MEDICAL GRAND ROUNDS

Parkland Memorial Hospital
November 20, 1964

Congenital Absence of Active Sugar Transport in the Intestine AND Intestinal Disaccharidase Deficiency

Case #1: Disaccharidase Deficiency Causing Chronic Diarrhea in an Adult

[redacted] a 29-year-old [redacted] female, was seen because of intermittent mild to moderately severe diarrhea. She had previously been told she had ulcerative colitis but her x-rays of the colon and sigmoidoscopy failed to substantiate this diagnosis. The impression of the referring doctor was irritable colon syndrome and functional diarrhea.

She stated she had had intermittent diarrhea for as long as she could remember. A brother, now living in California, has had similar symptoms. During diarrheal periods, the stools were large in volume and were accompanied by passage of large amounts of gas. No rectal bleeding had occurred.

On direct questioning, it was learned that milk seemed to accentuate her diarrhea and associated cramping pain. This apparently had been one fact that led her first doctor to diagnose ulcerative colitis.

She had had no definite improvement on anticholinergics or Lomotil.

Physical examination was normal.

Stools were negative for fat while she was not having diarrhea. A xylose test produced 7.2 gm. urinary xylose per 24 hrs. (normal). GI x-rays were normal, including the small bowel. A small intestinal biopsy was histologically normal.

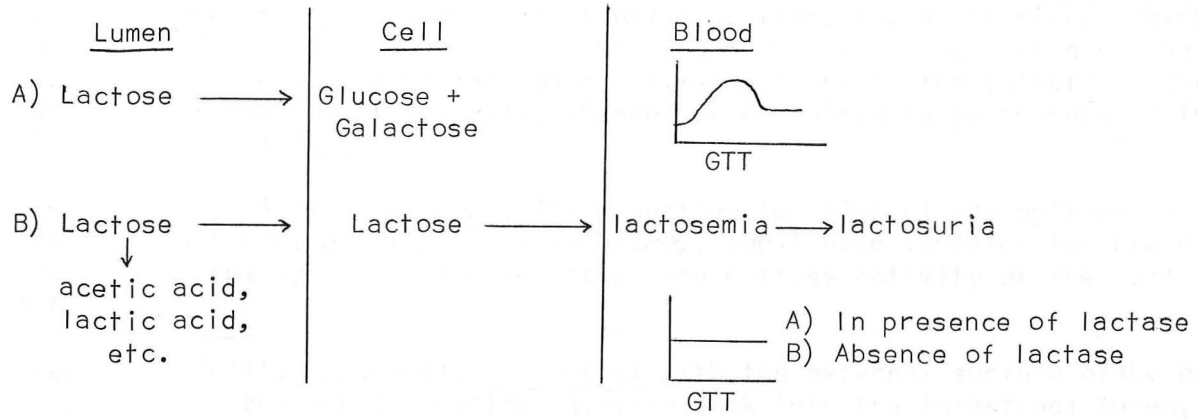
Intestinal lactase deficiency seemed possible and the following tests were performed:

Oral Tolerance Test 50 gm. each	Blood Sugar (Nelson) Fasting	30'	60'	90'	120'	180'	Clinical Response
Glucose	80	130	124	80	88	70	No GI symptoms
Lactose	86	92	75	87	90	82	Severe cramping pain and diarrhea
Sucrose	77	126	110	83	88	73	No GI symptoms

The pH of a stool specimen when she was on a lactose-free diet was 6.85; it fell to 4.96 after lactose was ingested.

The patient was put on a milk-free diet, except for yoghurt and buttermilk (in which the lactose has been fermented to lactic acid), and has subsequently done well.

