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Disaccharides and Cystic Fibrosis of the Pancreas*

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Disaccharide intolerance has been described in cystic fibrosis of the pancreas (Cozetto, 1963; Nordio *et al.*, 1966; Sunshine and Kretchmer, 1964).

However, the relation between clinical signs and symptoms, and biochemical investigations is not clear. For instance, Cozetto (1963) reported isolated depressed lactase activity in an otherwise normal mucosa, but gave no clear clinical evidence in support of lactose intolerance. Two patients of Nordio *et al.* (1966) with cystic fibrosis of the pancreas showed evidence of disaccharidase deficiency in jejunal biopsies, and flat glycaemic responses to lactose, but disaccharide loads did not produce diarrhoea.

In this paper, an attempt has been made to correlate biochemical studies with clinical evidence of disaccharide intolerance. The term 'disaccharide intolerance' will be taken to mean, as suggested by Townley (1966), that there is 'the development of symptoms after ingestion of disaccharide and this is a clinically observed phenomenon'.

Seventeen children with cystic fibrosis of the pancreas have been investigated to determine whether intolerance to disaccharides from ordinary sources in the diet contributes to the gastrointestinal symptoms in this disease.

Patients

All the children studied were established cases of cystic fibrosis at The Hospital for Sick Children (Mantle and Norman, 1966) and were convalescent at the time of the tests; their ages ranged between 2 and 16 years. There was no interruption of treatment with antibiotics or pancreatic supplements. Three patients (14, 15, and 16) had undergone resection of small bowel for meconeum ileus at birth.

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Materials and Methods

Urine was preserved with merthiolate. Stools were deep-frozen on solid carbon dioxide immediately after defaecation. Both red (carmine, 200 mg.) and blue (Edicol Supra Blue E.G., Imperial Chemical Industries Ltd., 10 mg.) markers were given by mouth as described in the investigations.

Sugars in urine and stools were examined by paper chromatography (Arthur *et al.*, 1966). Total reducing substances in blood and urine were determined by a modification of the method of Folin and Wu (Wilkinson, 1960) and blood glucose by a modified glucose oxidase method (Hugget and Nixon, 1957).

Measurement of 3-O-methyl-D-glucose in urine. This sugar is considered to be actively absorbed in the gut, possibly along the same pathway as glucose, not metabolized by the body, and almost quantitatively excreted in the urine (Fordtran *et al.*, 1962). It was decided to follow the excretion of this substance in the urine and stool to measure the total absorption of a monosaccharide.

Urines collected for the 3-O-methyl-D-glucose load (see investigations) were examined for sugars by paper chromatography (Arthur *et al.*, 1966). The identification of reducing sugars except 3-O-methyl-D-glucose in any urines excluded that patient from the series. After desalting the urine for paper chromatography, an aliquot of the supernatant was diluted to a 1% solution with distilled water and 0·5 ml. taken for examination for total reducing substances. Non-specific reducing substances were measured in the baseline urine, and the result was subtracted from the figure for total reducing substances obtained on urine collected after the load. The quantitative measure of 3-O-methyl-D-glucose by the Folin and Wu method was checked for agreement against the quantitative measure for that sugar using paper chromatography.

Investigations

Excretion of sugars in urine on ward diet. 24-hour urines obtained from 52 patients with cystic fibrosis were examined for sugars. All were on a normal ward diet.

Increased carbohydrate diet. For 3 days the dietary carbohydrate (mostly sucrose with some lactose)

TABLE I

Effect of Increased Dietary Sugar

Case No.	24-hour Urine Sugars (mg./100 ml.)		Stool Sugars (mg./100 g.)		Stool Transit Time (hr.)	
	Before Diet	On Diet	Before Diet	On Diet	Before Diet	On Diet
1	None	None	None	Lactose 60 Sucrose 10	22	25
2	Sucrose 30	Sucrose 50	None	Fructose 10	20	22
3	None	Fructose 20 Glucose 20	None	None	22	23
4	None	None	None	Glucose 60	20	9
5	Sucrose 80	None	None	None	21	20
6	None	None	Glucose 10	Galactose 150	33	36
7	Sucrose 100 Fructose 20	Sucrose 80 Fructose 40	None	None	25	25
8	None	None	None	None	18	20
9	Sucrose 40 Fructose 15 Glucose 500	Sucrose 80 Glucose 10	Glucose 20	None	40	48
10	None	None	None	None	22	23
11	None	Glucose 10	None	None	25	—
12	Sucrose 30	Sucrose 150 Fructose 5 Lactose 5	None	None	20	24
					Average 24	26

of 12 patients was increased to 65% (normal 45%) of the total daily calories. Blue and red markers were given at the beginning and end of the period respectively. On the last day of the diet, a 24-hour urine specimen and individual stools were collected and examined for sugars. In addition, stool transit times and any symptoms of nausea, vomiting, or abdominal cramps were recorded, and compared with the same studies when the patients were on a normal ward diet.

