to the state of the body as a whole is shown by the following quotation from his first lecture:

"I do not profess to give an elaborate account of the progress of ophthalmic knowledge, but may briefly mention, in these preliminary observations, that, in former times, the treatment of diseases of the eye was in a great measure confined to *Oculists*,—to a class of persons assuming that name,—who very frequently acquired, with great notoriety, considerable wealth and importance. You will not fail to remark that these persons, as their conduct and writings evinced, were characterized by extreme assurance and extraordinary ignorance, and that their treatment of ophthalmic disease consisted almost entirely in the rude and unscientific application of disgusting local remedies. If, however, by the term *Oculist* is meant a person competent to treat the various maladies of the human eye, without any, or only a very slight acquaintance with general anatomy, pathology, and therapeutics, we may confidently assert that there is no such individual in existence; for he only can be considered adequate to the treatment of disease, in whatever part it may be situated, who is conversant with the natural structure of parts, with the laws which regulate the healthy functions, and with the derangements and alterations produced by the encroachments of disease,—with the sympathies, the influences and the connexions subsisting between every part of the animated machine. If, however, in defiance of common sense, you do attempt to disconnect the study of diseases of the eye from the cultivation of the other branches of your profession—if, in short, you isolate, as it were, the pathology of the eye, and affect to study its diseases for the purpose of becoming mere *oculists*, you must inevitably fail in your attempts to obtain even an approach to a sound and perfect acquaintance with them. Such, at least, are the views I have formerly expressed and always entertained, and they are decisively sanctioned by my learned friend Mr. Lawrence, in his recently published work. I shall take the liberty of reading to you his opinion upon the subject. Referring to the human body, he says, 'in such a system, then, of intricate connexion and mutual influence, each part will be best understood by him who has the clearest notions of the general economy.'"

The principles expressed by Richard Middlemore have been upheld by those who have followed him, and this Memorial Lecture is designed for general practitioners as well as for ophthalmologists. It therefore seemed appropriate for me to choose a subject relating the eye to the reactions of the body as a whole and to

base my observations on research work conducted in this hospital. Some of the work is familiar to you already, but on this occasion I propose to review it from the point of view of the "nature of the systemic action of certain diuretics as compared with others, and of the concurrent effect of each upon the eye."

Diuretic Action of Urea and of Water in Migraine

My interest in the action of diuretics began during the war, when there was a marked increase in cases of migraine, many of which found their way to my ophthalmic department.

At about that time Dr. J. A. Brown (1943), a general practitioner of this city, but who was then the R.M.O. at the General Hospital, had reported that a patient who had suffered from severe migrainous headaches for many years, and who had been admitted to hospital for investigation with a view to operation for cerebral decompression, suddenly became free from headache on the morning after a urea concentration test. This patient escaped operation and was later discharged on regular doses of urea and remained free from symptoms for nine years, so long as he continued to take urea.

Urea is, of course, a relatively harmless diuretic, and in view of this case, and of the fact that the natural termination of an attack of migraine is a spontaneous diuresis (Fig. 1), I treated the patients as a temporary measure with regular oral doses of urea. Many of them responded well, especially those in whom oedema developed before an attack. Their attacks gradually diminished in frequency and severity, and in many cases ceased entirely.

The opening of the Research Department of this hospital in 1947 provided an opportunity of investigating the nature of the biochemical changes which follow the use of a diuretic in migrainous subjects. My colleagues and I (Campbell, Hay, and Tonks, 1951) explored the effects of water diuresis, and found that, whereas the increase in the volume of urine was the same in normal and in migrainous subjects, the latter excreted an unusually large amount of sodium and chloride (see Fig. 5). Furthermore, they appeared to retain both sodium and water prior to an attack—as shown by the high level of sodium in the blood, and by its low colloid osmotic pressure (Fig. 2). In the natural diuresis which followed an attack there was a large output of sodium (Fig. 1). From this we concluded that the beneficial effect of a diuretic was probably due to the fact that it prevented this accumulation of sodium and water.

Action of Diuretics in Glaucoma

During the course of this work Dr. Hay (1952) collected some interesting family histories in which either glaucoma or migraine occurred in individual

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members of the same family, and this led us to investigate the effects of diuresis in glaucomatous subjects also.

