TABLE VIII.—Follow-up Micturating Cystourethrograms of Gross and Moderate Reflux

Time Interval	Gross Reflux		Moderate Reflux	
	Reflux Stopped	Reflux Continued	Reflux Stopped	Reflux Continued
6 months		1	4	3
12 months		2		3
2 years		2	6	1
4 years			2	
5 years	1	2	6	2
Total	1	7	18	9

Discussion

The classification of vesicoureteric reflux into the three grades of severity—gross, moderate, and slight—has provided a valuable guide on which treatment can be based. Our results have shown that the grossly refluxing ureter is accompanied by a high incidence of initial renal damage and, if this reflux is allowed to continue, may lead to depressed renal growth and further loss of renal substance.

The kidneys of ureters showing slight or moderate reflux do not appear to be associated with initial or progressive renal changes, but the numbers involved in this study are not sufficient to be certain of this point. Our findings, however, would suggest that this type of reflux in the infant has a reasonably good prognosis.

The results of follow-up micturating cystourethrograms would support the opinion expressed by Stephens (1962) that there is a strong tendency for spontaneous cessation of reflux in the course of several years, and it may well be that the ureter showing moderate vesicoureteric reflux and renal damage in childhood was, in fact, a grossly refluxing ureter in infancy.

Most writers have strongly emphasized the part that infection plays in producing the renal damage, and there can be little doubt that vesicoureteric reflux is an important mechanism by which infection of the bladder reaches the kidney. In support of this concept is the finding of pyelotubular back-flow of contrast into segments of the renal parenchyma which

we found on several occasions during micturating cystourethrography. Hodson (1965) concluded that coarse focal scarring begins in early childhood in most cases and is due to infection. In only 3 of the 29 damaged kidneys in our infant group, however, were the changes of a focal nature; in the remainder the damage was generalized. This would suggest that the hydrodynamic effect of vesicoureteric reflux is an important factor in producing renal damage in the prenatal and neonatal period. It seems probable that the continuing insult of the refluxing ureter may result in depressed growth and atrophy of the sensitive developing renal tissue.

Though most of our patients with gross vesicoureteric reflux suffered from recurring infection in the follow-up period there were two examples of progressive generalized renal damage in children who had remained free of infection during the five-year follow-up period and whose initial pyelograms had shown no evidence of renal damage. In both cases regular bacteriological examination of urine had been negative over the follow-up period. Fig. 1 shows one of these cases.

The evidence that has resulted from this follow-up study would indicate that the contracted atrophic “pyelonephritic” kidney of children and adults is the result of gross vesicoureteric reflux in infancy. We have also shown that if gross vesicoureteric reflux is allowed to persist progressive renal damage may occur in apparently normal infant kidneys as well as in those showing initial damage. It would appear, therefore, that the grossly refluxing ureter of infancy is potentially dangerous to the kidney and should be surgically corrected as soon as possible. There would not appear to be any indication to correct moderate or slight reflux.

REFERENCES

Hodson, C. J. (1965). *Proceedings of the Royal Society of Medicine*, **58**, 785.

Hodson, C. J., Drewe, J. A., Karn, M. N., and King, A. (1962). *Archives of Disease in Childhood*, **37**, 616.

Little, P. J., McPherson, D. R., and de Wardener, H. E. (1965). *Lancet*, **1**, 1186.

Scott, J. E. S., and Stansfeld, J. M. (1968). *Archives of Disease in Childhood*, **43**, 323.

Shannon, F. T., Sepp, E., and Rose, G. R. (1969). *Australian Paediatric Journal*, **5**, 97.

Stephens, D. S. (1963). *Journal of the College of Radiologists of Australasia*, **7**, 17.