Mixed disaccharide load. The test was performed on 16 patients according to the method of Menzies and Seakins (1968). Equal parts of finely ground sucrose and lactose in a total dosage of 20, 30, and 40 g. for children weighing 0–10, 10–20, and more than 20 kg., respectively, were administered as a 10% w/v solution in water, together with a stool marker, after an overnight fast. Urine collected for 5 hours after the load plus one further specimen, and the marked stool, were examined for sugars.

Intolerance to this load (as well as to the individual disaccharide load) leads to clinical symptoms of nausea, vomiting, or abdominal cramps, and a shortened transit time of bowel contents of 2 to 10 hours. The biochemical findings are disaccharidiuria greater than 15 mg./100 ml. and the presence of monosaccharide or disaccharide in the stool. In normals, under the conditions of the test, significant disaccharidiuria does not occur and the stools are free of sugar.

Sucrose load. A 10% w/v solution of sucrose in a dosage based on the Poulton-Payne dosage for glucose (Wilkinson, 1960) was administered to 15 children after an overnight fast. Urine and stool specimens were collected as for the mixed disaccharide load. Blood sugars were determined in a capillary sample obtained by finger prick before, and at 15-minute intervals after, the load for 60 minutes.

Lactose load. This was performed by the same procedure as the sucrose load in 2 patients.

3-O-methyl-D-glucose load. This test was a modification of that of Nordio *et al.* (1965). A 5% w/v solution of 3-O-methyl-D-glucose in a dosage of 12 g./1·76 sq. m. body surface and a marker were administered to 14 patients after an overnight fast. A further drink of water was given 2 hours later to promote urine flow. Urine was collected for 9 hours after the load, and the marked stool was saved.

Peroral mucosal biopsy of jejunum. This was performed with a Crosby paediatric capsule using an image intensifier for accurate placement, and the specimen of mucosa was examined histologically, and preserved for measurement of enzymes, as described by Arthur (1966).

Results

Urinary excretion of sugars on ward diet. Of the 52 children studied, 26 excreted sucrose in amounts ranging from 30–500 mg./100 ml., and 9 had, in addition, glucosuria 30–800 mg./100 ml.

Effect of increased disaccharide diet. No patients refused the diet or had gastro-intestinal symptoms. Stool transit time was reduced in only one patient (Case 4).

The excretion of sugars in urine and stools when the patients received (a) an ordinary ward diet, (b) the excessive sugar are shown in Table I.

Sugars were found in the stools of 2 children before the diet and in 4 on the diet. 4 patients had sucrosuria both before and on the diet, while significant glucosuria was found in one child before the increased carbohydrate was given.

Mixed disaccharide load. 9 of the patients given this load had previously shown significant disaccharidiuria on the normal ward diet, but only 3 did so after the load. Only one patient (Case 15) produced a clearly abnormal response. After the load he had abdominal discomfort, and 8 hours later passed a loose stool containing lactose and glucose (normal transit time in this patient, 14 hours). In addition he had lactosuria and sucrosuria. One other child (Case 16) showed glucose in the stool and a shortened transit from 23 to 8 hours. However, there was no abdominal discomfort and no sugars were found in the urine (Table II). Despite the appearance of sugars in the stools of 5 others, all patients apart from Cases 15 and 16 were asymptomatic.

TABLE II

Effect of Mixed Disaccharide Load

Patient	Sugars in Urine after Load (mg./100 ml.)	Sugars in Marked Stool (mg./100 g.)	Stool Transit Time (hr.)
1	None	Lactose 60	24
13	None	None	20
14	Glucose 60	None	23
15	Sucrose 60 Lactose 150 Fructose 5 Galactose 5	Lactose 50 Glucose 80	8
2	Lactose 50 Galactose 25	Sucrose 10 Fructose 5	71
3	None	None	23
4	Glucose 100	Sucrose 10 Lactose 10 Glucose 10 Galactose 10 Fructose 10	22
5	None	Glucose 10	22
6	None	None	—
7	None	Sucrose 120 Lactose 20 Galactose 10 Glucose 80 Fructose 200	21
8	Sucrose 60 Lactose 80 Fructose 15 Galactose 60	None	22
16	None	Glucose 80	8
9	None	None	46
10	None	None	22
11	None	None	22
17	None	Fructose 10	14

Sucrose load. The blood sugars from 15 children are shown in Table III. In no instance did the blood glucose or total reducing substances fail to rise 30 mg./100 ml. or more above the baseline when taken at 15-minute intervals. In all except 3 patients (Cases 1, 11, and 14) the blood glucose peak was reached at 30 minutes and was beginning to fall again at 45 minutes.