FATE OF LACTOSE IN THE SMALL INTESTINE

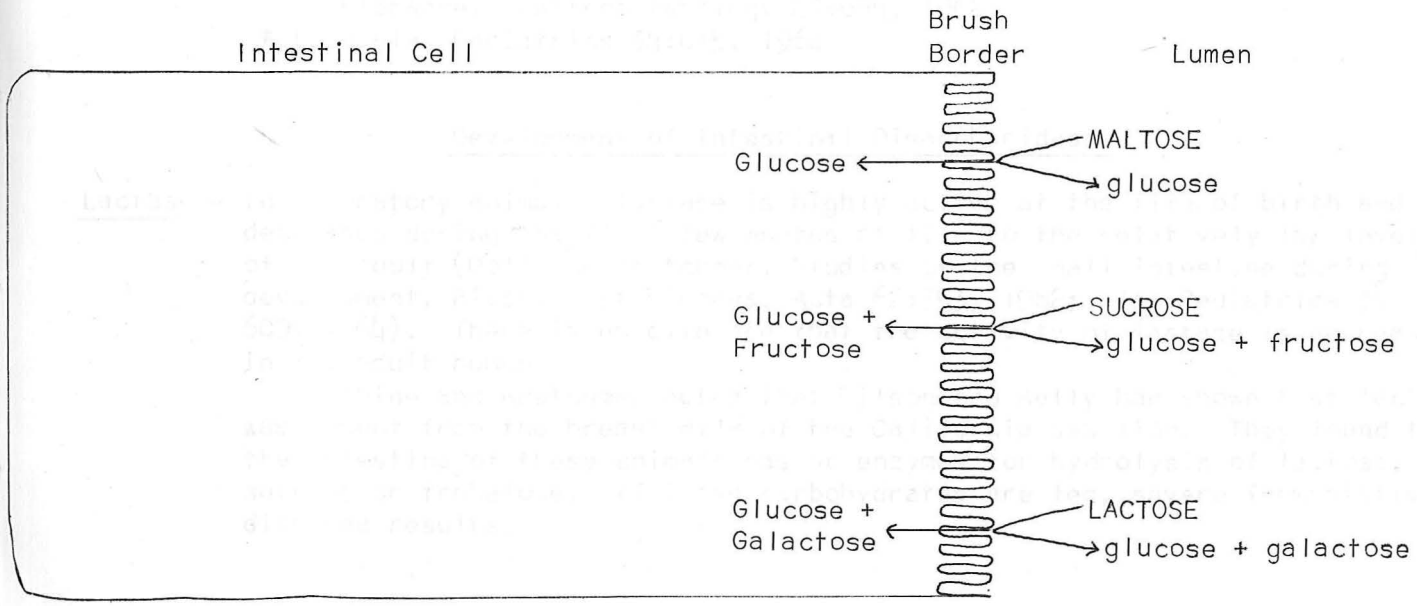


Absorption and Malabsorption of Disaccharides

Starch, Glycogen } —Amylase→ { Maltose, Isomaltose } —Disaccharidases→ Glucose

Sucrose → Glucose + fructose
Lactose → Glucose + galactose
Trehalose → Glucose

Disaccharides per se cannot be absorbed in significant amounts, but must be split into their respective monosaccharides by intestinal disaccharidases.



For a long time the disaccharides were believed to be secreted into the intestinal lumen with the succus entericus. However, Cajori (The enzyme activity of dogs' intestinal juice and its relation to intestinal digestion, Am. J. Physiol. 104:659, 1933) demonstrated that disaccharides are absorbed much more rapidly than can be accounted for by the levels of disaccharidase enzymes present in the intestinal contents. He also showed that the intestinal cells themselves contained large amounts of these enzymes (JBC 109:159, 1935).

More recently, Miller and Crane (The digestive function of the epithelium of the small intestine, Biochim. et Biophys. Acta 52:293, 1961) have isolated the brush border and showed that virtually all of the invertase and maltase activity of the cell is in this fraction.

After being split, apparently on contact with the external surface of the brush border, a portion of the monosaccharides diffuse back into the intestinal lumen, to be absorbed subsequently (Gray and Ingelfinger, unpublished observations).

Human Disaccharidases*

Enzyme	Substrate	
Maltase Ia	Maltose	? one enzyme with activity against maltose, isomaltose and sucrose‡
	Isomaltose	
Invertase =	Sucrose	
Maltase Ib	Maltose	
Maltase II	Maltose	
Maltase III	Maltose	
Trehalase	Trehalose	
Lactase	Lactose	

* From Dahlquist, A. The intestinal disaccharides and disaccharide intolerance. Gastroenterology 43:694, 1962

‡ Launiala, Pediatrics 34:615, 1964

Development of Intestinal Disaccharidases

Lactase - In laboratory animals, lactase is highly active at the time of birth and decreases during the first few months of life to the relatively low levels of the adult (Doll and Kretchmer, Studies of the small intestine during development, Biochim. et Biophys. Acta 62:353, 1962; also Pediatrics 34: 609, 1964). There is no evidence that the activity of lactase is decreased in the adult human.

