Summary

A study has been made of the incidence of urinary infection following a routine cystoscopy on 110 occasions in the out-patient department. In 11% of the patients an established asymptomatic urinary infection was found before cystoscopy. This is discussed.

The risk of cystoscopy producing a serious urinary infection appears to be slight, less than 2%, provided adequate precautions are taken for sterilization of the instruments.

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CARBOHYDRATE AND SODIUM METABOLISM IN PERIODIC PARALYSIS

BY

P. B. DOAK, M.B., Ch.B.

Medical Registrar, Public Hospital, Auckland, New Zealand

AND

K. E. D. EYRE, M.D., M.R.A.C.P.

Assistant Neurologist, Public Hospital, Auckland, New Zealand

It has long been recognized that the administration of glucose, with or without insulin, will usually precipitate weakness in a person with periodic paralysis. The finding of a flat oral glucose-tolerance curve in such people by Aitken *et al.* (1937) and by Tyler *et al.* (1951) also suggests that their carbohydrate metabolism may be abnormal. The significance of these findings was largely neglected until MacGregor and Shaper (1957) confirmed the presence of a flat oral glucose-tolerance curve and also demonstrated hypoglycaemia unresponsiveness in a patient with the sporadic form of periodic paralysis. These authors believed that there was increased peripheral uptake of glucose in cases with periodic paralysis and that abnormality in glucose storage was important in the reduction of serum potassium levels and in the production of paralysis. However, the evidence was slight and the possibility of delayed intestinal absorption as the cause of the flat oral glucose-tolerance curve was not excluded.

The discovery that sodium retention often precedes attacks of paralysis (Conn *et al.*, 1956) suggested that

an abnormality of sodium metabolism might be the primary disorder in this condition. However, sodium retention does not always precede attacks (Jones *et al.*, 1959), and the protective effect of a low sodium intake cannot always be demonstrated (de Graeff and Brocker, 1958).

The present study of members of a family with familial periodic paralysis was undertaken to reinvestigate carbohydrate metabolism in this condition and to re-examine abnormalities of sodium and creatine metabolism which have previously been reported.

Clinical Details

Four members of the family were studied.

The father, aged 45, had his first attack of paralysis at 6 years of age. Attacks reached a maximum frequency (three or four a week) when he was between 16 and 19 years and have since diminished to one or two monthly. The longest attack occurred at age 19, when he remained paralysed for six days.

A twin son (Antony) and daughter (Susan), aged 14, had their first attack on the same day when aged 3 years, after a long train journey. Antony is the more severely affected and suffers six or seven attacks weekly. Susan has three or four attacks weekly. The twins have always received potassium chloride (up to 24 g. daily) for their attacks. As a result the maximum duration of a single attack is only 48 hours.

The fourth member studied, the only other sibling, is a brother (Peter) aged 10 years, who has never suffered attacks.

All affected members display the typical features of attacks of periodic paralysis. They often wake with complete paralysis of the limbs and trunk. Some movement of the head and neck is always possible, and bulbar and sphincter disturbances have not occurred. Examination at these times shows flaccid paralysis of all limbs with absent tendon reflexes. Less severe attacks can occur at any time of the day, and in some attacks isolated muscle groups were affected alone. Even between attacks muscle strength is impaired. Paralysis is more severe in cold weather, and each affected member recognizes that carbohydrate ingestion is likely to precipitate paralysis.

Methods

Glucose Tolerance

All tests were performed in the early morning after an overnight fast. The subjects were on a normal diet containing 200-300 g. of carbohydrate daily except for the three final oral glucose-tolerance tests performed on Susan when she was on a balance diet containing about 125 g. of carbohydrate.

Oral glucose-tolerance tests were performed using 100 g. of glucose. Venous blood was taken just prior to the administration of glucose and half-hourly for two hours thereafter. On one occasion a Miller-Abbott tube was passed into the jejunum of Antony, its position being confirmed by x-ray examination, and 100 g. of glucose in 150 ml. of water delivered into the small bowel.

Intravenous glucose-tolerance tests were carried out by the method of Amatuzio *et al.* (1953). For each test a glucose-disappearance rate was calculated.

Insulin-sensitivity tests were made using 0.1 unit of soluble insulin per kilogram of body weight injected

intravenously, and the blood glucose was followed at intervals of 10 to 15 minutes for two to two and a half hours.

Serial E.C.G. tracings were made during most of these tests. Lead V3 was found to be the most sensitive to changes in the serum potassium levels and was mainly used.