Six children produced monosaccharides and disaccharides in their stools, but did not have any sugars in the urine. The stool transit time was shortened to 8 and 9 hours in 2 of these only (Cases 5 and 14). Significant sucrosuria occurred in 5 children, ranging from 40 to 400 mg./100 ml. Only one of these had sugar in the stool, but the transit time was normal (Table IV). Clinical

TABLE III

Glycaemic Responses to a Sucrose Load

Case No.	Blood Sugars (mg./100 ml.)									
	0 min.		15 min.		30 min.		45 min.		60 min.	
	Total Sugar	Glucose	Total Sugar	Glucose	Total Sugar	Glucose	Total Sugar	Glucose	Total Sugar	Glucose
1	78	60	120	95	210	139	181	149		
13	88	63	118	76	162	98	109	98		
14	81	73	116	108	154	148	183	176	183	
15	51	30	77	60	95	78	107	76		
2	82	65	144	108	—	118	100	99		
3	81	65	130	97	117	100	103	102		
4	80	50	205	165	114	100	90	61		
5	76	49	102	88	110	91	114	91		
6	84	52	115	79	136	106	110	73	102	58
7	83	73	127	102	109	82	97	74		
8	91	72	150	140	178	140	197	135	195	—
16	78	53	98	80	120	107	—	—		
9	77	—	135	—	132	—	—	—		
10	75	67	126	112	177	154	169	147		
11	92	65	100	67	138	105	158	127	202	155

TABLE IV

Urine and Stool Findings after a Sucrose Load

Case No.	Sugars in Urine after Load (mg./100 ml.)	Sugars in Marked Stool (mg./100 g.)	Stool Transit Time (hr.)
1	Sucrose 300 Fructose 50 Glucose 2400	Glucose 10	24
13	Sucrose 60	None	21
14	None	Glucose 30	9
15	Sucrose 400 Fructose 5	None	22
2	None	Glucose 50	22
3	Sucrose 40	None	21
4	None	Sucrose 10 Fructose 10	22
5	None	Sucrose 20 Fructose 20 Glucose 100	8
6	None	None	—
7	None	None	22
8	None	None	22
16	None	None	23
9	Sucrose 80	None	30
10	None	None	23
11	None	Glucose 10	21

TABLE V

3-O-Methyl-D-Glucose Load

Case No.	% of Dose Excreted in 9 hr.	3-O-methyl-D-glucose in Stool (mg./100 g.)
1	73	None
13	61	None
14	64	None
15	42	None
2	62	Trace
3	63	None
4	58	None
5	70	40
6	31	None
7	63	None
9	60	None
10	75	None
11	68	None
17	79	None

TABLE VI

Effect of Lactose Load in 2 Selected Patients

Case No.	Sugar in Urine After Load (mg./100 ml.)	Sugar in Marked Stool (mg./100 g.)	Stool Transit Time (hr.)
15	Lactose 60	Lactose > 500 Galactose > 400 Glucose > 200	6¼
16	None	None	10

and biochemical evidence did not correlate to support intolerance in any of the children studied.

3-O-methyl-D-glucose load. The normal excretion in urine collected up to 9 hours after the load is given by Nordio *et al.* (1965) as ranging widely from 55 to 100% of the dose given. On this basis only 2 out of 14 children given the load were clearly abnormal; Case 6 with 30% and Case 15 with 42% (Table V). The excretion by Case 6 remains unexplained, as none of her other tests suggested abnormal handling of sugars. She continued to excrete 3-O-methyl-D-glucose in the urine for 4 days.

Lactose load. The results on 2 patients (Cases 15 and 16) are shown in Table VI. These children (2 of the 3 who had undergone small bowel resection at birth) were selected for a lactose load because both developed symptoms after the mixed disaccharide load and neither had proved intolerant to sucrose.

