

HEREDITARY SUCROSE INTOLERANCE: LEVELS OF SUCRASE ACTIVITY IN JEJUNAL MUCOSA

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Though the amylase of duodenal juice hydrolyses the polysaccharides of the diet to oligosaccharides and disaccharides, the final cleavage of the latter to the monosaccharides, which is essential for absorption, is almost entirely effected by specific enzymes located in the intestinal mucosa. An inherited deficiency of intestinal lactase was first suggested as a possible cause of chronic diarrhoea and failure to thrive in a 13-month-old infant, by Durand (1958) and later by Holzel, Schwarz, and Sutcliffe (1959) for a similar condition in two sibs. Since then a number of cases, not only of lactase deficiency but also of sucrase deficiency, have been reported. The diagnosis has almost always rested upon severe diarrhoea following ingestion of the carbohydrate, an inability to metabolize the sugar as shown by the presence of the carbohydrate in the urine and faeces and the failure of the blood glucose to rise after oral administration of the disaccharide.

It has long been known that extracts of the intestinal mucosa of mammals have invertase activity. Following his characterization of several specific disaccharidases in hog intestinal mucosa, Dahlqvist (1961) has demonstrated the specific character of the disaccharidases in human intestinal mucosa as well as the overlapping specificities of some of them. He has shown in particular that human intestinal sucrase (invertase), like the corresponding enzyme in the pig, has also some maltase activity.

Anderson, Messer, Townley, Freeman, and Robinson (1962) and Anderson, Messer, Townley, and Freeman (1963) have demonstrated the absence of sucrase in biopsy specimens of duodenal mucosa in two sibs with sucrose intolerance. Mucosal homogenates were incubated with sucrose and the incubation mixture was subsequently examined by paper chromatography. Only a visual estimate of the enzyme activity as judged by the amount of

monosaccharide produced by hydrolysis was possible by this method.

In the present article, we present 7 further cases of an inherited absence of intestinal sucrase, including 2 in one family. The initial diagnosis was made on clinical grounds, and confirmed by the usual laboratory findings. In each case, a biopsy specimen of the jejunal mucosa has been obtained and the enzyme activities to a number of carbohydrate substrates, including sucrose, determined quantitatively. Only on this basis is it possible to diagnose with certainty the specific sucrase defect, and to differentiate it from the acquired carbohydrate intolerance that may occur in disease involving the small intestine. It is likely that cases of hereditary sucrose intolerance are not uncommon, as these now described were detected within a relatively short period.

Though the ultimate prognosis may be good even in untreated cases, it is nevertheless desirable to eliminate as soon as possible the responsible carbohydrate from the diet, otherwise weight gain and progress in the affected infant will be unsatisfactory.

Case Reports

Case 1. A boy (sib of Case 2) was born at Plaistow Maternity Hospital on October 13, 1958 at term after a normal pregnancy and delivery, birth weight 5 lb. 11 oz. (2,578 g.). He was fed from the beginning on dried milk with added cane sugar. On the 9th day he developed diarrhoea with loose green stools, which became more severe, so that on the 12th day he was transferred to the Queen Mary's Hospital. On admission he appeared very dehydrated, his weight being 13 oz. (368 g.) below that at birth. He was given intravenous therapy for 24 hours and then tube fed, and made a slow recovery (Fig. 1).

When discharged at 1 month of age, weighing 6 lb. 2 oz. (2,778 g.) he was still being given dried milk feeds with added cane sugar. Six days after discharge he was admitted to the Queen Elizabeth Hospital for Children

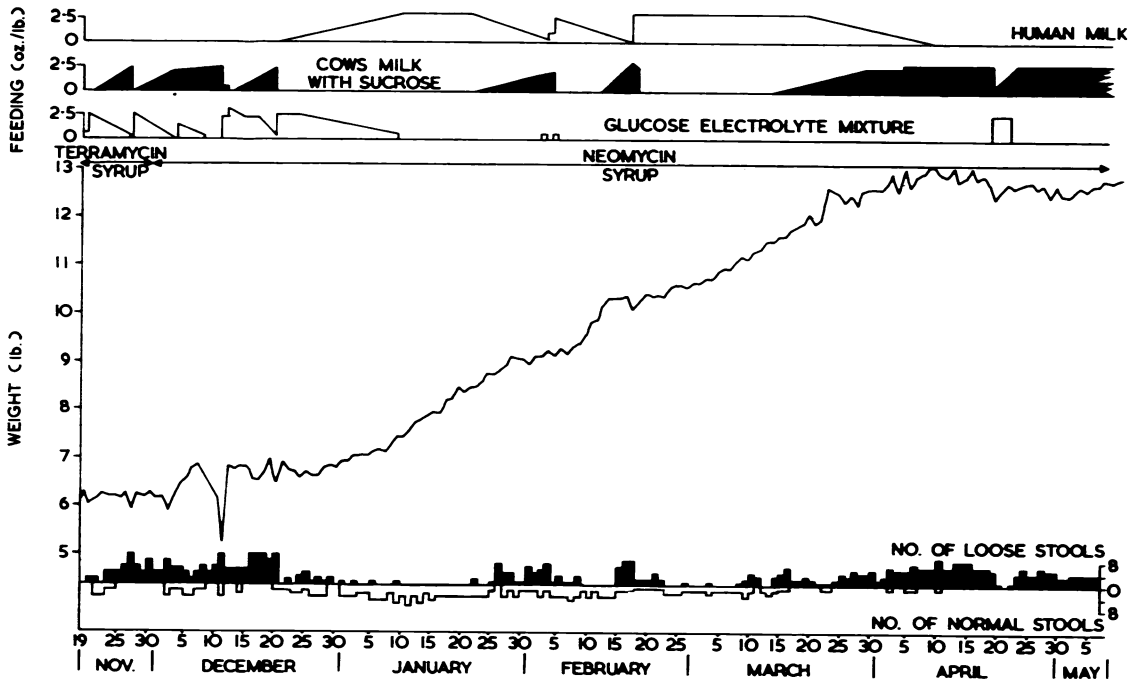


FIG. 1.—Case 1: Male, born October 13, 1958. Hereditary sucrose intolerance not diagnosed till the age of 5 years. Chart shows progress from 1 to 7 months of age.

Note (a) close correlation between intake of sucrose and the loose stools and loss of weight, (b) steady weight gain over a period of 11 weeks when sucrose was excluded except for 2 short periods when sucrose was reintroduced into the diet with resulting diarrhoea, and (c) immediate cessation of weight gain over a long period when sugar added to feeds.