Sunshine and Kretchmer noted that Pilson and Kelly had shown that lactose was absent from the breast milk of the California sea lion. They found that the intestine of these animals has no enzymes for hydrolysis of lactose, sucrose or trehalose. If these carbohydrates are fed, severe fermentative diarrhea results.

Invertase - Species variation. In pigs, rats and mice, invertase is absent at birth and develops during the first few months. In man, invertase is present at birth (Doll and Kretchmer, Intestinal invertase: Precocious development of activity after injection of hydrocortisone, Science 143:42, 1964).

Maltase and Trehalase - ?

Disaccharidase Deficiency

Now a rather commonly recognized cause of chronic diarrhea and malnutrition in infants, and adult cases are also being recognized. Symptoms occur upon ingestion of the offending carbohydrate—starch in the case of maltase and isomaltase deficiency, sucrose in the case of invertase deficiency, and milk in the case of lactase deficiency. Diarrhea and cramping pain occur soon after ingestion of the offending food. Patients characteristically do not vomit.

Steatorrhea may or may not be present.

Stools have an acid pH, due to formation of lactic, acetic, butyric and other volatile fatty acids by bacterial fermentation of unabsorbed sugars (Weijers, et al., Diarrhea caused by deficiency of sugar splitting enzymes, Lancet, Aug. 6, 1960).

Isomaltase Deficiency - Can occur as isolated defect theoretically (isomaltase or maltase Ia deficiency), but has only been reported in association with invertase deficiency (Auricchio, S., et al., Isomaltase intolerance causing decreased ability to utilize dietary starch, J. Pediatrics 62:165, 1963). This may represent the simultaneous occurrence of two enzyme deficiencies in the same individual, not previously known in man, but known to occur in bacteria. However, Launiala disagrees with this explanation (Pediatrics 34:615, 1964).

Invertase Deficiency - Associated with severe symptoms since cane sugar is an important dietary disaccharide. Symptoms occur when sucrose is added to the infant's diet. Has been described in adults (Sonntag, et al., Sucrase-isomaltose malabsorption in an adult woman, Gastroenterology 47:18, 1964), although it was previously believed that most chidren have a spontaneous remission.

Weijers, H. A., et al., Diarrhea caused by deficiency of sugar splitting enzymes, Acta Pediatrica 50:55, 1961.

Anderson, C. M., et al., Intestinal sucrase and isomaltase deficiency in two siblings, Pediatrics 31:1003, 1963.

Trehalase Deficiency - Theoretically possible, but would not be recognized since our diet contains this disaccharide only in mushrooms.

Lactase Deficiency - Symptoms begin in first few days of life. Many case reports in children (see Dahlquist, Gastroenterology 43:694, 1962), and in adults this seems to be at least one definite cause of milk intolerance (Dahlquist, et al., Intestinal lactase deficiency and lactose intolerance in adults, Gastroenterology 45: 488, 1963; Kern, et al., Lactose intolerance as a cause of steatorrhea in an adult, Gastroenterology 45:477, 1963).

Maltase Deficiency - Cannot occur as a result of a single enzyme defect since there are four separate maltases. It may occur if multiple enzymes are absent (Weijers, et al., Acta Pediatrica 50:55, 1961).

Acquired Disaccharidase Deficiency and Disaccharidase Deficiency in Other Diseases

1. Sprue and other malabsorptive diseases associated with villous atrophy of the intestinal mucosa. Plotkin and Isselbacher, New Eng. J. Med. 271:1033, 1964.

2. Tropical sprue. Jeejeebhoy, K. N. Milk intolerance in tropical malabsorption. Role of lactose malabsorption. Lancet, Sept. 26, 1964.

3. Cystic fibrosis. Cozzetto, F. J. Intestinal lactase deficiency in a patient with cystic fibrosis. Pediatrics 32:228, 1963.
   Only one case found. Eight others did not have the defect.

