Glucose-galactose Malabsorption

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Primary disaccharidase deficiency is a well-known cause of diarrhoea in infancy. The offending disaccharide appears in the stool after ingestion due to the absence in the intestinal mucosa of the appropriate splitting enzyme. A much rarer cause of diarrhoea in this period is a failure of absorption of the monosaccharides, glucose and galactose, in the presence of histologically normal mucosa and full disaccharidase activity. The clinical and biochemical picture of this newly-described entity is characteristic. Watery diarrhoea, with glucose and/or galactose in the stools, develops within three days of milk feeding and continues as long as the feeds contain these monosaccharides or any carbohydrate composed of them. Carbohydrate tolerance studies show that the patient can absorb fructose well, and diarrhoea stops with subsequent thriving when this monosaccharide is substituted for other carbohydrates in the feeds.

A total of 13 cases has so far been reported from various parts of the world (Laplane, Polonovski, Etienne, DeBray, Lods, and Pissarro, 1962; Lindquist, 1965; Linneweh, Schaumlöffel, and Barthelmaï, 1965; Anderson, Kerry, and Townley, 1965; Schneider, Kinter, and Stirling, 1966; Marks, Norton, and Fordtran, 1966; Eggermont and Loeb, 1966). In this paper we report our studies on the first case to be described from this country.

Case Report†

The patient, a girl (T.T.), was born at full term, after normal delivery, weight 3270 g. She developed profuse watery diarrhoea within 2 days of breast-feeding. This continued when the feeds were changed to a glucose-electrolyte mixture. The stools were acid and contained a relatively large amount of glucose. The proteolytic activity was normal, and no pathogenic organisms were isolated.

By the 10th day of life the patient was 735 g. below her birthweight, with severe dehydration and hyper-

electrolytaemia. On the 16th day, therefore, feeds were changed to Nutramigen without improvement, and 9 days later this was substituted by Velactin. Both of these low-lactose preparations contain, in addition to protein, large amounts of dextrin and starch, and Nutramigen also includes maltose, while Velactin also has glucose and sucrose. All these carbohydrates on digestion give rise to glucose. The diarrhoea now decreased and the stools became less liquid; but there was no weight gain (Fig. 1) and glucose was still present in the stools. After 12 days on this régime, an extensive rash developed on the buttocks and groins, with stomatitis (Fig. 2), anaemia, hypokalaemia, and hyperchloraemic acidosis (Na 138, K 2.4, Cl 112, standard bicarbonate 13.7 mEq/l.). This electrolyte imbalance was corrected by parenteral glucose-electrolyte fluids, after which Velactin was resumed with added fructose and supplements of potassium and vitamins (Parentrovite). Diarrhoea continued and glucose was always present in the stools, but intermittently in the urine. There was a slow gain of only 225 g. in weight over the next ten weeks, after which a glucose/galactose-free formula‡ was introduced and the vitamin supplements changed to a mixture prepared in this hospital. This resulted in an immediate response: diarrhoea ceased, the stools became firm, the skin lesions cleared dramatically, and there was a gain of 450 g. in weight over the next 4 days. Solid foods containing no carbohydrates other than fructose were introduced at the age of 6 months. Strict adherence to this régime had to be observed, since inadvertent ingestion of small amounts of any carbohydrate other than fructose resulted in prompt diarrhoea. While on this régime, carbohydrate tolerance tests were performed at the age of 4–5 months and again at 9–10 months, on both occasions showing lack of absorption of the actively transported monosaccharides, glucose and galactose.

At 18 months of age the patient is on the 50th centile for weight and 3rd centile for height. Her skeletal age is that of a 12-month-old child and her psychomotor development is normal.

Family history. The patient is the second child of a 27-year-old Irish mother and a 26-year-old Chinese father. A sister now aged 3 years, is healthy with no history of infantile diarrhoea. Since arrival in this country 7 years ago the father develops diarrhoea on milk ingestion.

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‡ Casein soluble 3.5 g., butter fat 4 g., fructose 7.5 g., NaCl 160 mg., K_2HPO_4 315 mg., water to 100 ml.

Fig. 1

FIG. 1.—Chart of progress during the first 6 months of life. Note: (1) uninterrupted gain in weight and decrease in diarrhoea following the substitution of fructose for other carbohydrates in feeds, (2) increased stool frequency during stress tests with galactose, lactose, and glucose.

G.E.M. = glucose electrolyte mixture.

FIG. 2.—Vitamin B deficiency. (a) Rash on buttocks. (b) Stomatitis and cheilosis.