We again used the water-drinking test, which in this instance was of particular significance in relation to the eye, since it is often used as a diagnostic test for glaucoma. It was introduced by Leydhecker (1950), and we confirmed his observations that after imbibition of 1 litre of water the intraocular pressure in normal subjects was affected by only 2–3 mm. Hg, whereas in glaucomatous subjects it often showed a rise of 8 mm. or over (Fig. 4).

FIG. 1.—Spontaneous diuresis of sodium and water in migraine (Campbell, 1952, p. 479).

FIG. 2.—Retention of water and sodium in migraine. Normal range: sodium, 320–350 mg./100 ml.; colloid osmotic pressure, 25–30 mm. Hg.

FIG. 3.—Family tree of glaucoma patient (Campbell, 1952, p. 468; after Hay).

We found, moreover, that the ocular response is accompanied by a sharp diuresis of the same type as in the migraine subjects—that is to say that, whereas the volume of urine and rate of excretion is the same as for normal subjects, there is a notable increase in the excretion of sodium (Fig. 5). We found no direct relationship between the levels of intraocular pressure and the concurrent levels of blood sodium. There was, however, evidence of a retention of sodium in glaucomatous patients, as shown by the high average level of blood sodium in the resting state as compared with normal subjects. In these respects there was an obvious similarity between migrainous and glaucomatous subjects, a biochemical finding which was of some interest in view of their likeness in temperament and the familial tendency of these diseases.

We then investigated the action of some of the newer diuretics which had been introduced for the treatment of cardiac oedema, but whose action on intraocular pressure was still unknown, apart from that of acetazolamide ("diamox"), which came into common use at about this time for the relief of glaucoma.

Our observations on human subjects were directed particularly to the action of diuretics in cases of glaucoma with an open angle, for by excluding eyes with a narrow angle—or with obstruction due to secondary

FIG. 4.—Effect of water diuresis on intraocular pressure in normal and glaucomatous subjects.

FIG. 5.—Diuresis after water-drinking test (1,000 ml. H_2O), showing increased excretion during four hours after test as compared with four hours before. In normal (N), migraine (M), and glaucoma (G) subjects.

glaucoma, the resultant effect on ocular pressure could be regarded as being unaffected by any pathological obstruction to the outflow of aqueous.

The comparison of the systemic changes with the effect on intraocular pressure was based throughout on a series of careful estimations carried out under standard conditions. The patients were admitted to the research ward, where they co-operated most willingly in the taking of a long series of blood and urine samples and of records of intraocular pressure. They were given a uniform diet (Campbell, Tonks, and Jones, 1956; Campbell, Jones, Renner, and Tonks, 1957; Campbell, Renner, and Tonks, 1958; Campbell, 1960), with a sodium intake of not more than 40–45 mEq in 24 hours. They were also maintained in a state of steady hydration, 140 ml. of water being given at hourly intervals two hours before and three hours after the test dose. No miotics were used, so that the effect of the diuretics on intraocular pressure was not obscured, as has been the case in so much of the work previously recorded by other investigators.

An initial period of observation for the first three days provided an opportunity for observing the diurnal variations during the resting state and allowed the patient to become accustomed to the routine of investigation. Furthermore, we were able to assess the effect of the diuretic over and above the normal diurnal variations during the control period.

Throughout this work we had in mind two considerations: (1) to discover the clinical effect and optimum dosage of those diuretics which reduce intraocular pressure; and (2) to ascertain the nature of the relationship, if any, with the concurrent systemic biochemical changes.

Effect of Diuretics on Intraocular Pressure

Response to Single Doses of Diuretic

According to Pitts (1959) the various types of diuretics can be classified on a functional basis according to their action on the kidney. Those which we selected for investigation are shown in this way in Table I. Their diuretic action depends largely on the amount of sodium excreted, since this ion always carries water with it, and they either increase the filtered load of sodium and chloride ions or antagonize the tubular reabsorption of these ions. Their effect on intraocular pressure is summarized in Table II.

TABLE I.—*Functional Effect of Selected Diuretics (After Pitts, 1959)*

Physiological	
1. Water:	Impairs reabsorption of sodium by increasing velocity of flow.
2. Urea:	Promotes osmotic diuresis by inhibiting tubular reabsorption of sodium and water.
Pharmacological	
1. Diuretics which specifically inhibit transport mechanisms for sodium and/or chloride ions.	
(a) Meralluride ("mercaldan")	(mercurial diuretic + theophylline).
(b) Chlorothiazide ("saluric").	
(c) Chlorthalidone ("hygroton").	
(d) Aminometradine ("mictine").	
2. Diuretics which interfere with hydrogen for sodium exchange.	
(a) Potassium salts.	
(b) Acetazolamide ("diamox").	
Methazolamide ("neptazane").	