4. Kwashiorkor. Bowie, Brinkman and Hansen. Diarrhea in protein calorie malnutrition. Lancet 2:550, Sept. 14, 1963.
   Diarrhea is almost invariable accompaniment of this syndrome and the cause is unknown. Bowie, et al. have presented convincing evidence that disaccharidase deficiency is a cause in many of these cases. Diarrhea stopped or markedly decreased when carbohydrate-free diet was instituted.

5. Ulcerative colitis and regional ileitis. J.E. Struthers, et al. Intestinal lactase deficiency in ulcerative colitis and regional ileitis. Clin. Res. 12:343, 1964.
   Postulate this as a cause of milk intolerance in one case of each. Apparently many patients were screened to find these two cases.

6. Acquired during enteritis in children. This apparently is acquired and transient, the defect disappearing after weeks to months on a disaccharide-free diet. Although Sunshine and Kretchmer were able to find 6 cases they felt belonged in this category (Infantile diarrhea associated with intolerance to disaccharides, Pediatrics 34:38, 1964), they mention 15 infants with acute diarrhea without disaccharidase deficiency at a time when the acute symptoms subsided. They also mention 7 other patients with intermittent or prolonged diarrhea, who have had normal response following oral sucrose and lactose.

Case #2: Chronic Diarrhea Caused by Absence of Active Transport System for Monosaccharides

[redacted] a one-year-old [redacted] female, who is the first and only child of her parents (who are not related), was born on [redacted] 1963, and weighed 7 lbs. 4 oz. at birth. Large watery stools and subsequent dehydration began on the second or third day of life, and were so severe that she was unable to leave the hospital. Numerous formulas and medications were tried without success and practically continuous intravenous fluids had to be administered.

She was transferred to the [redacted] on [redacted], 1963. She was, at this time, one month old, and weighed 6 lbs. 2 oz. She was markedly dehydrated and was having 8 to 10 yellow stools per day, containing large amounts of watery fluid but no blood. Oral fluids were taken well without vomiting. Physical examination revealed no abnormalities except for the dehydration and emaciation. Her hemoglobin was 9.8 gm.%, hematocrit 29 vol.%, white count 16,800/mm^3. The Na was 155 mEq/L., Cl 149, K 5.2, and CO_2 12. The BUN was 55 mg.%.

Chest x-ray, intravenous pyelogram and barium enema were normal. An upper GI series and small bowel series were normal. The intestinal mucosa appeared normal and the small intestine itself was not dilated.

Stool cultures and search for parasites were negative. The stool contained 3+ fat by Sudan stain. Sweat chloride was 80 mEq/L. when she was dehydrated and 42 mEq/L. when serum electrolytes were normal. Disaccharidase levels of the stool were normal. Chromatography of the urine for amino acids was normal. The urine intermittently showed 1+ to 3+ reaction for glucose but usually contained none.

Intravenous fluids were necessary almost continuously to prevent dehydration. She did not have diarrhea when she was on IV fluids alone, but when formula diets were given, frequent and massive watery stools occurred and resulted in severe dehydration that was always characterized by hypernatremia.

She was tried on lactose- and sucrose-free diets, on a gluten-free diet, on Probana, on a milk-free diet, on a low-fat diet, on Nutramigen and other dietary preparations, none of which were successful and all of which resulted in severe diarrhea.

Therapeutic trial with several different antibiotics was without effect on the diarrhea.

She developed a genitourinary infection after bladder catheterization, and this was treated successfully with appropriate antibiotics.

At 3 months of age, her weight was 6 lbs. 1 oz. and she appeared near death. Review of her case at this time brought out the fact that she did not have diarrhea when she was not on oral intake of fluids or formula. Also, the upper GI and small bowel series gave evidence that water absorption was normal since the barium was highly concentrated in the lower ileum and colon and diarrhea had not resulted after the barium swallow studies.

(See end of case report for oral d-glucose, d-galactose, 3-methyl-glucose, L-glucose and fructose curves in this patient. The IV glucose tolerance curves were normal. The mannose tolerance tests produced equivocal results. The first showed a rise of 23 mg.%, the second was flat. Neither produced diarrhea. Sucrose produced a flat curve and diarrhea.)