Use of Oral Mannitol in the Oedematous Patient

J. W. JAMES,* M.R.A.C.P. ; R. A. EVANS,† M.R.A.C.P.

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Summary: Oral mannitol 200 g. was given on 24 occasions to patients with intractable oedema (cardiac, renal, or hepatic) and produced a mean weight loss of 3 kg. The procedure was found to be a safe, rapid, and effective method of treating oedema, and it should be used when diuretic therapy proves ineffective, particularly in the presence of hyponatraemia.

Introduction

Most oedematous patients respond to bed rest, salt restriction, digitalization (if indicated), and moderate doses of diuretics.

Patients and Methods

Sixteen patients were treated with oral mannitol on 25 occasions. Nine had congestive cardiac failure, six had advanced renal failure, and one had cirrhosis of the liver. All patients, however, had both cardiomegaly and some degree of azotaemia, the lowest blood urea level being 70 mg./100 ml. They

*Medical Officer.
†Specialist Resuscitation.
Repatriation General Hospital, Concord, New South Wales, Australia.

were referred from general medical wards after failing to respond to conventional therapy. Most were dyspnoeic at the time of referral and the mannitol administration was often an urgent procedure.

Mannitol 200 g. dissolved in a litre of water was taken over a two-hour period (if taken more rapidly vomiting usually ensued). During the profuse diarrhoea that followed the patients were allowed to sit on a bedside commode. No fluids were allowed for 24 hours, and then moderate fluid restriction (usually 1 litre per day) was continued unless a sustained improvement was shown.

The diarrhoea fluid was collected in a tared plastic bucket and weighed. Samples were taken, and sodium and potassium estimations were made with an E.E.L. flame photometer. A Technicon AutoAnalyzer was used for estimating the blood urea and serum electrolytes; these were estimated in all patients before administration of mannitol and on the following day in 15 patients.

Results

Diarrhoea began half an hour after the first glass of mannitol and continued for about six hours. There was no associated colic, and though the patients were tired by the end of the procedure they were not distressed. As the first call to stool follows a significant reduction in blood volume, even severely dyspnoeic patients with cardiac failure were able to sit on a bedside commode. In one patient a fall in systolic blood pressure from 120 to 80 mm. Hg near the conclusion of the diarrhoea was corrected by his remaining horizontal for about three hours.

The volume of faecal fluid varied from 1.9 to 4.7 l. with a mean of 2.9 l. This includes the original litre ingested, and so indicates a mean fluid loss of 1.9 l. The weight lost by the patient was higher, the mean being 3.0 (range 0.9 to 7.3) kg.

The faecal fluid had a mean sodium concentration of 31 (range 12 to 59) mEq/l. and a mean potassium concentration of 10 (range 5 to 20) mEq/l. Following the procedure the serum sodium rose by a mean of 6 (range -8 to +15) mEq/l. and the serum potassium fell by a mean of 0.5 (range -1.9 to +0.8) mEq/l., as shown in the Chart. The blood urea fell by a mean of 5 (range -72 to +20) mg./100 ml.

After mannitol three patients (all with cardiac oedema) responded to diuretics which had previously been ineffective. The remainder were treated with large doses of ethacrynic acid, fluid restriction, and mannitol as required.

Four examples are cited to illustrate the use of mannitol in different situations.

Case Reports

Case 1.—A 44-year-old man with advanced chronic glomerulonephritis was admitted to hospital because of dyspnoea and oedema, which was increasing despite salt restriction, digoxin, and ethacrynic acid 1,000 mg./day. On admission there was gross congestive cardiac failure and the blood pressure was 190/125 mm. Hg. Investigations included: blood urea 210 mg./100 ml., serum creatinine 9.6 mg./100 ml., and serum sodium 125 mEq/l. Oral mannitol 200 g. produced a weight loss of 4.6 kg., partial resolution of the oedema, and a rise in serum sodium to 132 mEq/l. Four days later the mannitol was repeated with a further weight loss of 4.0 kg., disappearance of the signs of cardiac failure, and a fall in blood pressure to 160/90 mm. Hg. He was then discharged with his original therapy except that fluids were now restricted to 1 l./day. There was no change in serum creatinine during the admission.