Fig. 2a

Fig. 2b

Methods

D-glucose was estimated by the glucose oxidase method on an auto-analyser; D-galactose by galactose oxidase; D-fructose and L-sorbose by the Selivanoff reaction; 3-O-methyl-D-glucose by the anthrone method; and the total reducing substances by the method of Folin and Wu. Disaccharidases were estimated by a method described previously (Burgess, Levin, Mahalanabis, and Tonge, 1964); insulin by the immuno-assay method of Yalow and Berson, 1964).

Results

Routine investigations. Except in the initial stages of severe diarrhoea, the serum electrolytes were always normal, as were serum or plasma Ca, Mg, P, alkaline phosphatase, urea, protein, and cholesterol. The stools contained no excess fat. Urine chromatogram showed normal amino acid pattern. Serum milk antibodies were absent.

Carbohydrate absorption tests. The carbohydrates (1.75 g./kg. body weight in 10% aqueous solution) were introduced through a gastric tube after a 10-hour fast. Urine and stools were collected for 6 hours following ingestion and examined for reducing substances which, when present, were identified by paper chromatography.

Table I shows that, except with sucrose, there

was no appreciable rise in blood glucose or galactose levels following the introduction of any carbohydrates composed of these substances, and that the corresponding monosaccharide appeared in the stools. With sucrose there was a small rise of 14 mg./100 ml. in blood glucose after half an hour. With fructose there was a normal rise of 33 mg./100 ml.

Diarrhoea followed the ingestion of 3-O-methyl-D-glucose with the recovery from the stools over 6 hours of 35% of the dose given (Table II), indicating a poor intestinal absorption. On the other hand, a very small amount of the L-sorbose introduced appeared in the stools and a larger quantity in the urine, with a substantial rise in its blood level indicating good absorption. D-xylose was absorbed in a manner intermediate between these two monosaccharides. No diarrhoea followed the introduction of L-glucose (1 g./kg. body weight). Although there was no proper stool or urine collection, in one specimen of stool the concentration of L-glucose was high (4% by weight) and the urine contained only 0.08 g. carbohydrate. The blood D-glucose level remained flat and there was a rise of only 10 mg./100 ml. in total blood reducing substances in the half hour following ingestion.

The mother and older sister showed normal

TABLE I
Blood Levels of Monosaccharides Following Ingestion of Mono- and Disaccharides

Age (mth.)	Carbo- hydrate given	Blood Carbo- hydrate Estimated	Fasting (mg./ 100 ml.)	½ hr. (mg./ 100 ml.)	1 hr. (mg./ 100 ml.)	2 hr. (mg./ 100 ml.)	3 hr. (mg./ 100 ml.)	4 hr. (mg./ 100 ml.)	5 hr. (mg./ 100 ml.)	6 hr. (mg./ 100 ml.)	Carbo- hydrate Detected in Stool
5	D-glucose	Glucose	40	42	44	37	28	—	29	—	Glucose
4	D-galactose	Glucose	51	51	55	—	47	29	35	—	Galactose
		Galactose	0.1	0.1	0.2	—	1	0.7	0.3	—	
5	D-fructose	Glucose	50	83	59	67	59	—	53	—	Nil
		Fructose	3	16	10	16	5	—	3	—	
5	Sucrose	Glucose	53	67	63	51	55	50	—	43	Nil
		Fructose	5	10	8	5	4	3	—	3	
4	Lactose	Glucose	59	61	57	54	48	42	—	46	Galactose; trace of lactose
9	Palatinose	Galactose	1.2	1.5	1.7	1.6	1.6	1.3	—	1.6	
10	Maltose	Glucose	42	42	46	43	43	36	30	—	Palatinose Glucose
		Glucose	50	50	49	50	46	41	39	—	

TABLE II
Carbohydrate Excretion Following Test Dose

Age (mth.)	Carbohydrate	Dose (g.)	Period of Collection (hr.)	Total Excreted (g.)		Comments
				Stool	Urine	
3	3-O-Methyl-D-glucose	4.5 (1.5 g./kg.)	6	1.6	0.06	35% of dose appeared in stool and only 1.3% in urine
5	L-sorbose	6.7 (1.75 g./kg.)	22	0.3	1.1	A rise in sorbose blood level of 58 mg./100 ml. in 2 hours
5	D-xylose	3.18 (0.9 g./kg.)	7 24	— —	0.25 0.45	8% Excretion in urine 14% Excretion in urine

absorption of glucose, galactose, and lactose. The father was intolerant to lactose (50 g.) and high doses of galactose (100 g.), developing prompt watery diarrhoea after ingestion, with the appearance of lactose and galactose, respectively, in the stools and a flat blood-glucose level. His tolerance tests with glucose (50 and 100 g. dosages), galactose (50 g. dose), sucrose, and maltose were normal.