with a history of cough for a day, one vomit, and refusal of feeds. On admission he appeared ill, with pallor, abdominal distension, and tachypnoea. His feeds of dried milk with sugar were continued, and on the day of admission he had a moderate diarrhoea which became more severe, with many fluid yellow stools. He became dehydrated and was given a glucose electrolyte mixture by mouth. No cause for the diarrhoea was revealed by laboratory investigation. When his feeds were fully regraded to dried milk with added sugar, diarrhoea recurred with loss of weight. The pattern of cessation of diarrhoea on an oral glucose electrolyte mixture, followed by its recurrence on regrading to full feeds, was repeated on four successive occasions during the first month of stay. Finally he was given expressed breast milk in increasing amounts over a period of 3 weeks. He began to gain weight steadily, $1\frac{1}{2}$ lb. (680 g.) in one month, and the stools improved though they still remained loose. The breast milk feeds were now gradually replaced over a period of a fortnight by an evaporated milk with added sugar. Weight gain ceased and diarrhoea again became more severe. His feeds were therefore changed to expressed breast milk, with added Horlick's milk preparation, but without added sugar. He began to gain weight and diarrhoea improved. A return to dried milk feeds with added sugar led to another relapse. Breast milk was again instituted with fruit *purées* and cereals. He gained 1 lb. 3 oz. (538 g.) in weight in the next 3 weeks, and the

character of the stools became more normal. Evaporated milk feeds were now gradually introduced at the same time as his expressed breast milk feeds were decreased, until, at about $5\frac{1}{2}$ months of age he was being fed wholly on evaporated milk with added sugar and with fruit *purées* and cereals. Weight gain ceased and diarrhoea returned. At 7 months of age he was discharged on a dilute evaporated milk with added sugar and mixed feeding. Although he slowly gained weight the stools were always loose. He weighed only 18 lb. (8.16 kg.) at 1 year. He was admitted at 5 years of age for carbohydrate absorption tests and jejunal biopsy. He is now, at $5\frac{1}{2}$ years, a well child, but has occasional loose stools. He continues to have some sugar in his diet, though much less than the average child.

Case 2. A girl (sib of Case 1) was born on November 5, 1962 at the Mile End Hospital at term after a normal pregnancy and delivery, birth weight 5 lb. 12 oz. (2,607 g.). She was breast fed for 2 months. When she was changed to dried milk with added sugar, she refused the sweetened feeds, but readily accepted them unsweetened. Although after this, cane sugar was not added to the milk feeds, sucrose was not completely excluded from the diet when mixed feeding was later introduced. There was an unexplained short episode of diarrhoea at 11 months of age, responding satisfactorily to glucose solution by mouth. She was admitted to the Queen Elizabeth

Hospital for Children at 1 year of age for investigation as a sib of an affected child. Her milestones had been normal but her weight, 17 lb. 12 oz. (8 kg.), was below the normal for this age (Levin, Mackay, Neill, Oberholzer, and Whitehead, 1959).

Case 3. A girl was born at term on April 11, 1962 after a normal pregnancy and delivery, birth weight 7 lb. 12 oz. (3,515 g.). She was breast fed for 3 weeks and then changed to an evaporated milk feed with added cane sugar. Within a few days, she developed a severe and explosive diarrhoea, with very fluid stools. When admitted to the Queen Elizabeth Hospital for Children on the 26th day, she was a crying but somewhat lethargic baby, with severe dehydration, weighing 1 lb. (453 g.) less than her birth weight. Her temperature was 100.5° F. (38° C.), and laboratory investigations revealed a metabolic acidosis with dehydration. Stool culture was negative. She was given intravenous therapy and recovery was complicated by convulsions lasting over 6 hours. Subsequently, two attempts at regrading the feeds to a dried milk mixture with added cane sugar resulted in diarrhoea and loss of weight, necessitating further intravenous therapy. She began to gain weight only when expressed breast milk was given, though the stools were still loose. When sucrose intolerance was suspected, glucose was substituted for cane sugar in her feeds, with further improvement. Throughout this period, however, she was on antibiotic therapy, and the antibiotic was dispensed in a syrup of a high concentration of cane sugar. The complete elimination of the sugar from the medicine led to marked lessening in the diarrhoea,

and a maintained or increased weight gain. Several attempts since then to introduce sugar in the form of sweets etc. have led to relapse. At 14 months of age, she was readmitted for carbohydrate absorption tests and jejunal biopsy. She was then a well child, with normal milestones, weight 19 lb. 10 oz. (9 kg.), i.e. still below the normal weight for her age.

Case 4. A boy was born at the German Hospital on February 25, 1958 at full term after a normal pregnancy, birth weight 7 lb. 12 oz. (3,515 g.). He was breast fed for 2 weeks when he was gradually changed to dried milk with added cane sugar. When on full artificial feeds he developed diarrhoea, became irritable with crying, and refused his feeds. Believing that cane sugar was the cause of the diarrhoea, the mother largely replaced it by glucose, with cessation of diarrhoea. Cereal was introduced at 6 weeks and vegetable *purées* at 9 weeks. At 2 months of age cane sugar was reintroduced but led to refusal of milk feeds (Fig. 2).

At 9 weeks of age he again developed diarrhoea and was seen in the casualty department at the Queen Elizabeth Hospital. He was given an electrolyte mixture with cane sugar. Next day he had to be admitted because of continual screaming, refusal of feeds, vomiting, and diarrhoea. He was pale, mildly dehydrated, with no abdominal distension. He was treated with a glucose electrolyte mixture and an antibiotic. Faeces cultures were negative. When he was back on full feeds of dried milk with added cane sugar, diarrhoea recurred and he lost weight. This sequence of improvement in diarrhoea on an oral glucose electrolyte mixture followed by deteriora-

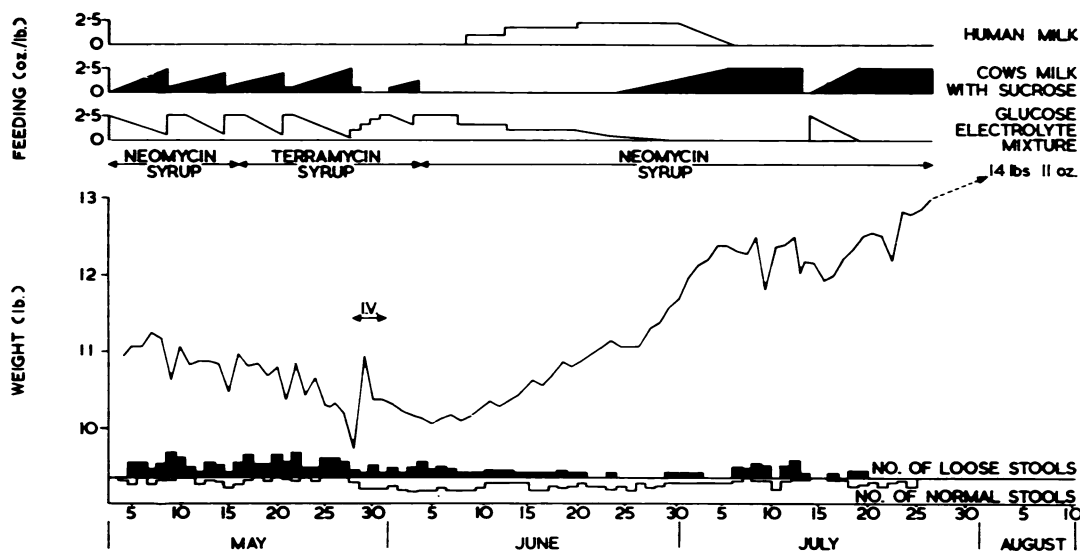


FIG. 2.—Case 4: Male, born February 25, 1958. Hereditary sucrose intolerance not diagnosed till 5 years old. Progress from 2 to 5 months of age.