TABLE II.—*Effect of Selected Diuretics on Intraocular Pressure*

Acetazolamide .. 250 mg.	} Fall; maximum in { 2 hours 3 hours 1 hour
Methazolamide .. 250 mg.	
Urea .. 45 g.	
Chlorothiazide .. 1.5 g.	} No effect above usual diurnal variation
Chlorthalidone .. 200 mg.	
Aminometradine .. 200 mg.	
Meralluride .. 1 ml. intra-muscularly	} Slight rise in 1–3 hours
Water .. 1,000 ml.	
	Rise; maximum in ½ hour

If the records taken on the test day are compared with those on the control day the true effect is shown—that is, over and above the usual diurnal variation (Fig. 6).

It is apparent that in the normal therapeutic doses urea and the carbonic anhydrase inhibitors acetazolamide and methazolamide each promote a considerable fall in intraocular pressure. This is also true of their related compounds ethoxolamide ("cardrase") and dichlorphenamide ("daranide"). The effect of chlorothiazide and chlorthalidone is negligible, as is also that of aminometradine, while meralluride causes a slight rise in pressure of 2–3 mm. Hg only in the course of three hours.

In the case of acetazolamide (Campbell *et al.*, 1956) and the related compound methazolamide (Campbell,

FIG. 6.—Effects of diuretics on intraocular pressure, each administered at 10 a.m. Pressure readings corrected for diurnal variation.

FIG. 7.—Effect of acetazolamide and methazolamide on intraocular pressure and urinary output.

1960) we have been able to show that there is a close time-relationship between the effect on urinary excretion and the changes in intraocular pressure in glaucomatous patients. The period of hypotensive action coincides with the period of diuresis, and of the increased excretion of salts, particularly of sodium.

The response to a single dose of 250 mg. of either acetazolamide or methazolamide is almost identical (Fig. 7) in causing a maximum fall in intraocular pressure in four hours which may last for 24 hours. In practice, the time of choice for administration is just before the peak of diurnal variation.

The minimal effective dose of urea proved to be 45 mg. (30 mg. having no effect). It is unpalatable in any kind of vehicle, and is apt to cause nausea or vomiting. It also gives rise to an occipital headache spreading into the cervical region, the onset of which coincides with the fall in intraocular pressure and disappears when the latter rises again to normal. The administration of 25 mg. of promethazine theoclate two and a half hours prior to the urea will obviate the gastric symptoms but not the headache, while having no effect on the intraocular pressure. The immediate effect of urea is much more pronounced than that of either methazolamide or acetazolamide, being at a maximum within an hour and lasting for only three hours. This confirms the observations of Galin, Aizawa, and McLean (1959a, 1959b), who used a similar dose of lyophilized ammonia-free urea (1.5 g./kg.) dissolved in iced cherry syrup, which caused a marked fall in intraocular pressure in two and a half to three hours.

The development of headache actually precludes its use in large doses, but there is a possibility, which we have not yet explored, that urea might prove efficacious if given in divided doses throughout the day.

In comparison, intravenous urea (Javid, 1958; Galin *et al.*, 1959a, 1959b), when given in a dose of 1 g./kg. in 30% solution in 10% invert sugar, has a maximum effect on the eye in 30 to 45 minutes, and is potentially a useful method for the pre-operative reduction of intraocular pressure. (Cf. its use for the reduction of intracranial pressure (Stubbs and Pennybacker, 1960).)

So far as the medical treatment of glaucoma is concerned, it is apparent that acetazolamide must still be the diuretic of choice, since urea is so unpalatable, and methazolamide is not yet available in this country.