The serum potassium level was estimated serially during all of these tests. Antony received daily supplements of 12–20 g. of potassium chloride throughout the study period. Susan received 3–4 g. of potassium chloride as necessary to relieve weakness.

Paralysis was produced by withholding the evening dose of potassium and substituting 100 g. of glucose at 9 p.m. The attacks during which glucose tolerance was tested were characterized by severe weakness, absent tendon jerks, and serum potassium levels below 3.2 mEq/l.

Blood glucose was estimated by the method of Asatoor and King (1954).

Balance Studies

Susan was given a diet containing 22 mEq of sodium and 80 mEq of potassium daily throughout the trial period of 50 days. A constant supplement of 26 mEq of potassium was given daily as potassium chloride capsules. The sodium intake was varied by the addition of sodium chloride capsules. For the first 15 and the last 7 days of the balance period the total daily sodium intake was 126 mEq. On the other days the total daily sodium intake was 22 mEq. Urine was collected over 12-hour periods from 6 a.m. to 6 p.m. and from 6 p.m. to 6 a.m. Each specimen was analysed for sodium, potassium, creatinine, and creatine.

Results of Glucose-tolerance Tests

Figures for these tests are given in the Table or in Fig. 1.

Antony.—On two occasions oral glucose-tolerance tests were performed with the patient on a high potassium intake. These showed flat curves, but no change in the serum potassium levels was observed and paralysis did not appear. The same tests performed with the

patient on a normal potassium intake invariably caused a fall in serum potassium, with paralysis. To investigate the cause of these flat curves 100 g. of glucose was delivered into the small bowel via a Miller–Abbott tube. Paralysis began at 10 minutes and was complete at 25 minutes. Over this period the blood glucose level did not rise. The changes in the E.C.G., serum potassium, and blood glucose are shown in Fig. 1. The early changes indicate that delayed intestinal absorption of glucose is not the cause of the flat oral glucose-tolerance curve. Intravenous tolerance tests were performed on four occasions—two during attacks of paralysis and two within eight hours of recovery from paralysis. During attacks the glucose disappearance rate was normal, but after attacks an abnormally low disappearance rate was seen. A normal response to insulin was observed during one attack of paralysis, but on the one occasion when tested between attacks hypoglycaemia unresponsiveness was demonstrated.

Susan.—On a normal diet 100 g. of glucose similarly produced a flat oral glucose-tolerance curve and precipitated a severe attack. On a restricted carbohydrate intake 100 g. of glucose on two occasions produced

FIG. 1.—Effect on the E.C.G. and serum potassium (---) and blood glucose (—) levels of 100 g. of glucose delivered into the jejunum at time 0 minute. Paralysis began at 10 minutes and was complete at 25 minutes.

Results of Glucose-tolerance and Insulin-tolerance Tests

	Blood Sugar in mg./100 ml. at Minutes											K	Comments
	0	10	20	30	40	50	60	70	80	90	120		
100 g. glucose orally:													
Antony, normal state	80 (3.9)			84			90			68	76 (3.7)		Increased glucose tolerance
Susan, "	76 (4.0)			88			94			82	80 (2.7)		" " "
25 g. glucose i.v.:													
Antony, paralysed	120 (3.0)	213	239	195	159 (2.5)	141	109	96	104 (2.7)			4.9	Normal disappearance rate
" "	98 (3.0)	198	194	153	140	125	98	90	98 (3.0)			3.8	" " "
" post-paralysis	21 (3.8)	215	185	165	145	119	128	102	94	78 (4.1)		1.4	Low disappearance rate
" "	76 (4.4)	164	162	144	126	118	120	103	96 (3.6)			2.1	" " "
Susan, normal state	91 (4.1)	292	270	175	150	129	92	92	63 (3.9)			5.7	Increased disappearance rate
" paralysed	68 (2.5)	243	192	175	150	112	94	72	64 (2.7)			4.1	Normal " "
" post-paralysis	87 (4.1)	280	250	207	191	166	146	120 (3.8)				2.3	Low " "
6 units soluble insulin i.v.:													
Antony, normal state	68 (3.6)	47		7	22		16	22		33	55 (2.4)		Hypoglycaemia unresponsiveness
" paralysed	48 (3.1)	51	34	8		21	54		50	52	65 (2.6)		Normal response
5 units soluble insulin i.v.:													
Susan, normal state	67 (3.9)	50	8	6		25	41	46		55 (3.4)	54		Hypoglycaemia unresponsiveness
" paralysed	91 (2.7)	100	74	65		52	35	17 (2.5)		22	35		" "

Figures in parentheses are serum potassium values in mEq/l. K = glucose disappearance rate in %/minute.

diabetic curves and 70 g. of glucose a normal response. On all these occasions marked paralysis and a profound fall in the serum potassium level occurred. Intravenous glucose-tolerance tests revealed a rapid disappearance rate between attacks, a normal rate during an attack, and a low rate immediately after an attack. Hypoglycaemia unresponsiveness was demonstrated between and also during attacks of paralysis.