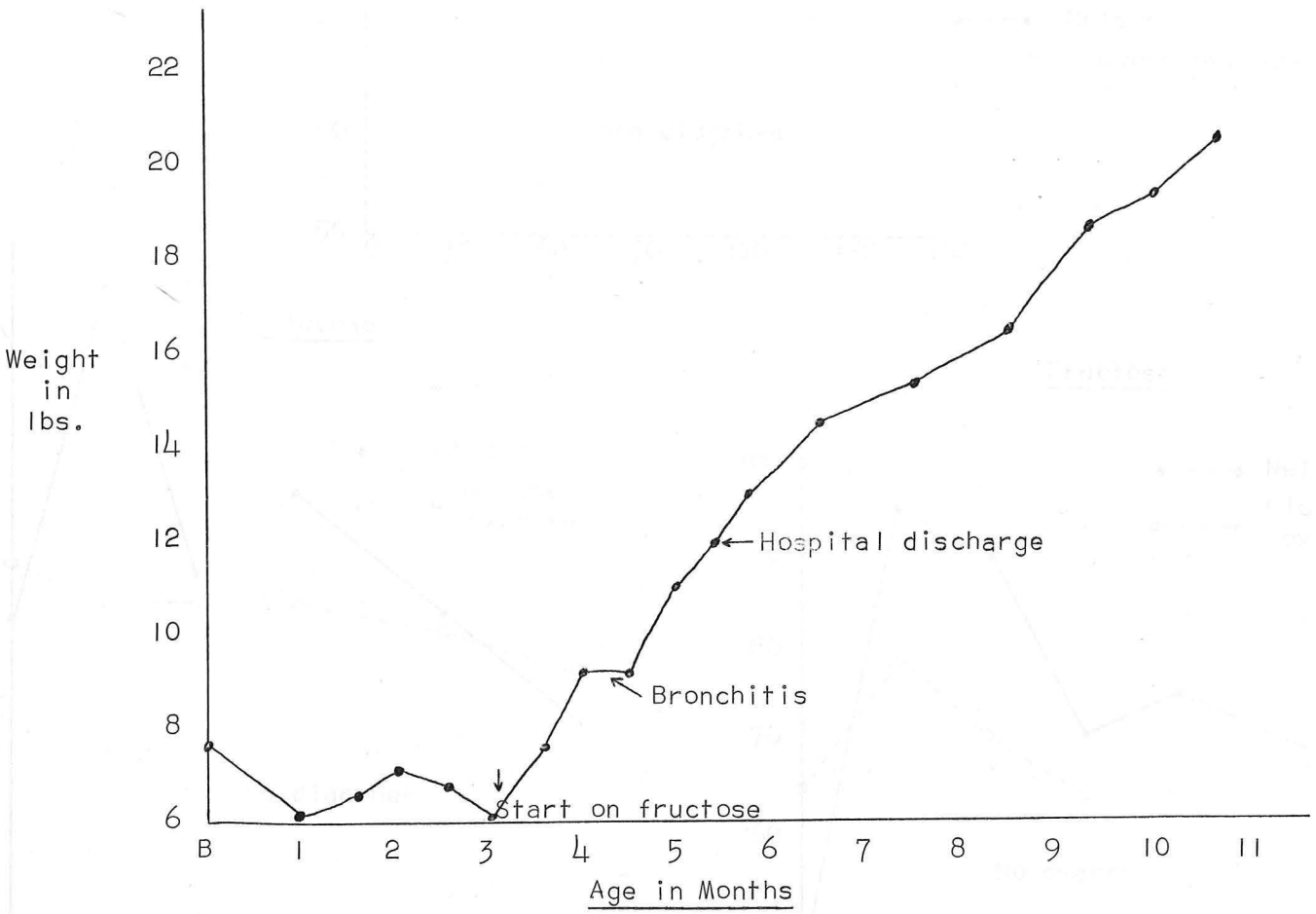
It was therefore decided to start her on oral electrolyte solutions alone and distilled water and lactated Ringer's solution were given. On this, she did not have diarrhea and hydration was maintained for the first time since birth without intravenous fluids.