Enzyme activity in jejunal mucosa. Disaccharidase activities were estimated on peroral biopsy specimens of jejunal mucosa obtained from the father and the patient when she was 1 year old. Both showed normal histology. Enzyme activities are shown in Table III; apart from a marked lactase deficiency in the father, they fell within normal range.

TABLE III

Disaccharidase Levels in Jejunal Mucosa from Patient and Her Father

	Enzyme Levels (units)			
	Lactase	Maltase	Palatinase	Sucrase
Patient	5.6	14.2	1.8	6.4
Father	1.0	26.9	2.3	9.2
Normal (mean) ..	3.5	25.0	2.7	7.0

1 unit = 1 μ mole substrate split per g. mucosa per min.

Renal tubular reabsorption of glucose. In view of the occasional finding of glucosuria when the capillary blood glucose was much below the accepted renal threshold, the maximum tubular absorption of glucose (Tm_g) was determined at the age of 10 months. It was found to be 282 mg./min. 1.73 sq. m., a value similar to that obtained in a boy of the same age with normal intestinal absorption of glucose.

Intravenous carbohydrate tolerance tests. The elimination of parenterally administered glucose and galactose (Hamilton and Stein, 1942) was determined when the patient was 18 months old and well nourished. Glucose preceded the galactose test by a fortnight. The assimilation coefficients (K values) were 1.72 and 8.4 for glucose and galactose, respectively (Fig. 3) (for interpretation, see under Discussion).

Blood insulin levels. These were determined during the oral glucose test and were found to be less than 2 μ units/ml. throughout.

FIG. 3.—Blood glucose and galactose levels following the intravenous injection of the monosaccharides (40 g./1.73 sq. m.) plotted on semilogarithmic scales. The half-time ($T_{1/2}$) and assimilation coefficients (K) are shown.

Discussion

Defect in 'active' transport mechanism. Clinically and biochemically this case closely resembled those previously described. There was a failure to absorb the actively-transported monosaccharides, D-glucose and D-galactose, either alone or as constituents of a disaccharide, as well as 3-O-methyl-D-glucose, a sugar not metabolized in the body. For all of these there is a common pathway of transportation across the mucous membrane of the intestine (Wilson, 1962). L-glucose behaved similarly. The passively transported L-fructose and L-sorbose were absorbed normally. D-xylose was less readily absorbed than would have been expected if this sugar was wholly passively transported. It has been shown experimentally, however, that glucose inhibits D-xylose movements from mucosal to serosal surfaces, and it is thought

that a carrier on the membrane with affinity for both glucose and xylose is involved (Wilson, 1962).

Some absorption, probably by passive diffusion, of glucose and galactose does take place, however. This was shown by Linneweh, Schaumlöffel, Graul, and Bode (1966) who found, by determining the absorption rate of orally administered ^{14}C -labelled glucose and galactose, that their patient absorbed 7.6% and 4.5%, respectively, the corresponding values in normal controls being 95.5% and 83.0%.

That glucose can be normally metabolized is shown by the fact that the assimilation coefficient of parenterally administered glucose ($K = 1.72$) was normal for age, though in the lower range (Loeb, 1966), and that of galactose was actually high ($K = 8.4$), again indicating normal intermediary metabolism.

It is most likely that the defect in these cases is in the transport mechanism across the intestinal mucosal cells. Using an autoradiographic technique, Schneider *et al.* (1966) demonstrated a failure of these cells of their patient to take up ^{14}C -galactose. Eggermont and Loeb (1966) and Meeuwisse and Dahlqvist (1966) also showed that there was no differential concentration in the intestinal mucosal cells of their patients when incubated in media containing ^{14}C -glucose, compared with a normal concentration factor of between 4 and 9. Applying techniques similar to those used by the above groups of workers, we failed to demonstrate an increased tissue concentration of ^{14}C -labelled glucose in the intestinal mucosa of either a normal human control or in that of the patient.