Serum Potassium

During precipitated and spontaneous attacks of paralysis the characteristic fall in the serum potassium was observed. The lowest levels recorded were 1.8 and 2.1 mEq/l. Although there was a tendency for the serum potassium level to reflect the severity of paralysis the relationship was not exact.

The changes observed during intravenous glucose-tolerance tests were within normal limits. During the two insulin-sensitivity tests performed with the patients in the normal state the serum potassium fell rapidly to 2.6 and 2.7 mEq/l., with a total fall of over 1 mEq/l. On each of these occasions hypoglycaemia unresponsiveness was observed. On neither occasion was an attack precipitated, although on one occasion a tendency might have been masked by 4 g. of potassium chloride which was given at the end of the test. This response was compared with that of five normal controls (aged 19–27). The lowest serum potassium level recorded in these subjects was 3.5 mEq/l., and on no occasion was the total fall more than 0.9 mEq/l.

The Electrocardiogram

Antony's E.C.G., taken in the normal state, showed tall peaked T waves resembling those seen with hyperkalaemia. The R and S waves suggested slight left ventricular hypertrophy. Susan's E.C.G. in the normal state was normal. During attacks the usual features associated with hypokalaemia were observed. Flattening of the T wave was the earliest change, but inversion did not occur until the serum potassium level fell below 2.4 mEq/l. On many occasions the E.C.G. showed marked changes before a significant fall in the serum potassium occurred, persisting for up to two hours after the serum potassium had returned to normal levels. This was especially seen after intrajejunal glucose and intravenous insulin. Compared with normal controls intravenous insulin caused a more rapid and profound change in the E.C.G., correlating with the greater fall in serum potassium levels, and a delayed return to normal after the restoration of a normal serum level.

The changes in the E.C.G. suggest that membrane potential changes occur before the serum potassium changes and persist after it is restored to normal.

Creatine and Creatinine Excretion

Each twin showed a persistent creatinuria of 300–900 mg. daily with a creatinine excretion of 500–1,000 mg. daily. Serial estimations each 12 hours for five weeks were performed for Susan. On one occasion the 12-hour creatine excretion dropped from over 200 mg. before the attack to under 80 mg. for 36 hours during and after the attack. On four other occasions no significant change occurred in relation to an attack.

Studies on Father and Peter

Limited studies were carried out on these members. Each showed hypoglycaemia unresponsiveness to intravenous insulin but a normal response to intravenous glucose. The father, during the insulin-sensitivity test, showed a fall in serum potassium from 4.2 to 2.7 mEq/l.,

with the production of moderate weakness of the arms and legs. Peter, although not weak, showed a resting serum potassium level of 3.2 mEq/l., which fell to 2.3 mEq/l. during the insulin sensitivity test. He was able to walk away apparently unaffected at the conclusion of this test.

The father showed a creatinuria of 286 and 323 mg./day. The creatinine output was 1,040 and 1,240 mg./day. Peter showed a creatinuria of 126 and 283 mg./day, with a creatinine output of 723 and 564 mg./day.

Results of Balance Studies (Susan)

On a daily sodium intake of 126 mEq, sodium retention of 50–60 mEq/l. in 24 hours occurred on three occasions. On two occasions 100 g. of glucose was given during this period of sodium retention. On each occasion a severe attack of paralysis resulted with a fall in the serum potassium level. On the occasion when glucose was not given paralysis did not occur, nor did the serum potassium fall (Fig. 2). Sodium diuresis followed the retention irrespective of whether or not paralysis had occurred. On a restricted sodium intake (22 mEq/l./day) a severe attack of paralysis was precipitated by 150 g. of glucose in two doses when minimal sodium retention (less than 10 mEq/l.) was occurring (Fig. 3).

On the restricted sodium intake minor attacks were not reduced in frequency nor was there any clinically demonstrable improvement in muscle strength.

After 14 days on this regime the aldosterone antagonist spironolactone in a dose of 200 mg. twice daily was given. This produced an immediate increase in sodium excretion with a negative sodium balance of 100 mEq in six days. Minor attacks were frequent during this period. After seven days' treatment with spironolactone the patient complained of headache and muscle aches which were thought to be due to sodium depletion. 100 g. of glucose given at this stage again produced a major attack of paralysis with only slight preceding sodium retention (Fig. 4).