Note (a) the sequence, in 4 consecutive periods, of improvement of diarrhoea and gain in weight on treatment with glucose electrolyte mixture; loose stools and loss of weight when full feeds of cows' milk with added sucrose are attained, (b) moderate weight gain over period of one month when sugar excluded from feeds: but loose stools persist because of the sucrose in the neomycin syrup.

tion on full feeds was repeated on four successive occasions in the first month of his stay in hospital. On the last occasion diarrhoea and dehydration were severe, necessitating intravenous therapy, after which he was given a glucose electrolyte mixture by mouth with added apple powder and casein hydrolysate for 11 days. Expressed breast milk was now introduced with gradual increase of feeds over 10 days. He began to gain weight steadily, and his stools improved though they still remained loose. Gradual replacement of breast milk by dried milk with added cane sugar resulted in failure to gain weight and increased diarrhoea.

He was discharged from hospital at 5 months of age on mixed feeding, but when home his mother again substituted glucose for cane sugar: diarrhoea ceased and an excellent weight gain followed (1 lb. 10 oz. (746 g.) in 17 days). Since then he has been a well child except for occasional loose stools. He was readmitted at the age of 5 years for the present investigation. His milestones were normal. At that time, he was still being given glucose for sweetening purposes. Sucrose in the form of sweets, chocolates, and ice-cream still caused loose stools, with some abdominal pain, though tolerance to small amounts of cane sugar had improved.

Case 5. A boy was born at home on February 5, 1960 after a normal pregnancy and delivery, birth weight 8 lb. 4 oz. (3,741 g.). He was breast fed for 9 weeks, after which he was weaned on to dried milk with added cane sugar, and cereals were introduced. Within two days of this diet the stools became loose and frequent, and this persisted in spite of a change to a half cream dried milk, though weight gain was satisfactory. His abdomen was noticed to be distended at the age of 7 months. Though there was some improvement in his diarrhoea as he grew older, it was made worse when sweet foods were eaten, and since abdominal distension persisted he was referred at 2 years of age to the Queen Elizabeth Hospital for Children. He appeared then to be a rather hypotonic child with a moderately distended abdomen, but both by weight and height he was only on the 25th percentile for his age. His appetite was very good, even excessive. He was passing 4-6 loose stools per day. These showed moderate numbers of fat globules on microscopic examination and a 3-day stool collection showed a raised fat excretion, 4.7 g. per day, the stools being fluid and bulky. A xylose absorption test proved normal. A radiograph of the abdomen was reported, 'This looks like a combination of Chilaiditi's disease and coeliac disease,' (Dr. C. J. Hodson). A barium meal (non-flocculating medium) revealed, 'clumping of medium in the small bowel,' (Dr. C. J. Hodson) and a radiograph of the wrist showed a bone age corresponding to his chronological age. A diagnosis of Chilaiditi's syndrome was made, though steatorrhoea is not normally considered part of this disorder. Because of the history of the diarrhoea being made worse by sweet foods, a form of sugar intolerance was suspected and the substitution of cane sugar by glucose in his diet for 2 months at home resulted in an improvement in the diarrhoea, though the abdominal distension persisted. At 2½ years faecal fat excretion

(4.1 g. per day) was still high though slightly less than before, the stools being still bulky.

On September 3, 1962 he was admitted to hospital for further investigations for coeliac disease. He was given a diet from which cane sugar was largely though not completely excluded, and episodes of diarrhoea occurred once or twice a week. Abdominal distension was unchanged. A jejunal biopsy at this time showed no histological abnormality and this was thought to exclude coeliac disease. He was discharged on a low fat, high calorie, and high protein diet, which included restriction of added cane sugar to about 15 g. per day, apart from some small amounts in the ordinary food. His clinical state remained unchanged during the next 12 months, occasional diarrhoea and abdominal distension persisting. He was readmitted on July 16, 1963 for investigation of a possible sucrose intolerance. Carbohydrate tolerance tests and a jejunal biopsy for enzyme estimation were carried out. When discharged he was given a sucrose-free diet at home. His stools are now nearly normal but abdominal distension remains. His weight at 37 lb. 8 oz. (17 kg.) is between the 50th and 75th percentile for his age, and his milestones have been normal.

Case 6. A girl was born at Hackney Hospital at term on April 16, 1962, birth weight 6 lb. 4 oz. (2,834 g.), by forceps delivery for foetal distress, after a pregnancy complicated by toxæmia. She was asphyxiated at birth, and resuscitated with difficulty. She was admitted to the Queen Elizabeth Hospital on the next day with cyanotic attacks and convulsions, from which she gradually recovered. She was given expressed breast milk at first, but after discharge at 10 days this was changed to dried milk with added sugar. Soon afterwards she developed diarrhoea and was again seen at the Queen Elizabeth Hospital for Children, and given an electrolyte mixture with added sugar and an antibiotic. Diarrhoea became more severe and she was admitted the next day when 17 days of age. She was then severely dehydrated, having lost over 1 lb. (453 g.) in the previous 7 days, and was drowsy with deep and rapid respirations. There was a metabolic acidosis with severe dehydration for which intravenous therapy was given. No cause for the diarrhoea was found. When oral feeding was resumed with dried milk and added sugar, diarrhoea recurred and she lost weight. Improvement again followed treatment with an oral glucose electrolyte mixture with subsequent relapse on dried milk with added cane sugar. Though diarrhoea persisted she did maintain a steady weight gain while in hospital. When discharged at 7 weeks of age she weighed 7 lb. 14½ oz. (3,580 g.), but she was readmitted the next day because of severe diarrhoea. Once again improvement followed intravenous therapy with relapse when normal feeding was resumed.

Sucrose intolerance was then suspected and glucose substituted for sucrose in the feeds. In the next 2 days her diarrhoea almost ceased, and she began to gain weight. After 18 days, a trial replacement of glucose by sucrose over seven days resulted in a prompt relapse with diarrhoea and cessation of weight gain. During her whole stay in hospital, she was given prophylactic antibiotics dispensed

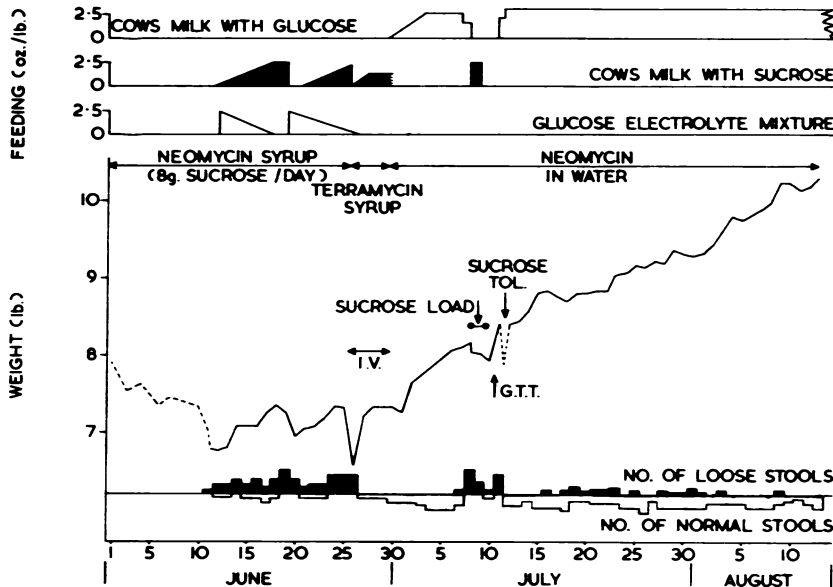


FIG. 3.—Case 7: Male, born June 1, 1963. Hereditary sucrose intolerance diagnosed and treated in early infancy.