Response to Repeated Doses of Diuretic

Our experience has shown that in repeated daily doses the effect of acetazolamide on the intraocular pressure steadily diminishes (Fig. 8). This is associated with a decline in the excretion of bicarbonate, of sodium, and to a less extent of potassium (Campbell *et al.*, 1957). The loss of bicarbonate from the body is counter-balanced by the retention of chloride, and as a result a state of acidosis develops which may last as long as 48 hours after a single dose, and the eye becomes resistant. Furthermore, after prolonged dosage there may be a serious degree of hypopotassemia; but this deficiency can be overcome, and the effect of acetazolamide can be restored by giving additional doses of a potassium salt—for example, potassium bicarbonate in doses of 1 g. three times a day. In the case shown in Fig. 9, for instance, the state of glaucoma in the left eye was resistant to the combined action of acetazolamide and miotics, but responded well to acetazolamide and potassium bicarbonate, each of which has a similar action on the kidney.

In practice, in mild cases, such as the elderly patient with chronic glaucoma for whom surgical measures are undesirable, it is often sufficient to give a dose of acetazolamide twice a week, thus allowing the body time to recover from acidosis in the intervals. The blood potassium can often be maintained effectively from naturally rich sources of diet—for example, orange juice, etc. In cases in which the intraocular pressure rises in the evening miotics can also be used with advantage, thus avoiding the serious diminution in vision which is caused in the daytime by miosis in patients who have the added complication of senile cataract.

Long-term Therapy

Long-term therapy with acetazolamide (or methazolamide) should not be embarked upon lightly. In the

FIG. 8.—Decline in effect of acetazolamide (Campbell *et al.*, 1957, p. 754).

FIG. 9.—Adjuvant effect of potassium (Campbell *et al.*, 1957, p. 751).

first place, it is wise to exclude the presence of renal disease and to ascertain whether a patient is being treated with other diuretics for another cause. Particular care should be taken in giving acetazolamide to diabetics.

So far as the development of hypopotassaemia is concerned, it is our practice in the glaucoma clinic of this hospital to estimate the blood electrolytes at intervals of two to three months in all patients who are on long-term therapy. They are readmitted for control of the dosage if the electrolyte balance is not satisfactory.

A query has also been raised whether long-term administration of acetazolamide might cause osteoporosis by an excessive loss of calcium. We could find no biochemical evidence of this in the level of the blood calcium or any evidence of osteoporosis in a series of x-ray films on patients on long-term therapy. In addition, over 100 alkaline phosphatase tests carried out on the blood were all normal, thus verifying the absence of bone or liver damage.

Cases of renal colic have been reported (Becker, 1955; Barraquer and Escribano, 1957; Wynne Davies, 1959) some of which were found to have renal calculi—which may have been pre-existent. All of them had had most intensive therapy, receiving in one instance as much as 250 mg. four times daily; in another (Glushien and Fisher, 1956), crystals resembling acetazolamide were actually found in the renal tubules. There is no doubt that the persistent acidosis which the drug provokes would favour the deposition of crystals, but this can be prevented if potassium bicarbonate is always given in long-term therapy and acetazolamide is limited to a single daily dose. This helps to maintain a normal electrolyte balance and to prevent the progressive loss of potassium to which I have already referred.

With these precautions acetazolamide can be continued for several years.

Methazolamide.—In America, methazolamide has been used successfully (Becker, 1957) in cases which do not respond to acetazolamide. It is also particularly suitable for long-term therapy, since, according to our observations (Campbell, 1960), its effect does not appear to diminish (Fig. 10) and a daily dose of 125 mg. is

FIG. 10.—Effect of methazolamide and acetazolamide on intraocular pressure (Campbell, 1960, p. 426).

quite adequate (Fig. 11). It is noteworthy that a second dose given at night after an interval of 12 hours has little additional effect on intraocular pressure, but increases the output of potassium and sodium (Fig. 11).

Relationship Between Systemic Effects of Diuretics and Concurrent Variations in Intraocular Pressure

From experimental work on animals it was at first thought that acetazolamide reduced the intraocular pressure by preventing the secretion of aqueous humour, as the result of the inhibition of the formation of the bicarbonate ion within the eye. Langham and Lee (1957) proved, however, that it only brings about a reduction in intraocular pressure when it is administered systemically, and is without effect when introduced locally. Becker (1955) also had shown, in rabbits, that its action on the eye still occurred in nephrectomized animals, which suggests that it is the indirect outcome of a readjustment in the body fluids.

Sir Stewart Duke-Elder (1957), in his Bowman Lecture on the aetiology of simple glaucoma, attributed the fall in intraocular pressure after acetazolamide to a decrease in the base-binding capacity of the blood, and suggested that the decrease in the formation of aqueous humour arises primarily from a disturbance of the osmotic relation between blood and aqueous humour.