It appeared that a change in sodium balance in either direction resulted in an increased incidence of minor attacks manifested by weakness and loss of reflexes. Serum potassium levels rarely fell below 3.5 mEq/l. during these attacks.

Potassium excretion fell during major attacks in parallel with the fall in serum levels. Minor attacks were usually, but not invariably, accompanied by a fall in urinary potassium excretion. On these occasions a close parallel between the degree of potassium retention and the serum potassium level was observed.

No significant changes in the serum sodium level were observed at any time.

Discussion

The almost invariable occurrence of paralysis in these patients after the ingestion of moderate amounts of glucose directs attention to the possibility of altered carbohydrate metabolism. Increased peripheral uptake of glucose as suggested by MacGregor and Shaper (1957) is confirmed by hypoglycaemia unresponsiveness and by flat oral glucose-tolerance curves in the presence of efficient intestinal absorption of glucose. Studies of peripheral uptake, using the intravenous glucose-tolerance test, indicate that this varies between wide limits. Because of the frequency and duration of severe attacks it was often not possible to be sure whether glucose

tolerance was being tested in a pre- or a post-attack phase. However, although not conclusive, our results are consistent, in each case, with the suggestion that after an attack of paralysis the peripheral uptake of glucose is reduced, due either to exhaustion of the membrane carrier mechanism or to saturation of intracellular storage mechanisms. Increased peripheral uptake was found on the only occasion when this was tested with the patient (Susan) in an unequivocally normal state.

The findings after intrajejunal glucose and intravenous insulin suggest that rapid peripheral uptake of glucose precedes the fall in serum potassium and is responsible, at least in part, for this. The changes in the E.C.G. suggest that, in cardiac muscle at least, the membrane potential changes before the serum potassium falls, and this is likely to be due to intracellular binding of potassium, probably to glycogen. Studies in the yeast cell (Pulver and Verzá, 1940), the human erythrocyte (Harris, 1941), and the liver (Fenn, 1939) have previously demonstrated the close relationship of potassium and glucose and glycogen metabolism.

The fact that skeletal muscle plays a dominant part in the uptake of potassium in patients with periodic paralysis has been shown by Jantz (1947), using serial muscle biopsy, Zierler and Andres (1956), and Grob *et al.* (1957). The last-mentioned workers also demonstrated a greater fall in venous potassium levels after glucose and insulin in these patients than in normal controls. This observation has been confirmed in our cases.

The mechanism of paralysis is still not clear. Several factors may be involved. Grob *et al.* believed it to be consequent on hyperpolarization of the cell membrane due to an increase in the ratio of intracellular to extracellular potassium. It is likely that much of the excess intracellular potassium is bound to glycogen, although Denny-Brown (1953) suggested abnormal binding of potassium to muscle protein as an early event in the production of paralysis.

Potassium has been shown to be essential for the production of adenosine triphosphate (A.T.P.) (Boyer *et al.*, 1943); and Beccuau *et al.* (1955) found that paralysis in this condition was relieved by the administration of this substance. The high energy bonds of A.T.P. are believed to be the immediate source of energy for muscle contraction, and a deficiency of these bonds is a possible factor contributing to paralysis.

Persistent creatinuria and diminished creatinine excretion was similar in degree to that observed by Talbott (1941). Abnormalities in creatine and creatinine excretion have long been recognized in periodic paralysis. These findings indicate that creatine metabolism in muscle is decreased. This is consistent with the observation of Brand and Harris (1932) of diminished creatine and, to a less extent, phosphocreatine content of muscle in a patient with periodic paralysis. Since the main function of creatine is that of a storage mechanism for high-energy phosphate bonds as phosphocreatine, it is possible that these cases lack the normal reserve of these bonds.

This possibility is of interest in view of the investigations of Randle and Smith (1958), who found that anaerobiosis and substances which inhibit oxidative phosphorylation accelerate the entry of glucose into the cells of the rat diaphragm. They concluded that the entry of glucose into cells was restrained under basal conditions by a process dependent on a supply of high-energy phosphate. The finding of an increased uptake of glucose by ascitic tumour cells due to a lack of mitochondrial A.T.P. (Wu and Racker, 1957) is consistent with this conclusion.