Note (a) improvement of diarrhoea and gain in weight on treatment with glucose electrolyte mixture; loose stools and loss of weight when full feeds of cows' milk with added cane sugar are attained, (b) severe diarrhoea on sucrose load, and (c) steady weight gain when sucrose excluded from diet.

in a syrup containing a high concentration of cane sugar. In the doses given, this constituted a considerable quantity of sugar, at least 8 g. per day.

She was discharged at the age of 3 months, weight 9 lb. 11 oz. (4,393 g.) on reconstituted dried milk with added glucose. Six weeks after discharge she had gained 2 lb. 13 oz. (1,275 g.), having been on a completely sucrose free diet. A test feed with sucrose as an out patient led to prompt relapse, which ceased when sucrose was stopped. The gradual reintroduction of sugar into her diet at 10 months of age led to intermittent but mild diarrhoea. She is still having a moderate amount of cane sugar with no more than occasional loose stools. Her milestones are normal. She was readmitted at 15 months of age for the present investigations.

Case 7. A boy was born on January 1, 1963 at the Annie McColl Maternity Hospital, after a normal pregnancy and delivery, birth weight 7 lb. 14 oz. (3,571 g.). From the beginning he was fed on dried milk with added cane sugar. On the 4th day of life he developed diarrhoea for which he was given clear fluids and neomycin orally. The diarrhoea improved but recurred on regrading the infant to milk feeds. He was admitted to the Queen Elizabeth Hospital for Children on the 10th day of life, his weight being 1 lb. 8 oz. (680 g.) below that at birth. He was lethargic and moderately dehydrated. His diarrhoea improved on a glucose electrolyte mixture with neomycin, but he relapsed as soon as he was given full feedings of dried milk with sugar added. The third sequence of improvement on a glucose electrolyte mixture therapy and relapse on full artificial feeds resulted

in a diarrhoea severe enough to require intravenous therapy. Sucrose intolerance was now suspected and from the age of 1 month this sugar was excluded from his diet. His diarrhoea ceased and he began to gain weight steadily. After 8 days on a sucrose free diet, introduction of about 4 g. of cane sugar in every feed for only one day resulted in immediate diarrhoea. A tolerance test giving 11 g. sucrose resulted in the infant passing several watery, acid smelling stools four hours later. His subsequent progress on a sucrose-free diet has been good. At 9 months of age he was readmitted for jejunal biopsy and further carbohydrate tolerance tests. He is now a well child, weighing 19 lb. 6 oz. (8.78 kg.) and his milestones are normal (Fig. 3).

Laboratory Investigations

Methods. Blood glucose was determined, after precipitating the protein by a neutral reagent, by the glucose oxidase method, and blood sucrose by the Seliwanoff reaction as for fructose, using sucrose as standard. The latter values obtained included, of course, fructose, but this would usually be small. Urine and stool specimens were analysed for carbohydrates by paper chromatography, using butanol-acetic acid-water as the solvent system. For the tolerance tests 2 g. kg. were usually given.

Enzyme Estimations in Jejunal Mucosa. Biopsy specimens of jejunal mucosa were obtained by the use of the Crosby capsule. Fluoroscopy was used to determine the position of the capsule before it was fired. The specimens were always examined under the dissecting

microscope before enzyme determination. In every case the villi appeared normal. About 15 to 20 mg. of tissue were usually obtained on each occasion, enzyme activities being determined on the fresh specimens within a short time after removal. For the estimations the biopsy was well washed in ice-cold saline, blotted dry, and weighed. It was then homogenized in ice-cold distilled water in a Ten-Broeck grinder, using 15 strokes of the plunger. For sucrose, two concentrations of homogenate were taken, 1 in 40 and 1 in 100. For cellobiase and lactase a concentration of 1 in 40 was used, for palatinase, 1 in 100, and for maltase, 1 in 400.

Principle. The glucose liberated by hydrolysis of the disaccharide by the enzyme in the homogenate after incubation for 20 minutes was determined by the glucose oxidase method.

Procedure. 25 μ l. of 0.2 M. potassium phosphate (KH_2PO_4) buffer adjusted to pH 6.0, 50 μ l. of 0.1 M. of the appropriate disaccharide, and 50 μ l. homogenate were incubated at 37° C. for exactly 20 minutes in a 2 in. \times $\frac{3}{8}$ in. glass test-tube. A control tube containing only buffer and homogenate was included for each estimation. Following incubation, 50 μ l. of a 0.1 M. solution of the appropriate disaccharide were added to each control tube, and then from both test and control 50 μ l. of the mixture were taken and incubated for a further 20 minutes with 1 ml. glucose oxidase reagent prepared by dissolving glucose oxidase (Boehringer) in 0.05 M. tris buffer, pH 7.0. The use of tris buffer rather than water is necessary to inhibit disaccharidase activity in the glucose oxidase reagent (Sols and de la Fuente, 1961). After centrifuging, the optical density was read at 436 $m\mu$. The enzyme activity was calculated as μ moles disaccharide hydrolysed per min. per g. wet weight of tissue.

Carbohydrate Tolerance Tests. The blood glucose response after an overnight fast to a test dose of sucrose was determined, and in most cases glucose and lactose tolerances were investigated in addition, in order to confirm the specific nature of the failure to hydrolyse sucrose. In view of the ability of sucrose to act upon maltose, though it constitutes only 25% of the total maltase activity, the effect of a loading dose of maltose and starch was also usually tested. In several cases, a palatinose absorption test was also done, in an attempt to ascertain whether any associated defect of isomaltase activity was present, since palatinose, like isomaltose is a 1 : 6 linked glucoside and is hydrolysed by isomaltase.

Results

Case 1. The results of the full range of carbohydrate tolerance tests performed in Case 1 are shown in Fig. 4. There was a rise in blood glucose of between 50-100 mg./100 ml. in the first hour after the administration of glucose, lactose, or maltose. Following sucrose, the rise of glucose was only 8 mg./100 ml. Paper chromatography of urine passed 3 hours after sucrose was given revealed the presence

of large amounts of sucrose. Though the blood glucose level rose 40 mg./100 ml. after oral starch administration, this did not occur until 1½ hours afterwards. Following palatinose there was a maximum rise in glucose of only 16 mg./100 ml. occurring 2½ hours after the dose. It is interesting to note that vomiting was provoked by both sucrose and palatinose test doses and a second amount had to be given. The urine obtained after administration of palatinose contained the disaccharide. Owing to an error, no stool specimen was available for chromatography. However, in contrast to the normal, the stool was a loose one.

Case 2. The results obtained in Case 2 are shown in Fig. 5 and are similar to those of Case 1. The blood glucose following lactose and maltose administration rose between 38 and 50 mg./100 ml. Whereas in Case 1, the maximum rise following a starch load was found in the second hour, that in Case 2 occurred in 30 minutes though the level achieved was about the same. As in Case 1, sucrose gave a flat blood glucose curve, the rise in the first 2 hours being only 5 mg./100 ml. The levels of blood sucrose in this test were also measured and reached a maximum of 11 mg./100 ml. 3 hours after sucrose administration. A similar result was obtained with palatinose, the rise in blood glucose over the whole period of the test amounting to no more than 6 mg./100 ml. No vomiting occurred but two diarrhoeal stools were passed during the period of the test, and these contained large amounts of the carbohydrate concerned.