One patient (Case 15) produced a frankly abnormal response with some abdominal cramps, disaccharides in urine and stool, and a loose stool with a short transit time.

Case 16 did not produce disaccharides in urine or stool, but the stool transit time was shortened from a usual 23 hours for this patient to 10 hours.

Jejunal biopsy. This was reserved for those patients who showed intolerance to disaccharides by both clinical and biochemical tests. On this basis only one patient (Case 15) qualified. The biopsy showed a flattened mucosa with villous atrophy, and reduced activity of disaccharidases, especially lactase. Lactase activity was 0·15 units (normal > 2·5), sucrase 0·54 units (normal > 3·0), and maltase 5·4 units (normal > 10·0), all per g. wet weight of mucosa.

Discussion

The occurrence of disaccharidiuria in half of the children studied on a ward diet, and the high carbohydrate diet, is consistent with similar findings by Gryboski *et al.* (1963). Sucrosuria has been shown in normal children and in those with cystic fibrosis of the pancreas, and may be partly related to the concentration of the sugar reaching the small bowel mucosa (Menzies and Seakins, 1968). On a normal or high carbohydrate diet this concentration may be sufficiently hypertonic to cause sucrosuria. Using the sugar load technique described overcomes this difficulty, and disaccharidiuria due to dietary variation is easily distinguished from that due to disaccharide malabsorption.

Glucosuria greater than 30 mg./100 ml. occurred in 9 of 52 cases. Whether the findings represent a lowered renal threshold to glucose or are indicative of a latent diabetic state is not clear, but one child (Case 14) developed diabetes mellitus with ketosis 12 months later.

Increasing the dietary sugar for 3 days produced no clinical evidence of malabsorption except that one patient (Case 4) had a shortened stool transit time. She had no symptoms and on subsequent testing was not shown to be intolerant of any particular sugar. The reason for the short transit time remains unexplained.

At this hospital the mixed disaccharide load has proved a useful screen for suspected intolerance in children who are not severely ill. The two children (Cases 15 and 16), who reacted to the mixed disaccharide load, on further testing were not intolerant of sucrose. However, a lactose load on Case 15 produced all the biochemical and clinical criteria of intolerance, while in Case 16 it produced only a shortened stool transit time. The clinical evidence of lactose intolerance in this latter child was not supported by the biochemical studies, but he presumably had some depressed lactase activity which led to a clinical reaction under the load conditions.

Results of the sucrose load show the dangers of placing faith in one particular test of intolerance. All the glycaemic responses were normal, in terms of the rate of rise of blood sugar, but 10 out of 15 cases showed some other biochemical abnormality either in the urine or stool, or both. Though these 10 children were not coping entirely normally with the load conditions, only 2 (Cases 5 and 14) showed clinical intolerance. The biochemical findings in these 2 did not correlate with the clinical evidence of intolerance to sucrose.

The appearance of significant sucrosuria in many children with cystic fibrosis suggests that sucrose moves unchanged across the bowel wall more easily than in the normal child. This does not necessarily mean that such cases are intolerant of sucrose.

Only 2 of the 14 children tested with 3-O-methyl-D-glucose were clearly abnormal. One of these (Case 15) was proved intolerant of lactose. This suggests that with the exception of this child, there was no severe impairment of the total absorption of the monosaccharide glucose in the other 12.

The correlation of biochemical and clinical evidence of intolerance to lactose, together with impaired total active monosaccharide absorption, led to biospy in one child (Case 15). It is possible that if more of these children had been subjected to biopsy they would have revealed some depression of sucrase and especially lactase activity. Case 15 was not intolerant of sucrose though the area of biopsy showed considerably depressed sucrase activity. However, like many of the other children this case frequently produced sucrosuria. It is clear, therefore, that depressed disaccharidase activity is not always synonymous with clinical and biochemical intolerance.

Villous atrophy has been reported before in cystic fibrosis (Nordio *et al.*, 1966), but most biopsies in this disease show a normal mucosa (Rubin and Dobbins, 1965). Both Cases 15 and 16 showed intolerance of lactose and both had small bowel resections in infancy. In this respect they can be compared with the case reported by Sunshine and Kretchmer (1964) in which half the ileum, caecum, and ascending colon had been resected at birth. The only other child (Case 14) who had undergone bowel resection in infancy did not have disaccharide intolerance.