Experimental

In order to explore this hypothesis as applied to the human subject, we carried out a further series of experiments to compare the systemic effects of several of these diuretics—namely, chlorothiazide, aminometradine, and urea, together with that of the carbonic anhydrase inhibitors acetazolamide and methazolamide. The results given are the average for a group of five patients in each case—except in the case of aminometradine, with which only two patients were tested. Detailed analyses of blood and urine were carried out con-

FIG. 11.—Methazolamide and intraocular pressure (Campbell, 1960, p. 427). Day 0=control day. Each daily output is the total for 24 hours.

currently with the records of intraocular pressure, under the standard conditions already described. Except in the case of aminometradine, full analyses were also made on the (pre-dosage) control day. Each diuretic was administered in its normal therapeutic dose.

Urine estimations were confined to volume, pH, and sodium, potassium, and chloride excretion. Bicarbonate estimations were omitted owing to the technical difficulty and the undesirable disturbance of the patient, which would have been necessary for the collection of specimens. In the blood we were able to analyse all the constituents, including bicarbonate, as required.

In assessing the relationship between the systemic and intraocular effects the comparison is limited to the period of four to six hours after the dose—that is, to the period during which the maximum effect on intraocular pressure occurred (Figs. 12 and 13).

FIG. 12.—Diuresis in relation to intraocular pressure. —: Test day. ----: Control day.

Urinary Output

It can be seen from Fig. 12 that except in the case of urea the fall in intraocular pressure does not run parallel with the volume or rate of urinary output. In comparison, after acetazolamide, methazolamide, and aminometradine the urinary output, although moderate in amount, is accompanied by a sustained fall in intraocular pressure in the case of the first two diuretics and by no change at all after aminometradine. Chlorothiazide, on the other hand, promotes a very large diuresis with virtually no effect on intraocular pressure.

Electrolyte Excretion

Acetazolamide and methazolamide, being carbonic anhydrase inhibitors, cause a considerable disturbance in the electrolyte balance. There is a notable increase in the excretion of sodium (Figs. 7 and 12), which is in excess of chloride and known to

be accompanied by a heavy loss of bicarbonate. Both of these diuretics cause a conspicuous fall in intraocular pressure.

Chlorothiazide combines the diuretic properties of a carbonic anhydrase inhibitor and mercurial diuretic—that is, it blocks the reabsorption of sodium and chloride with little effect on the bicarbonate excretion. Sodium and chloride were excreted in equimolar amounts. This also occurred after aminometradine, and neither of these diuretics had any significant effect on intraocular pressure (Fig. 12).

Urea differs from the other diuretics in promoting an osmotic diuresis that is diminished by the extent to which urea itself is reabsorbed by the renal tubules. We found that during the first four hours only one-sixth of the dose was excreted, which meant that the concentration of urea in the blood remained very high. It caused a moderate excretion of sodium and chloride, with a slight preponderance of the latter, and the urine remained acid. The electrolyte pattern of the urine was in fact similar to that after chlorothiazide and aminometradine, which suggests that the disturbance in the electrolytes was not related to the hypotensive effect of urea on the eye.

Changes in Constituents of the Plasma

In considering the changes in the blood it is evident that there is a rapid and continuous adjustment to the excretion of water and of electrolytes on the one hand, and to the demand of the tissues for these substances on the other.

On the whole the pattern of the electrolytes in the blood was a reflection of the urinary excretion. Each of the four diuretics—acetazolamide, methazolamide, chlorothiazide, and urea—caused a fall both of sodium and of bicarbonate, which was, however, significant only in the case of the carbonic anhydrase inhibitors, when it was compensated by a rise in chloride.

In comparing the relative concentrations of sodium and chloride, no significant alteration was found after chlorothiazide and urea—as compared with that occurring at the same time on the control day. It is noteworthy that sodium and chloride were excreted in equivalent amounts after each of these diuretics.

After acetazolamide and methazolamide, however, there was a marked disturbance in the proportional concentrations of sodium and chloride in the blood during the period of fall in intraocular pressure as compared with the control day; this was mainly due to the rise in chloride.