Case 3. There was a rise of 60 mg./100 ml. of blood glucose following glucose administration, whereas the maximum rise was only 8 mg./100 ml. after sucrose and 14 mg./100 ml. 2½ hours after palatinose loading (Fig. 6). Both sucrose and palatinose produced loose, sour smelling, acid stools.

Case 4. The glucose absorption test showed a normal rise of 64 mg./100 ml. (Fig. 7), whereas the blood glucose rose only 4 mg./100 ml. following sucrose, which also induced loose, acid stools, containing large amounts of sucrose. A palatinose test was also attempted but vomiting ensued after about half an hour. There was, however, a significant fall in blood sugar of 5 mg./100 ml. during that time. A sib of this patient gave a normal blood glucose curve following sucrose.

Case 5. The rise in blood glucose following glucose or lactose loads was within normal limits

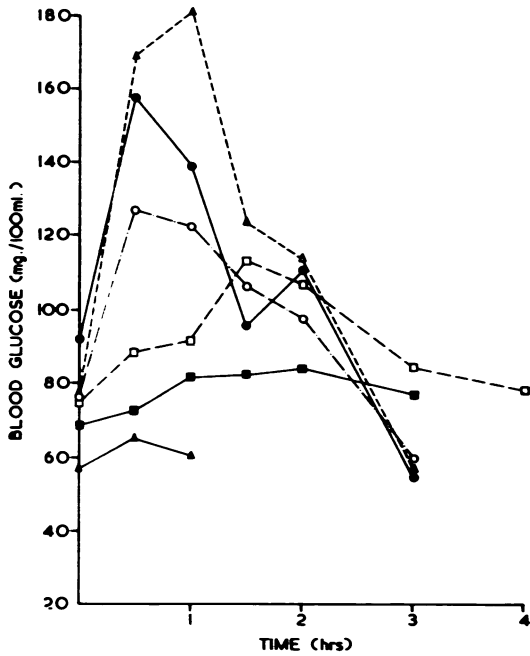


FIG. 4.—Case 1. Changes in levels of blood glucose after ingestion of lactose, glucose, maltose, starch, palatinose and sucrose (2 g. kg.). Lactose, \triangle — \cdots — \triangle ; glucose, \bullet — \cdots — \bullet ; maltose, \circ — \cdots — \circ ; starch, \square — \cdots — \square ; palatinose, \blacksquare — \cdots — \blacksquare ; sucrose, \blacktriangle — \cdots — \blacktriangle .

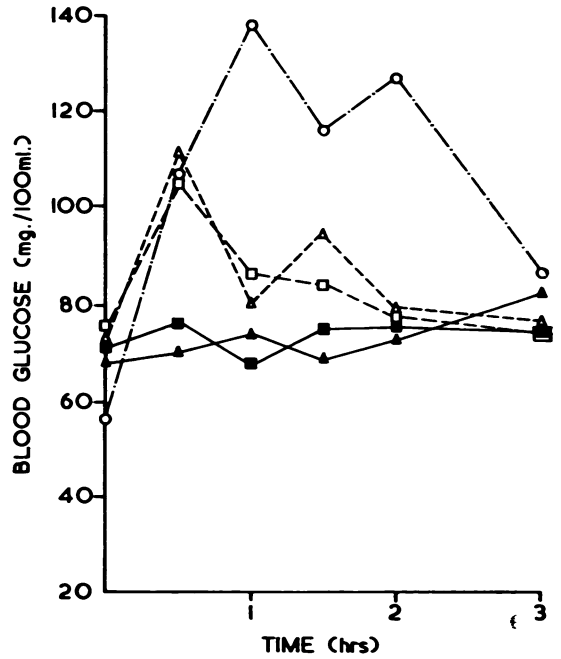


FIG. 5.—Case 2. Changes in levels of blood glucose after ingestion of maltose, lactose, starch, palatinose, and sucrose (2 g. kg.). Symbols as in Fig. 4.

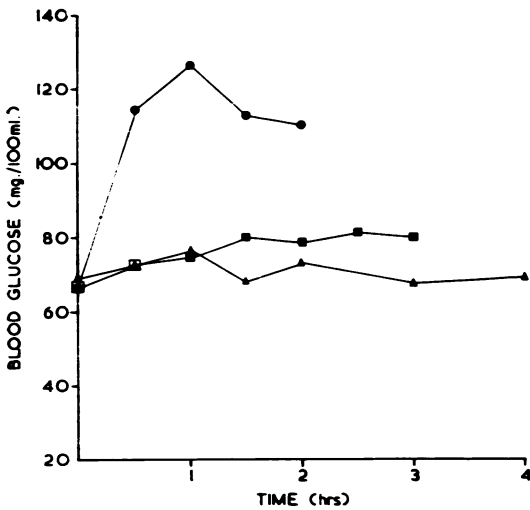


FIG. 6.—Case 3. Changes in levels of blood glucose after ingestion of glucose, palatinose, and sucrose (2 g./kg.). Symbols as in Fig. 4.

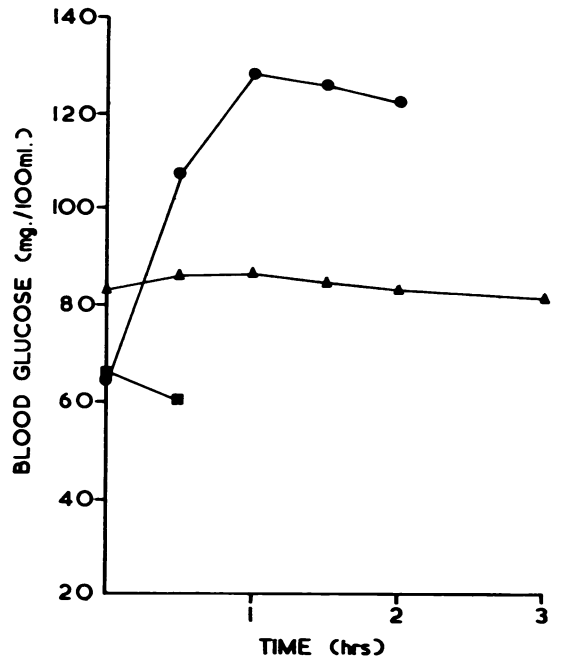


FIG. 7.—Case 4. Changes in levels of blood glucose after ingestion of glucose, sucrose, and palatinose (2 g./kg.). Symbols as in Fig. 4.

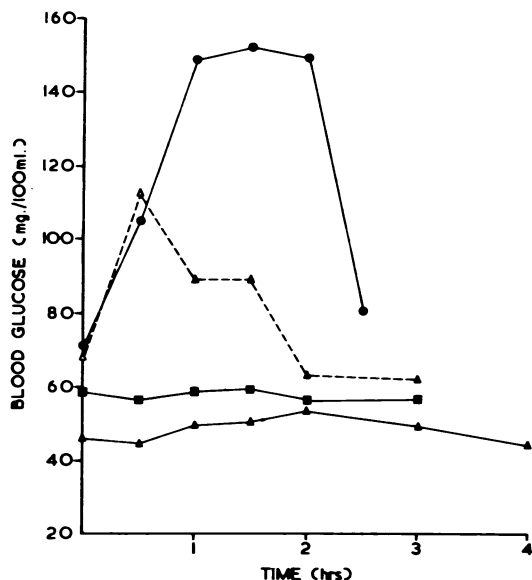


FIG. 8.—Case 5. Changes in levels of blood glucose after ingestion of glucose, lactose, palatinose, and sucrose (2 g. kg.). Symbols as in Fig. 4.

whereas there was little or no alteration in blood levels after sucrose loading (Fig. 8). In two sibs, the blood glucose rose 33 and 57 mg./100 ml. respectively half an hour after giving sucrose.