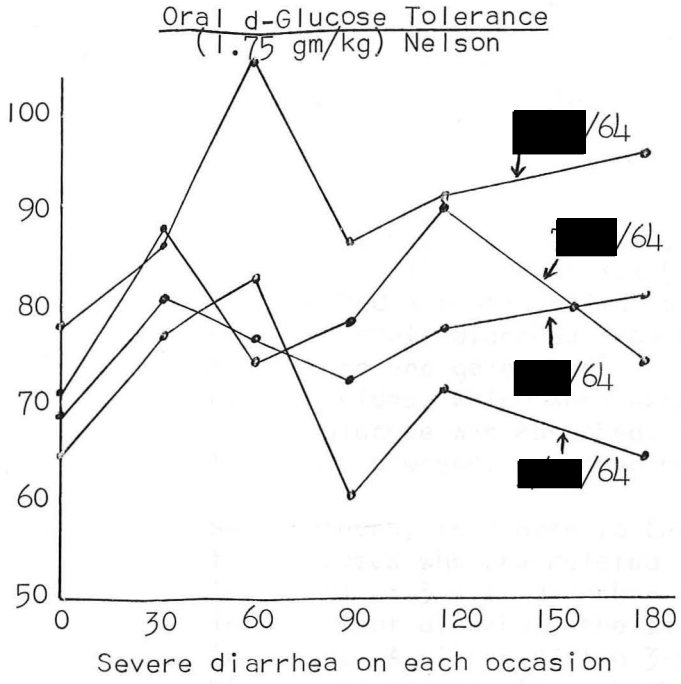
After 36 hours, glucose in an amount necessary to meet one-half of her calculated caloric needs was administered as a 5% solution. Within 2 hours she began to have large watery stools and in spite of a large oral intake severe dehydration resulted. Glucose was removed and the electrolyte solution was continued; the diarrhea stopped.

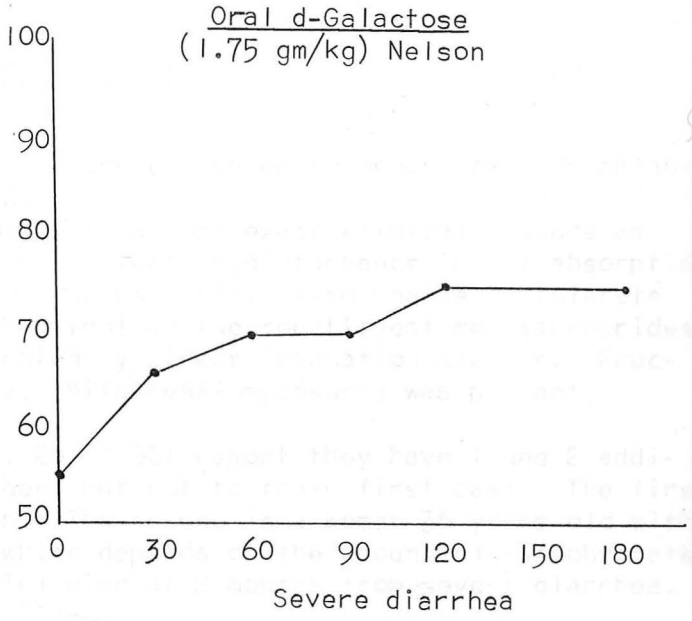
It seemed possible that the glucose might have been given in too concentrated a form, and glucose as a 2.5% solution was next administered. Severe diarrhea and dehydration resulted.