Case 2.—A 72-year-old man with congestive cardiac failure had been deteriorating at home despite a regimen that included frusemide 240 mg./day. On admission he was dyspnoeic and had

gross heart failure with anasarca. His blood urea was 76 mg./100 ml. and serum sodium 135 mg./100 ml. As there was no response to an immediate dose of ethacrynic acid 200 mg. he was given mannitol 200 g., which relieved the dyspnoea. Over the next eight days the ethacrynic acid was increased till a diuresis occurred when the daily dose was 800 mg. During this time it was necessary to give mannitol on two further occasions to control dyspnoea.

Case 3.—A 47-year-old man with chronic glomerulonephritis was admitted when a low protein diet did not adequately control his azotaemia. On admission his blood urea was 280 mg./100 ml. and creatinine 20 mg./100 ml. After taking a modified Giovannetti diet for three weeks his blood urea fell to 160 mg./100 ml. (with no change in serum creatinine) and he felt well. He became oliguric, however, and developed fluid retention with orthopnoea and oedema. This could not be controlled by restriction of salt and water, and there was no response to ethacrynic acid 800 mg./day. Mannitol 200 g. by mouth resulted in a loss in weight of 2.6 kg. and relief of symptoms. His weight again increased so the mannitol was repeated, and this time, owing to his better acceptance of fluid restriction, the weight loss was maintained. He then remained in fair condition till he could be accepted in a chronic dialysis programme some weeks later.

Case 4.—A 69-year-old woman with chronic pyelonephritis had required monthly blood transfusions of two units of packed cells to control a hypoplastic anaemia. During an acute episode of pyelonephritis she was anuric for several days and required peritoneal dialysis; at the time of writing she was asymptomatic despite a blood urea of 160 mg./100 ml. and serum creatinine of 10 mg./100 ml. Since the dialysis, however, her monthly blood transfusions were always accompanied or followed by pulmonary oedema. For the past six months she has therefore been given oral mannitol 150 g. before each transfusion, and has had no dyspnoea; her stay in hospital for each transfusion has been reduced to 36 hours.

Effect of mannitol by mouth on serum sodium, serum potassium, and blood urea concentrations.

Discussion

Though the use of mannitol intravenously has been extensively studied, little interest has been shown in its remarkable properties in the gut. Carr and Krantz (1953) showed that oral mannitol produced diarrhoea in rats; the mechanism has been partly elucidated by Hindle and Code (1962), who found that in the isolated duodenum of dogs hypertonic mannitol caused a profuse secretion of water and sodium into the lumen to produce an isosmotic solution. In the ileum this did not occur, and there was merely a slow absorption of both water and mannitol. The clinical use of osmotic diarrhoea has previously been made by Gertman *et al.* (1966) in treating ascites due to cirrhosis of the liver, and by Giovannetti *et al.* (1968), who used a sorbitol-mannitol mixture for correcting salt and water retention in uraemic patients.

As a 5.5% solution of mannitol is isosmotic with plasma the oral administration of 1 litre of 20% mannitol might be expected to produce almost 4 litres of diarrhoea fluid. There are, however, many variable factors such as absorption of mannitol from the gut, secretion of sodium into the gut, and perhaps inadequate time to achieve isosmolality. In practice, though the faecal volume varied considerably the mean of 2.9 litres was less than that predicted.

The commonest causes of failure were vomiting (due to too

rapid ingestion of the mannitol) and failure of fluid restriction during the ensuing 24 hours. Abdominal colic and electrolyte disturbances did not occur; indeed, when hyponatraemia was present the serum sodium usually rose significantly (as shown in the Chart).