Renal tubular absorption. Anderson *et al.* (1965) suggested the existence of a similar defect in the renal tubules to explain the finding of glycosuria in these cases, as the normal mechanisms of absorption may be the same in both the gut and the kidney. Lindquist (1965) confirmed this by finding reduced tubular absorption of glucose in his patients. On the other hand, the Tm_0 in our patient was in the lower limits of the normal range of adults when corrected for surface area (Best and Taylor, 1961). It is difficult to explain the initial intermittent finding of glucose in the urine, unless this reflected an early 'immaturity' of the tubules which had gained normal function by the age of 10 months when the test was performed. It seems probable that our patient has the defect only in the intestinal mucosa.

Plasma insulin and oral glucose. Normally there is a greater rise in plasma insulin levels during

the oral glucose tolerance test than when an equal load is administered intravenously. It has been suggested that the additional secretion of insulin is mediated by a hormonal substance released at the jejunal mucosa (McIntyre, Holdsworth, and Turner, 1964) or from the liver, due to the high portal vein concentration of glucose (Elrick, Stimmler, Hlad, and Arai, 1964). The failure of plasma insulin to rise following ingestion of glucose in our patient indicates that mere contact of glucose with the intestinal mucosa is not sufficient to provoke an insulin response. It seems necessary for the carbohydrate to be transported into the cell or probably even to reach the liver before this can occur.

Genetics. An autosomal recessive mode of inheritance was suggested for this disease in view of the finding of affected sibs (Lindquist, Meeuwisse, and Melin, 1962). The lactose intolerance present in the father is probably incidental, as this is a fairly common acquired defect in adults (McMichael, Webb, and Dawson, 1965; Cuatrecasas, Lockwood, and Caldwell, 1965). It is interesting to note that when challenged with twice the normal dose of galactose he developed profuse watery diarrhoea. This might be a manifestation of the heterozygous state of glucose/galactose malabsorption. However, the mother developed no untoward effect from similar doses of glucose and galactose.

Conditioned avitaminosis. When on milk-substitute feeds the patient developed a rash similar to that described by Mann, Wilson, and Clayton (1965) who attributed it to choline deficiency. The rash cleared dramatically on changing from Velactin with Parentrovite to the glucose/galactose-free feeds and, in addition, the hospital vitamin mixture. The latter contained between 2 and 10 times the amounts of riboflavine, vitamins B12, A, and D, that were present in the former, together with folic acid and calcium pantothenate, the latter being totally absent in Parentrovite (Table IV). Deficiencies of riboflavine and pantothenic acid are known to cause skin rashes; but since even the smaller amount of riboflavine which was given would have been adequate for the patient (Jackson, Hanna, and Flynn, 1962), the lack of pantothenic acid must have been responsible for the rash. This is supported by the experimental studies on rats of Mann *et al.* (1965) which strongly suggested that pantothenic acid was necessary to clear the skin manifestations. Furthermore, in a patient with a similar deficiency rash (Lorber, 1965), this improved with the addition of Ketovite tablets (containing Ca pantothenate) without choline.

TABLE IV

Approximate Daily Vitamin Intake when Rash Appeared (columns a+b) and When Rash Cleared (column c)

Vitamin	(a) Velactin Vitamin Content	(b) Parentrovite Vitamin Content	(a + b) Total Intake	(c) Hospital Vitamin Formula Intake
A (I.U.)	1500	—	1500	15,000*
D (I.U.)	300	—	300	3000*
B1 (mg.)	1	8	9	8
Riboflavin (mg.)	1	0.3	1.3	8
Niacin (mg.)	10	15	25	40
Pyridoxin (mg.)	1	4	5	0.8
C (mg.)	—	40	40	50
B12 (μg.)	6	—	6	14
Folic acid (mg.)	—	—	—	6
Calcium pantothenate (mg.)	—	—	—	8

* These high doses of vitamins A and D were inadvertently given for a short period only.

Summary

A female infant, who developed severe diarrhoea on breast-feeding, was found to have failure of intestinal absorption of the actively-transported monosaccharides, glucose and galactose, but normal absorption of fructose. When the latter was substituted for other carbohydrates in the feed, diarrhoea stopped with subsequent thriving. Disaccharidase activity in the jejunal mucosa was normal.

Parenterally administered glucose and galactose were normally metabolized. Renal tubular glucose reabsorption was also normal. There was no rise in plasma insulin levels following oral glucose.

A vitamin deficiency rash cleared with supplements of pantothenic acid, the lack of which is probably the cause of the skin lesions in children on synthetic foods.

The father was intolerant to lactose, with a low lactase activity of his jejunal mucosa; but this was thought to be incidental.

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