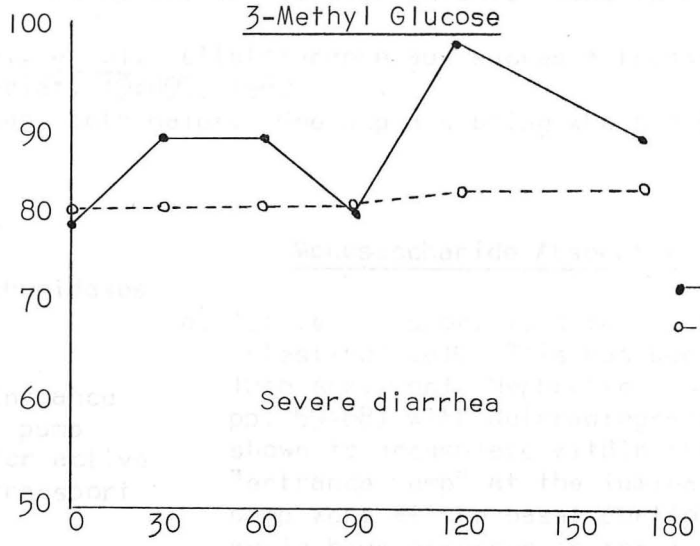
She was then switched back to simple electrolyte solutions and the diarrhea stopped and rehydration was accomplished. Protein in the form of casein was added to the electrolyte solution and diarrhea did not result. Mazola oil was then added and still the patient had no diarrhea. Lastly, fructose, as a 5% solution, was added and diarrhea did not result. She rapidly gained weight on fructose, Mazola oil and casein and had normal bowel movements.

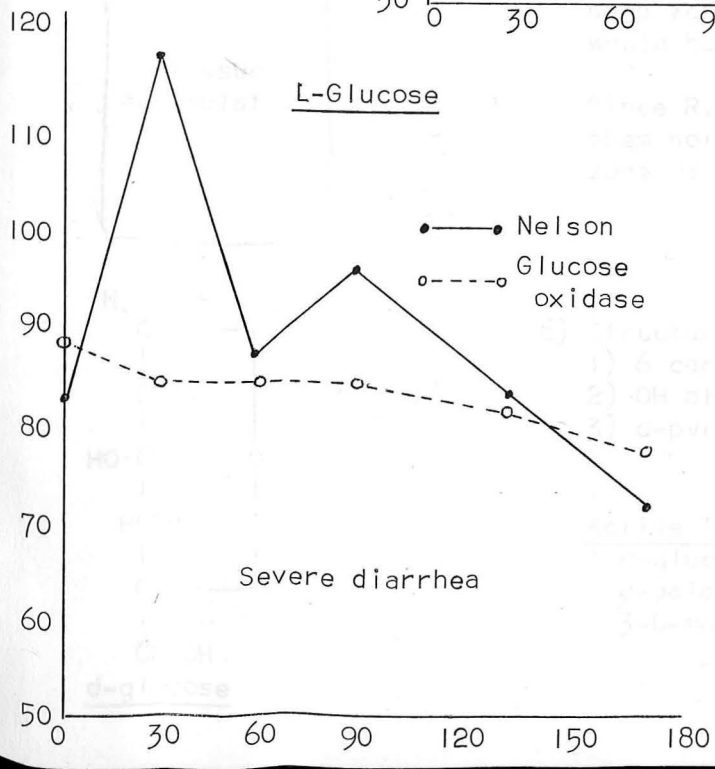
Following intravenous glucose it was shown that renal glucosuria began between blood glucose levels of 110 and 125 mg.%. She was challenged numerous times with dextrose, the last being at age 9-1/2 months, and each time developed severe diarrhea and dehydration. On [redacted]29, 1964, at 10-1/2 months of age, she weighed 20 lbs. 6 oz. and appeared normal. She is on a diet that excludes all carbohydrates except fructose.