Osmolarity

The combined effect of the disturbances of the principal ions of sodium, potassium, chloride, and the bicarbonate radical is shown in Fig. 13 in terms of

FIG. 13.—Change in serum osmolarity due to electrolytes. (Na⁺, K⁺, Cl⁺, and HCO₃⁻ on test day).

osmolarity. It falls to a varying degree after each diuretic, but when compared with the same period on the control day the fall is significant only after acetazolamide and methazolamide.

A comparison of the total protein-free osmolarity of the blood, as calculated from its total electrolyte and urea content, also showed a fall after acetazolamide (Fig. 14). But after urea there is a very marked rise,

FIG. 14.—Change in protein-free osmolarity of blood.

which is referable to the high concentration of urea. This was also found by Galin *et al.* (1959a, 1959b), who observed that after urea the maximum increase in blood isomolarity (as measured by the depression in the freezing-point) coincides with the maximum fall in intraocular pressure. It does not explain why in our cases the intraocular pressure rises again while the osmolarity is still high, and further investigation on this point is obviously required.

Discussion

In comparing our present knowledge with that of Richard Middlemore it is interesting to recall that before the invention of the ophthalmoscope he and his contemporaries found it difficult to distinguish clinically between cataract and glaucoma until Sir William Mackenzie (1830) observed that the intraocular pressure was raised in the latter condition. Richard Middlemore found by dissection of glaucomatous eyes that the fluidity of the vitreous was increased, and on this evidence treated acute glaucoma by a mercury diuretic in the form of blue pill. This was administered in doses of 5 gr. (0.32 g.) night and morning until "all sense of fullness and uneasiness of the eyeball had disappeared." If the gums were much affected before that beneficial change had occurred he resorted to aperients or to surgical treatment by paracentesis.

Some years later Priestley Smith (1879), also a surgeon of this hospital, suggested that glaucoma was due to faulty drainage at the angle of the anterior chamber rather than to hydrops of the vitreous.

The fundamental observations of these two surgeons have stood the test of time, and many others have been made since their day; but the problem of glaucoma still remains unsolved. Admittedly there are factors of a vascular, neurogenic, or hormonal nature which also influence intraocular pressure, but there is an increasing

amount of evidence that an exchange of water and ions is continually taking place between the eye and the plasma, and that intraocular pressure depends on this balance rather than upon any active selection in the secretion of aqueous humour.

It is obvious that the healthy eye with a free outflow can adjust itself readily to changes in the plasma engendered by water intake or by water or electrolyte output. As a result, for instance, it does not share in any state of generalized oedema of the body by developing an increased intraocular pressure, although it may occasionally develop oedema of the tissues of the retina. A sudden dilution of the plasma, as in the water-drinking test, again has little effect on the healthy eye, but causes a rise in intraocular pressure in the glaucomatous eye, in which the outflow mechanism is impaired. In the same way the hypotensive action of diuretics such as methazolamide and acetazolamide is much more pronounced in the glaucomatous eye than in the normal eye, which in itself suggests that diuretics exert their effect on the inflow. There is ample evidence to show, for instance, that neither water (Leydhecker, 1950) nor acetazolamide (Langham, 1955) affects the rate of outflow; indeed, according to Davson (1956) this is impossible on a physiological basis because the area of contact in the region of the angle of the anterior chamber is so small that it could not influence the process of diffusion between plasma and intraocular fluid at this site.

While agreeing with Langham and Lee (1957), that the essential difference in the final equilibrium between the plasma and the eye in normal and glaucomatous subjects is determined by the different properties of the hypertensive eye, this cannot be wholly so. There is evidence, as already stated, that the glaucomatous subject retains sodium—which is excreted in abnormally large amounts after water diuresis (Campbell *et al.*, 1951)—and exhibits a marked lability of his resting blood sodium (Campbell, 1952). Moreover, in the variation of the electrolyte balance in the blood after acetazolamide the change in the sodium content is far greater than that of any other ion (Campbell *et al.*, 1958) in relation to the changes in intraocular pressure. The importance of this systemic factor is supported by the work of Cole (1960), who found that in rabbits, when the effect of outflow is removed by blocking the anterior angle of the eye, the rate of active transfer of sodium appears to determine the rate of entry of water into the eye. On this conception it is possible that a reduction in the rate of sodium influx, which may depend in turn on the concentration of sodium in the plasma, will cause a fall in intraocular pressure in the glaucomatous eye but will have no effect on the healthy eye. In the human subject this response can be detected only when the underlying changes in the blood occur rapidly—as, for instance, after a diuretic.