In view of these observations it is possible that a basic abnormality in periodic paralysis is a deficiency of high-energy phosphate bonds in the muscle cells, probably related to an inability to store creatine. This would lead to increased uptake of glucose, intracellular deposition of glycogen, a fall in serum potassium, and hyperpolarization of the cell membrane. As well as this there is a deficiency of the immediate source of energy required

FIG. 2.—Sodium retention with and without related paralysis. Dotted lines in Figs. 2–4 represent the average 12-hourly intake of sodium and potassium. FIG. 3.—Paralysis precipitated, on low sodium intake, with minimal sodium retention. FIG. 4.—Precipitated paralysis despite low sodium intake and spironolactone-induced sodium diuresis.

for muscle contraction. The intermittent nature of the paralysis and the variability in glucose tolerance demonstrated in our cases, in particular the decreased tolerance after paralysis, is not well explained. However, the latter observation is likely to be due either to exhaustion of a carrier mechanism in the cell membrane or to saturation of intracellular storage of glycogen.

The well-recognized association of periodic paralysis with thyrotoxicosis might be related to the ability of the thyroid hormone to uncouple oxidative phosphorylation.

Since Conn *et al.* (1956) demonstrated that sodium retention was important in the precipitation of attacks of periodic paralysis and that treatment with a low-salt diet after preliminary desalting was effective in preventing attacks, a number of balance studies in patients with periodic paralysis have been reported. Although all studies have confirmed sodium retention in relation to some attacks, sodium retention does not appear to be an essential accompaniment to paralysis (Jones *et al.*, 1959). The finding of only minimal sodium retention, during sodium restriction, in our patient in relation to a severe attack of paralysis supports this. The observation, together with the finding of marked sodium retention without the production of paralysis, suggests that sodium retention is not the primary defect in this condition. The discovery of sodium retention after glucose and insulin administration (Conn *et al.*, 1957) suggests a possible relationship between the abnormalities in sodium and carbohydrate metabolism. The mechanism of this association and the initial trigger to the chain of events leading to paralysis have yet to be determined. However, since the extrusion of sodium from the cell is an active process requiring energy (Hodgkin, 1958), it is possible that a transient reduction in the available high-energy bonds would lead to sodium retention by the cell. This would provide a common cause for sodium retention and the rapid peripheral uptake of glucose.

The failure, in our case, of a daily sodium intake of 22 mEq and diuretic agents to prevent attacks is similar to that described by Eales *et al.* (1958), although in their case such treatment initially appeared effective. More rigid sodium restriction to 8 mEq daily as used by Conn might be more effective, but from the practical therapeutic aspect such treatment seems to have little to offer.

Summary

Glucose and insulin tolerance were studied in four members of a family, including non-identical twins, affected with periodic paralysis. Evidence was obtained indicating rapid peripheral uptake of glucose as a regular finding in these patients. With the use of the intravenous glucose-tolerance test, the glucose disappearance rate was variable, being rapid before paralysis and reduced after.

In the one case specifically studied sodium retention and paralysis at times occurred independently of each other.

It is suggested that there is a lack of high-energy phosphate in the muscle cells, related to an inability to store creatine, leading to increased glucose uptake. A similar mechanism may be responsible for intracellular sodium retention.

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NUTRITIVE VALUE OF BREAD MADE FROM FLOUR TREATED WITH CHLORINE DIOXIDE

BY

S. G. IMPEY

AND

T. MOORE, Sc.D.

From the Dunn Nutritional Laboratory, University of Cambridge, and Medical Research Council

The rejection of agene, NCl_3 , as a flour improver, which followed the finding that flour so treated causes hysteria in dogs (Mellanby, 1946), raised in the milling and baking industries the problem of finding a suitable substitute. In the U.S.A. and Canada chlorine dioxide was used to replace agene from 1950 onwards (Horder, Dodds, and Moran, 1954), and later this substance came into general use in this country. For the formation of methionine sulphoximine, the poison responsible for canine hysteria, the nitrogen atom of agene must combine with methionine present in flour (Bentley, McDermott, Moran, Pace, and Whitehead, 1950). On theoretical grounds, therefore, it is clear that chlorine dioxide could not produce this particular poison. In agreement with this conclusion, experiments in the U.S.A. by Newell, Gershoff, Suckle, Gilson, Erickson, and Elvehjem (1949) demonstrated that dogs remain free from hysteria when given flour heavily treated with chlorine dioxide for 13 weeks. Rats, rabbits, and monkeys also remained well when given the treated flour for periods of 5, 6, and 22 weeks respectively. In human subjects no evidence of poisoning could be found after they had received diets containing flour treated with chlorine dioxide at 80 p.p.m., and wheat gluten treated