Case 6. Only the sucrose tolerance test was performed in this case. The maximum rise in blood glucose was 6 mg./100 ml. and this was only achieved at 2 hours. Examination of the urine revealed moderate amounts of sucrose. Several hours after the test, two loose stools were passed but unfortunately these were not kept for investigation (Fig. 9).

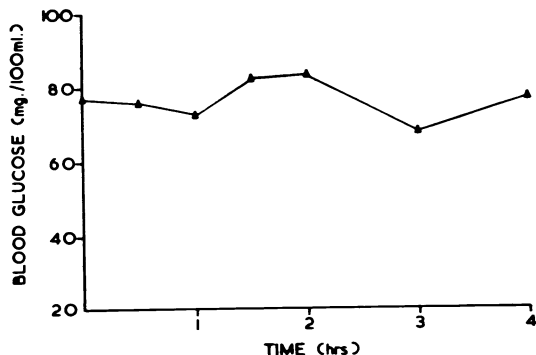


FIG. 9.—Case 6. Changes in levels of blood glucose after ingestion of sucrose (2 g. kg.).

Case 7. There was a fall in blood glucose in the first hour following sucrose administration, though there was a rise of 13 mg./100 ml. after 2 hours. Appreciable amounts of sucrose were detected in the blood after the first hour, up to 10 mg./100 ml. The urine contained sucrose and the stools passed after the test were watery and also contained sucrose. Both the maltose and lactose tolerance tests gave a normal response, though the latter did not show as great a rise of blood glucose as in other lactose tolerance tests, probably because it was performed the day following the jejunal biopsy (Fig. 10).

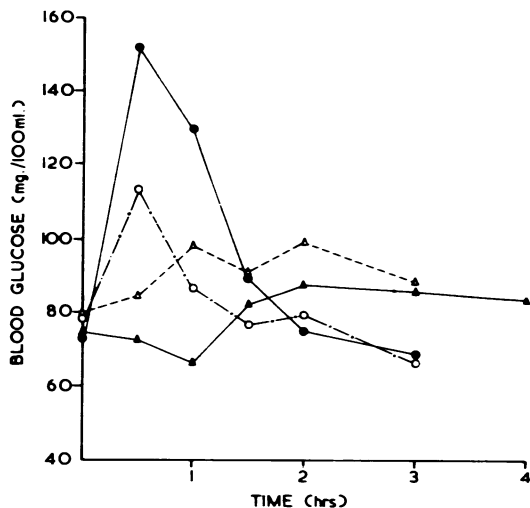


FIG. 10.—Case 7. Changes in levels of blood glucose after ingestion of glucose, maltose, lactose, and sucrose (2 g. kg.). Symbols as in Fig. 4.

Enzyme Activities. The sucrase, maltase, and lactase activities were determined in all 7 cases, the palatinase in 5, and the cellobiase was also estimated in one case. The results are given in Table 1. For comparison, the findings in 5 normal children from 1 to 6 years of age are shown in Table 2. These were mainly undertaken for diagnosis in children thought to have coeliac disease or a disaccharidase deficiency, but who from the histological examination of the biopsy as well as their subsequent progress proved not to have any condition that would seriously affect intestinal enzyme activities. All the enzymes show a wide variation in levels, except palatinase, of which, however, only 2 results were obtained.

In all the affected cases, the sucrase activities were almost absent, less than 1.5% of the mean normal value in 6 cases, and less than 3% in the remaining

TABLE 1

DISACCHARIDASE LEVELS IN JEJUNAL MUCOSA FROM PATIENTS WITH CONGENITAL SUCRASE DEFICIENCY

Case No. and Sex	Age (yr.)	Enzyme Levels (units)			
		Lactase	Maltase	Palatinase	Sucrase
1 M	5½	18.2	6.7	0.24	0.48
2 F	1½	19.8	46.4	1.1	0.24
3 F	2	27.9	2.9	1.7	0.14
4 M	6	15.5	13.2	—	0.29
5 M	3½	18.1	7.6	1.7	0.14
6 F	2	8.8	3.4	—	0.29
7 M	9 mth.	20.0	27.0	2.4	0.28
Means		18.3	15.3	1.4	0.27

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

one. Where it was estimated, the palatinase activity was reduced to 15-36% of the normal, except in one instance, where it was about 3% of the normal. Maltase activity was also variable. In 3 cases, it was 10% or less of the mean normal value, in one it was approximately 20%, in one 40%, and in one it was just within the normal range. On the other hand,

TABLE 2

DISACCHARIDASE LEVELS IN JEJUNAL MUCOSA FROM NORMAL CHILDREN

Sex	Age (yr.)	Enzyme Levels (units)			
		Lactase	Maltase	Palatinase	Sucrase
F	6	8.5	63.3	—	20.2
M	3½	6.6	88.9	—	12.4
M	2	12.4	43.2	6.9	19.0
F	1	8.5	53.0	—	18.0
M	1½	7.5	64.5	6.5	17.4
Means		8.7	62.6	6.7	17.4
Ranges		6.6-12.4	43.2-88.9	—	12.4-20.2

1 unit = 1 μ mole of substrate split g. mucosa/min.

lactase activities were all normal and were actually considerably higher than the normal in all but one instance, suggesting possibly that our normal values are somewhat low. In the only case where it was determined, the level of cellobiase activity also was within the normal range.

Table 3 shows the enzyme activities in jejunal

TABLE 3

DISACCHARIDASE LEVELS IN JEJUNAL MUCOSA FROM PARENTS OF PATIENTS WITH CONGENITAL SUCRASE DEFICIENCY

Parent	Enzyme Levels (units)			
	Lactase	Maltase	Palatinase	Sucrase
Mother of Cases 1 and 2	16.7	44.4	5.2	9.7
Father of Case 4	2.5	27.0	—	5.0
Father of Case 6	10.5	50.7	5.1	16.3

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

biopsies obtained from 3 parents of our series of affected infants. In one, the father of Case 6, all the results were within our normal limits. Only in the mother of the affected sibs, Cases 1 and 2, might the sucrase be considered to be below the normal. In the third parent, the father of Case 4, the 3 enzymes determined, including lactase, all showed lower activities than normal.

Discussion

Following the reports of lactose intolerance by Durand (1958) and Holzel *et al.* (1959), a number of cases of sucrose intolerance probably due to a congenital absence of intestinal sucrase were recorded in 1961 (Weijers, van de Kamer, Dicke, and Ijsseling, 1961; Prader, Auricchio, and Mürset, 1961; Auricchio, Prader, Mürset, and Witt, 1961; Nordio, La Medica, and Vignolo, 1961; Delaitre, Fonty, Varlet, and Fourrier, 1961). Since then there have been many further reports, all but one (Anderson *et al.*, 1963) from countries in Western Europe.