Oral mannitol should be used when diuretic therapy proves ineffective, particularly in the presence of hyponatraemia. In these circumstances it is used essentially as an alternative to peritoneal dialysis for those patients whose azotaemia is not severe enough to justify dialysis. Such patients include those incapacitated by congestive cardiac failure (Cases 1 and 2). It can be used in severe renal failure to correct overhydration (Case 3) and as a preliminary to infusion of sodium bicarbonate solution or blood (Case 4). Where the azotaemia itself is severe—for example, blood urea above 300 mg./100 ml.—dialysis is of course necessary.

REFERENCES

- Carr, C. J. and Krantz, J. C., jun. (1938). *Journal of Biological Chemistry*, **124**, 221.
Gertman, P. M., Gagnon, O., and Iber, F. L. (1966). *Journal of the American Medical Association*, **197**, 257.
Giovannetti, S., Maggiore, Q., and Giusti, C. (1968). In *Nutrition in Renal Disease*, edited by G. M. Berlyne, p. 141. Edinburgh, Livingstone.
Hindle, W., and Code, C. F. (1962). *American Journal of Physiology*, **203**, 215.
Maher, J. F., and Schreiner, G. E. (1965). *Annals of Internal Medicine*, **62**, 15.

Impaired Glucose Tolerance: A Late Effect of Insulin Shock Treatment

RICHARD HUNTER,* M.D.; MURIEL JONES,† M.B., PH.D.; B. A. L. HURN,‡ M.D.
CATHERINE DUNCAN,§ B.SC.

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Summary: Glucose tolerance tests were performed in a group of patients in a mental hospital who had been treated with insulin shock and in a matched control group. Five out of 31 (16%) patients in the insulin-treated group and 1 out of 22 (5%) controls had "diabetic" blood sugar curves. Median blood sugar values were significantly higher at 60 minutes and later in the insulin-treated group, as were mean blood sugar values when the "diabetic" patients were excluded. Small amounts of plasma insulin-binding antibody were found in two insulin-treated patients. In the absence of any other clear-cut explanation, it is suggested that in some patients massive doses of insulin by injection may leave diminished tissue responsiveness to insulin as a long-term after-effect.

Introduction

Insulin shock treatment (I.S.T.) as a method of reducing mental disturbance by the repeated induction of hypoglycaemic coma was introduced on a large scale in the 1930s (Wortis, 1959). It flourished again for a decade after the war, when

literally thousands of patients called "schizophrenic" were submitted to it. Though not "a cure," wrote Mayer-Gross (1953), a persistent advocate, "it supports Nature's curative tendencies." Sakel (1956), its chief protagonist, explained that it acted by causing "an intensification of the tonus of the parasympathetic end of the autonomic nervous system, by blockading the nerve cell" (*sic*). This effect by "strengthening the anabolic force . . . induces restoration of the normal function."

Many remained sceptical because of "the wide divergence in results reported by different investigators" (Jessner and Ryan, 1941). Others were soon convinced that its place in the treatment of "schizophrenia" was "firmly established" (Sargant and Slater, 1948). Opposing views were aired in the correspondence following the paper by Bourne (1953) under the title "The Insulin Myth." With the introduction of phenothiazine compounds discussion died down and soon insulin shock treatment, in all but a few isolated centres, was relegated to the limbo of psychiatric treatments which were supposed to have worked.

Insulin shock treatment consisted in giving daily intramuscular injections of crystalline insulin after overnight fast on five or six days a week, starting with a small dose and increasing until hypoglycaemic coma was induced. The dose was then adjusted to make coma last half to one hour. Patients were resuscitated by gastric or intravenous infusion of sugar:

* Consultant Psychiatrist, Friern Hospital, London N.11.

† Senior Registrar, Exe Vale Hospital, Exminster, Devon.

‡ Clinical Pathologist, the Wellcome Research Laboratories, Beckenham, Kent.

§ Member of Scientific Staff, M.R.C. Statistical Research and Services Unit, University College Hospital Medical School, London W.C.1.