This study has not included the age-group below 2 years when of course lactose is more important. Those children who have had small bowel resection for meconium ileus appear more likely to be affected by lactose intolerance, just as any neonate with small gut resection (Burke and Anderson, 1966). The mixed disaccharide load detects the disaccharide-intolerant infant as easily as the older child

Sugars are commonly found in the urine and stools of many children with cystic fibrosis. This suggests that such children may not deal normally with disaccharides. Results of further investigations do not suggest that this malabsorption of disaccharides contributes to the gastro-intestinal symptoms, except when clinical and biochemical evidence suggests frank intolerance.

The decision to modify the disaccharide content of the diet in cystic fibrosis should be based on correlated clinical and biochemical evidence of intolerance. The method of sugar load used in this study, which does not require blood specimens, is an advantage in children. The difficulty of interpretation of glycaemic responses is avoided (Nordio *et al.*, 1965; Holt and Somersalo, 1966). Disaccharide intolerance should be considered in children with cystic fibrosis who have had bowel resection for meconium ileus, or who appear to have more than usually severe gastro-intestinal signs and symptoms.

Summary

Seventeen children with cystic fibrosis of the pancreas have been examined for evidence of disaccharide intolerance. Both a normal and a high

carbohydrate diet produced sugars in the urine or stools of half the patients. Correlation of the clinical response with biochemical abnormalities after disaccharide loads showed frank intolerance to lactose in one child who had undergone bowel resection for meconium obstruction. Disaccharide intolerance should be considered in children with cystic fibrosis who have had bowel resection for meconium ileus, or who appear to have more than usually severe gastro-intestinal signs and symptoms. The method of sugar load used, which does not require blood specimens, is useful for children.

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References

Arthur, A. B. (1966). Intestinal disaccharidase deficiency in children with coeliac disease. *Arch. Dis. Childh.*, **41**, 519.

——, Clayton, B. E., Cottom, D. G., Seakins, J. W. T., and Platt, J. W. (1966). Importance of disaccharide intolerance in the treatment of coeliac disease. *Lancet*, **1**, 172.

Burke, V., and Anderson, C. M. (1966). Sugar intolerance as a cause of protracted diarrhoea following surgery of the gastro-intestinal tract in neonates. *Aust. paediat. J.*, **2**, 219.

Cozetto, F. J. (1963). Intestinal lactase deficiency in a patient with cystic fibrosis. *Pediatrics*, **32**, 228.

Fordtran, J. S., Clodi, P. H., Soergel, K. H., and Ingelfinger, F. J. (1962). Sugar absorption tests, with special reference to 3-O-methyl-D-glucose and d-xylose. *Ann. intern. Med.*, **57**, 883.

Gryboski, J. D., Thayer, W. R., Jr., Gabrielson, I. W., and Spiro, H. M. (1963). Disaccharidiuria in gastrointestinal disease. *Gastroenterology*, **45**, 633.

Holt, L. E., Jr., and Somersalo, O. (1966). The measurement of carbohydrate intolerance. *Helv. paediat. Acta*, **21**, 588.

Hugget, A. St. G., and Nixon, D. A. (1957). Use of glucose oxidase, peroxidase and O-dianisidine in determination of blood and urinary glucose. *Lancet*, **2**, 368.

Mantle, D. J., and Norman, A. P. (1966). Life-table for cystic fibrosis. *Brit. med. J.*, **2**, 1238.

Menzies, I. S., and Seakins, J. W. T. (1968). Sugar loading test. In *Chromatographic and Electrophoretic Techniques*, 2nd ed., Vol. I. Ed. by I. Smith. Heinemann, London.

Nordio, S., Lamedica, G. M., Berio, A., and Vignolo, L. (1966). Disaccharidase activities of duodenal mucosa in children. *Ann. paediat. (Basel)*, **206**, 287.

——, ——, Vignolo, L., and Berio, A. (1965). Problems regarding intestinal absorption of monosaccharides. The 3-methyl-O-glucose test. *ibid.*, **204**, 157.

Rubin, C. E., and Dobbins, W. O., III (1965). Peroral biopsy of the small intestine. A review of its diagnostic usefulness. *Gastroenterology*, **49**, 676.

Sunshine, P., and Kretchmer, N. (1964). Studies of small intestine during development. III. Infantile diarrhea associated with intolerance to disaccharides. *Pediatrics*, **34**, 38.

Townley, R. R. W. (1966). Disaccharidase deficiency in infancy and childhood. *ibid.*, **38**, 127.

Wilkinson, R. H. (1960). *Chemical Micromethods in Clinical Medicine*. Thomas, Springfield, Illinois; Blackwell, Oxford.