Nordio and La Medica (1964), in a recent review, have summarized the clinical findings in the 26 recorded cases. A normal maltose and starch tolerance was observed in 6, though in 4 of these no palatinase or isomaltose tolerance test was done. In most of the remaining 20, intolerance to starch and maltose as well as to sucrose was also noted.

The clinical findings in our series were similar to those previously described. The presenting symptom in all was profuse watery diarrhoea, provoked as soon as sucrose was introduced into the diet. In two, this observation caused the mother to substitute glucose for sucrose in the feeds, and perhaps in this way averted the worst results. In 5 out of 7 cases, diarrhoea was severe enough to require intravenous therapy, and it is interesting to note that in these 5, cane sugar was introduced within the first 3 weeks of life, whereas those not requiring intravenous therapy were not given sugar till after 9 weeks. The early introduction of artificial feeds with cane sugar may lead to the confusion of sucrose intolerance with lactose intolerance. Diarrhoea was always sour smelling and often projectile in nature. A less frequent clinical finding was refusal of feeds, and in at least one case, this was correlated with feeds sweetened with cane sugar, though unsweetened feeds were readily accepted. In one other case, the child still dislikes sweets and sweet foods. Appetite was usually good, and in one case was even excessive. This case also showed steatorrhoea and persistent abdominal distension and has a coincidental Chilaiditi's syndrome. It is possible that this association is significant, and sucrose intolerance may be an aetiological factor in other examples of

this syndrome. Vomiting occurred in only one case and only on one occasion. In none of our cases was starch or maltose intolerance a significant feature.

Sucrose intolerance should be suspected when diarrhoea is coincident with the introduction of cane sugar into the diet and no other cause for the diarrhoea, e.g. infection, is found. It is always highly significant when, after improvement of the diarrhoea with treatment by a glucose electrolyte mixture, relapse occurs on resumption of normal feeds including cane sugar. A similar significant recovery may occur with expressed breast milk, as happened in 3 of our cases. This may lead to a suspicion of cows' milk allergy. Diarrhoea may persist even after removal of cane sugar from the feeds, and if this is so it is necessary to look for some unexpected source of this carbohydrate. In our cases, the syrup in which the antibiotics were dispensed was a concentrated solution of sucrose.

The clinical diagnosis must be confirmed by carbohydrate tolerance tests, including examination of urine and stools obtained during and immediately afterwards. In infants, the stool passed after a test dose of sucrose or palatinose was always fluid, and usually very acid when tested with pH papers. However, this was not invariably so, possibly because the time interval was too short for large amounts of acid to be formed or because the routine antibiotic therapy given reduced the bacterial content in the bowel. In the case of the older children, when loose but not fluid stools were passed, pH papers were unsatisfactory for direct testing for acidity, and no quantitative determinations of lactic acid content were done. These tests should be carried out after sucrose has been excluded from the diet, and there is no longer diarrhoea. It may be necessary for enzyme levels in the jejunal mucosa to be determined.

The progress of the untreated or incompletely treated child may be judged from 3 of our cases who were not definitely diagnosed until the age of 4 or 5 years. Tolerance to cane sugar improved with age, stools became more formed, and less frequent. Weight gain, which was usually unsatisfactory in the first year, also improved later. The condition may become less noticeable to the parents, who may accept it as normal. There appears to be no simple explanation for the improvement. The increased tolerance to sucrose with age may be more apparent than real. Infants on artificial feeding often have as much as 7 or 8 g. sucrose per kg. body weight per day, whereas the older child is unlikely to be given a similar proportional amount.

Carbohydrate Tolerance. In our series of cases, the maximum rise in blood glucose following

administration of sucrose was no more than 8 mg./100 ml. except in two instances where it was 14 mg./100 ml., a level attained, however, only at the end of the second or third hour and this may have been due to some hydrolysis of sucrose by bacteria. In normal children, the maximum rise was usually between 30 mg. and 60 mg./100 ml. and this was always in the first 30 minutes. Though a normal rise in blood glucose following sucrose loading will exclude hereditary sucrose intolerance, the failure to rise does not necessarily confirm the diagnosis, since the cause may be malabsorption of varying aetiology, including a temporary or acquired depression of intestinal enzyme activity (Sunshine and Kretchmer, 1963).

Similar results were obtained when palatinose was given, with the maximum glucose rise being somewhat greater, up to 16 mg./100 ml., and always in the second hour. This slightly greater rise was probably due to the fact that the level of palatinase activity in most of the cases was still about one-third of the normal. Indeed, it is surprising that palatinose intolerance does occur with this percentage reduction of the level of palatinase activity. This, however, may be because the normal activity of this enzyme is only one-third that of sucrase, so that even a relatively moderate reduction in its activity will have a much greater effect on palatinose metabolism than a corresponding reduction in sucrase activity will have on sucrose metabolism.

The improvement in the clinical symptoms with age is not reflected in the sucrose or palatinose tolerance tests, which gave similar results in all our patients, whose ages ranged from 1 to 5 years. The younger the child, the more severe the effect of the carbohydrate load, watery diarrhoea being always provoked in the younger infant, whereas in the older child it was much more likely to be merely a loose stool. The carbohydrate given was always detected in the liquid stool, but was not a constant finding in the more formed stool. The disaccharide was sometimes found in those specimens of urine that were passed during or after the test, but unfortunately specimens of urine were not always available for examination. Whether the urine contains the carbohydrate depends probably on the amount absorbed unhydrolysed.

By contrast, the absorption of glucose and tolerance of lactose in all those cases in which these were carried out appeared normal. It is important to allow at least a week to elapse between a sucrose or palatinose test and the lactose test, otherwise there may be poor tolerance of the lactose, presumably owing to a toxic effect resulting from sucrose or palatinose loading. In 3 cases where a tolerance test

with maltose was performed, this was normal, as also were two starch loading tests. In Case 1, however, the maximum rise did not occur until the second hour, suggesting that there may have been a diminished tolerance to starch. This may possibly be correlated with the absent palatinase activity observed in this case.

Enzyme Defect. There has been much discussion as to the site of hydrolysis of the disaccharide during absorption by the intestine. Since sucrase, lactase, and maltase were found in the intestinal secretions, it was assumed that hydrolysis occurred in the lumen. On the other hand, enzyme assays on homogenates of intestinal mucosa as well as histochemical studies have demonstrated that disaccharidases are located in the intestinal mucosal cells. More recently, it has been conclusively shown that carefully collected intestinal juice contains practically no disaccharidase activity (Borgström, Dahlqvist, Lundh and Sjövall, 1957; Dahlqvist and Borgström, 1961). It seems certain, therefore, that the disaccharides are hydrolysed intracellularly and not in the lumen of the intestine.

In an investigation of the specificities of the human intestinal disaccharidases, Dahlqvist (1962, 1964) has shown by differential heat inactivation that four different maltases are present. He concluded that the whole activity of the intestinal mucosa towards both isomaltose and palatinose was present in one fraction which was termed maltase Ia (or isomaltase), and this same fraction accounted for 50% of the total intestinal enzyme activity towards maltose. The whole activity against sucrose was located in the fraction maltase Ib (or invertase), which accounted for 25% of the activity towards maltose. Maltases II and III were two separate enzyme fractions accounting for 15% and 10%, respectively, of the total activity against maltose. The whole of the activity against lactose and cellobiose was found in one enzyme, lactase, which was not associated with maltase activity. On this basis, Dahlqvist (1962) pointed out that an inherited absence of sucrase should be accompanied by a diminished activity towards maltose; as would an inherited absence of isomaltase. On the other hand, a congenital absence of either sucrase or isomaltase would not affect lactase activity.