The biochemical investigation of the action of diuretics in the human subject has provided a sounder basis for their therapeutic use in glaucoma and some additional evidence on their mode of action upon the eye.

The changes in intraocular pressure appear to be closely associated either with a disturbance in the acid-base balance of the blood, in which sodium plays an important part, or with alterations in osmolarity. To what extent these are interrelated is as yet unknown. It is a recognized principle that in the ordinary processes of exchange of fluid throughout the body no water can

pass through a cell membrane without its dissolved salt (O'Donovan, 1960). This probably applies also to the entry of fluid into the eye. There is also good evidence that the ciliary body maintains an active transport of sodium (Cole, 1960), which must be of primary importance in determining the volume of intraocular fluid—that is, the intraocular pressure throughout the day.

In conclusion, I would like to record my appreciation of the honour of being invited to give this Lecture—and of the facilities provided by the Birmingham and Midland Eye Hospital which have made this research work possible.

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"Drugs cost £10,500 more in 1959–60 and medical and surgical equipment £19,000 more. A good deal of the increase for 1959–60 was deliberate, since whatever spare resources were available towards the end of the year were devoted mainly to clearing requests for such items outstanding from previous years because of lack of funds. The results for the third financial year of the new method of hospital costing confirmed earlier impressions that the B'ward's hospitals are economical in comparison with other like hospitals. At the Royal Hospital in 1959–60, for instance, it cost £25 10s. 1d. to treat an in-patient for one week, which is the lowest cost of all acute teaching hospitals operating the main costing scheme and compares very favourably with an average cost of £30 14s. 11d. per week for acute teaching hospitals in the provinces and £36 6s. 8d. for those in the London area. It is even slightly lower than the average weekly cost of £25 12s. for all acute non-teaching hospitals in England and Wales. Similarly, the cost of an out-patient attendance at the Royal Hospital in 1959–60 was, at 4s. 9d., lower than at any other acute teaching hospital, and also lower than the average for any non-teaching hospital Region in England and Wales." (*United Sheffield Hospitals Twelfth Report*, 1960.)

A NEW VARIANT OF HUMAN INTERSEX WITH DISCUSSION ON THE DEVELOPMENTAL ASPECTS*

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The recent chromosome studies on the various intersex states in man suggest that the Y chromosome is strongly male-determining (Jacobs and Strong, 1959; Ford *et al.*, 1959). There is, however, some evidence to suggest that the presence of the Y chromosome is not sufficient to ensure normal development of male gonads and genitalia. In testicular feminization (Jacobs *et al.*, 1959; Grumbach, 1960) and in "pure" gonadal dysgenesis (Harnden and Stewart, 1959) a nearly normal female phenotype develops in the presence of a Y chromosome. Moreover, the development of testicular tissue, and masculinization, in the absence of a Y chromosome in some cases of true hermaphroditism (Harnden and Armstrong, 1959; Hungerford *et al.*, 1959; Ferguson-Smith *et al.*, 1960; Marques de Assis *et al.*, 1960; Shah *et al.*, 1961), suggests that other factors play an important part in influencing the course of sex development. This hypothesis is strongly supported by the present case, in which bilateral testes were found in a patient with apparently an XX sex-chromosome constitution. This patient, but for the cytological studies, would undoubtedly have been classified as a male pseudo-hermaphrodite. We feel that the detailed clinical, endocrinological, and cytological studies on this case provide valuable new information on the spectrum of intersexuality in man.

Case History

The patient was referred to the endocrine clinic at this institution on June 30, 1959, when he was 20 years of age, with ambiguous external genitalia. According to his father, the patient was a full-term spontaneously delivered baby. For the first two weeks after birth the patient's grandmother, however, doubted the correctness of the assignment of sex in view of the size of the phallus, and therefore a doctor was consulted. The family physician confirmed the male sex of the patient and thereafter he was reared as a boy. The father was advised to have the child operated on for hypospadias when he reached the age of 10 years. It was when he was presented for this operation in June, 1959, that he came to our notice.

The father was 35 and the mother 19 years old when the patient was born. The mother had no illness, nor was she given any hormone treatment during the first trimester of pregnancy. Inquiry into the history of the sibs of the father and mother and their children revealed nothing pertinent. The patient is the oldest in a sibship of nine (five males and four females). He has had no serious illness

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