Though the evidence in favour of an hereditary defect of sucrase in sucrose intolerance was strong, a definite proof of this required a quantitative assay of the enzyme activities in the intestinal mucosa. Anderson *et al.* (1963) showed that a homogenate of duodenal mucosa from one of their patients did not hydrolyse sucrose, and only slightly split isomaltose,

whereas lactose and maltose were normally hydrolysed. Though this afforded a direct proof of the enzyme defect, the method of paper chromatographic separation of the carbohydrates obtained after incubation of the intestinal homogenate with the disaccharide, afforded only a qualitative or semi-quantitative result. Also Dahlqvist (1964) has shown that enzyme activities of duodenal mucosa may be very low in normal subjects, at least in older persons, and are much lower than in jejunal mucosa.

The enzyme activities determined in the jejunal mucosa were palatinase, lactase, and maltase, in addition to sucrase. It would have been preferable to estimate isomaltase activity but this disaccharide was not available in sufficient quantity. It was therefore decided to use palatinose as substrate since it is hydrolysed by the same enzyme as that which splits isomaltose (Dahlqvist, 1962). Lactase was selected because the proof of a specific enzyme defect should be supported not only by the observation of the very low or absent specific enzyme activity, but also on the finding that at least one enzyme activity is normal. Maltase activity was estimated because it should be depressed when sucrase is absent.

Sucrase activity in all the affected children was negligible, 2% or less of the mean normal value, and this must be accepted as indicating a complete lack of sucrase activity. Palatinase activity, which was measured in 5 affected children, was very diminished, to 15-36% of the mean normal level in 3 cases and to less than 4% in one case, the latter value being sufficiently low to be considered as absent activity. Though only two normal values for palatinase were determined in control children under 5 years of age, the results obtained in older children with treated coeliac disease, as well as in adults, suggest that these were representative values.

The results of the maltase estimations in our cases of sucrase intolerance were consistent with those predicted by Dahlqvist (1962). If the enzyme defect were confined to sucrase alone, the maltase activity should be diminished to 75% of the normal value. This was so only in Case 6. The maltase activity in Case 7 was 40% of the normal, and in 4 other cases it was as low as 11%. It is likely that the greater than expected deficiency of maltase activity can be accounted for by the lowered palatinase activity, since according to Dahlqvist (1962) this enzyme fraction also contains 50% of the maltase activity. This is supported by the fact that the decrease in palatinase activity approximately parallels the decrease in maltase activity, though the parallel is by no means exact.

Lactase, and in one case cellobiase, activity was also normal in all our affected children, indeed most

were somewhat higher. The ratio of sucrase to lactase activity was also very low in these cases, between 0.005 and 0.03, compared with a normal ratio of approximately 2.

The association of sucrose intolerance with that of isomaltose (or palatinose) has been noted by Auricchio, Dahlqvist, Mürset, and Prader (1962, 1963) and Anderson *et al.* (1962, 1963). The presence of a diminished palatinase activity with the absent sucrase activity in our cases is difficult to explain. In the two affected sibs, one had a palatinase activity decreased to 15% of normal, whereas in the other this activity was absent (less than 4%). Neither has there been a satisfactory explanation for the simultaneous inherited absence of two enzymes, sucrase and isomaltase (palatinase), thus proved to occur in Case 1. The 'one gene—one enzyme' hypothesis (Beadle, 1945) would preclude the likelihood of this occurrence, since it would involve the simultaneous mutation of two genes, though this is not impossible. Wyngaarden (1960) has suggested that a single gene can control the synthesis of polypeptide fragments which can serve as a component of two or more enzymes, and this explanation could account for the absence of both sucrase and palatinase in our patient.

The clinical improvement with age was also not reflected in the levels of sucrase activity in the jejunal mucosa, since in the two cases of 5 years of age, no enzyme activity was detected. The absence of sucrase activity at this time supports the conclusion that the condition is an inborn error of metabolism, and not due to an immaturity of function.

Genetics. The hereditary nature of sucrose intolerance is suggested by the occurrence of affected sibs in a number of recorded cases, as well as by the fact that symptoms date from the first few days of life when sucrose had been given. Consanguinity has been noted in only one instance (Lelong and Alagille, 1963). Both males and females appear equally affected. On the basis of a history of transient diarrhoea in the father of two affected sibs and his intolerance to palatinose, Prader *et al.* (1961) suggested that the condition was inherited as an autosomal dominant. Gorouben, Bedu, Leballo, Grumbach, Yonger, Weill, and Kaplan (1963) and Rey, Frézal, Jos, Bauche, and Lamy (1963) believe that it is an autosomal recessive.

Our series of cases also shows an approximately equal sex distribution, 4 males and 3 females, and includes 2 sibs (Cases 1 and 2). The remaining sib of this family, as well as one sib of Case 4, and 3 sibs of Case 5 all showed normal sucrose tolerance. There was no history of consanguinity in any of the

families. In none of our cases could a history of diarrhoea in childhood in the parents be established, though information was not complete. This may merely illustrate the difficulty of recalling in adult life a diarrhoea occurring in infancy and improving after the first year. Jejunal biopsies were performed in 3 parents of 3 unrelated families. None showed the typical enzyme pattern found in our affected cases. However, the mother of the two affected sibs showed a level of sucrase activity about half that of the mean level in normal children (Table 3), whereas the other enzyme levels were normal. One other parent, the father of Case 4, showed an even lower level of sucrase activity, but the other enzyme levels, including lactase, were equally decreased (Table 3). These are inconclusive results but they tend to support the suggestion that the condition is inherited as an autosomal recessive.

Summary

Seven cases, including two sibs, are described of hereditary sucrose intolerance, an inborn error of sucrose metabolism. They were first diagnosed at ages ranging from 1 month to 5 years. All presented with profuse watery diarrhoea as soon as cane sugar was introduced into the diet, and the earlier this occurred the more severe the diarrhoea. A less frequent finding was early refusal of feeds, especially sweetened feeds, though later the appetite was good. Vomiting and abdominal distension also occurred. Neither starch nor maltose intolerance was clinically a significant feature. Improvement of diarrhoea on breast milk or treatment with glucose electrolyte mixture, with relapse when full feeds with cane sugar are resumed, is highly significant of sucrose intolerance.

The tolerance tests showed in all cases failure of blood glucose to rise following sucrose loading and, in the 5 cases in which it was performed, following palatinose. The lactose, maltose, and glucose tolerance tests were normal. The diagnosis was confirmed by a quantitative assay of sucrase, lactase, maltase, and palatinase activities in biopsy specimens of jejunal mucosa. In all cases, there was an absence of sucrase activity, whereas lactase activity was normal. Maltase and palatinase activities were decreased and in one case, palatinase activity was absent. The significance of the enzyme pattern is discussed, in particular the association of two specific hereditary enzyme defects occurring in one patient. From a consideration of the cases diagnosed at the later ages, it appears that clinical improvement with age is accompanied neither by increased sucrose utilization nor by restoration of normal enzyme activity. The enzyme activities in the jejunal

mucosa of three of the parents were determined, the genetics of the metabolic error are discussed, and it is concluded that the condition is inherited as an autosomal recessive.

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