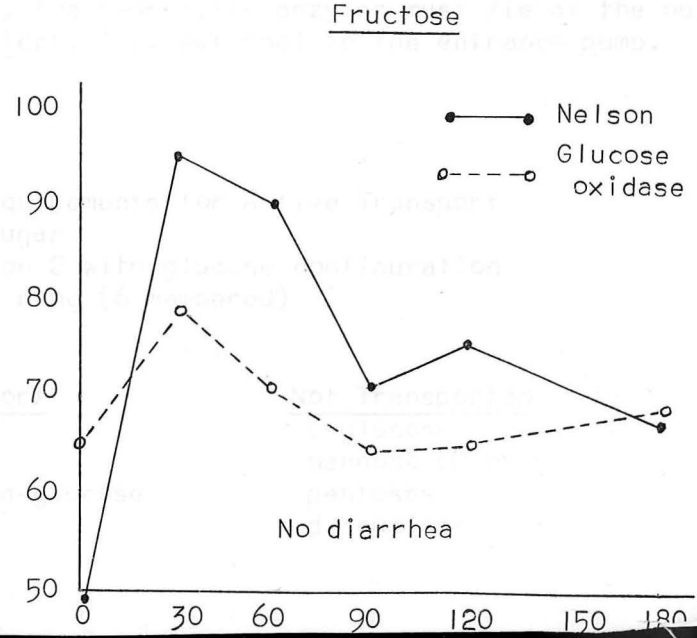



Oral d-Glucose Tolerance
(1.75 gm/kg) Nelson
[redacted]/64
[redacted]/64
[redacted]/64
[redacted]/64
100
90
80
70
60
50
0
30
60
90
120
150
180
Severe diarrhea on each occasion


Oral d-Galactose
(1.75 gm/kg) Nelson
100
90
80
70
60
50
0
30
60
90
120
150
180
Severe diarrhea


3-Methyl Glucose
100
90
80
70
60
50
0
30
60
90
120
150
180
Severe diarrhea
Nelson
Glucose oxidase


L-Glucose
120
110
100
90
80
70
60
50
0
30
60
90
120
150
180
Nelson
Glucose oxidase
Severe diarrhea


Fructose
100
90
80
70
60
50
0
30
60
90
120
150
180
Nelson
Glucose oxidase
No diarrhea

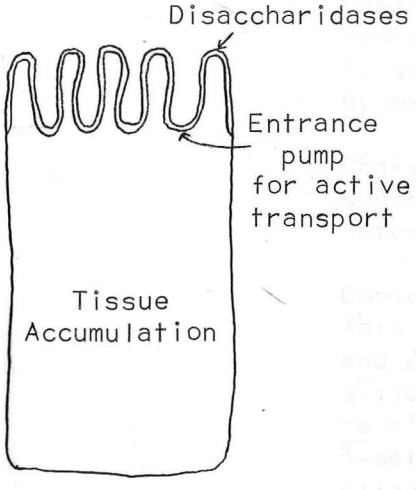
Other Similar Cases

1. Lindquist, B., and Meeuwisse, G. Chronic diarrhea caused by monosaccharide malabsorption. Acta Paediatrica 51:674, 1962.
   Described a female child, born in 1961, with almost exact clinical picture as R.G. - Chronic diarrhea from birth due to a selective disturbance in the absorption of glucose and galactose. She tolerated fructose well. Also unable to tolerate disaccharides, which were excreted in the stool as the constituent monosaccharides.
   Some glucose was absorbed, as demonstrated by direct intubation studies. Fructose was, however, absorbed more rapidly. Mild renal glycosuria was present.

2. Same authors, in a note to Lancet (Sept. 29, 1962) report they have found 2 additional cases who are related to each other, but not to their first case. The first is a girl of 3 with diarrhea since birth. The second is a woman 36 years old with intermittent diarrhea, the severity of which depends on the amount of carbohydrate ingested. A sister of the 3-year-old girl died at 2 months from severe diarrhea. Mild renal glycosuria in both.
   A "mutual relationship" between parents found in all of these cases.

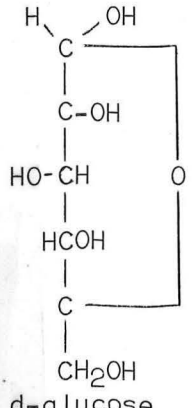
3. Lepane, A., et al. L'Intolerance aux sucres a transfeut intestinal actif. Arch. Franc. Pediat. 19:895, 1962.
   Two cases, both males. One had a sibling who had died of diarrhea at 8 days of age.

Monosaccharide Absorption



a) Active transport is a function of the luminal border of the intestinal cell. This has been shown best by Kinter (In Proc. 12th Ann. Conf. Nephrotic Syndrome [ed. J. Metcoff], 1961, pp. 59-68) with autoradiograms. C^{14}-labeled galactose was shown to accumulate within the mucosal cell, indicating an "entrance pump" at the luminal border of the cell. If the pump were at the basal portion of the cell, accumulation would have occurred in the lamina propria.

Since R.G. cannot tolerate disaccharides, although she splits them normally, the hydrolytic enzymes must lie at the outer zone of the microvilli, external to the entrance pump.



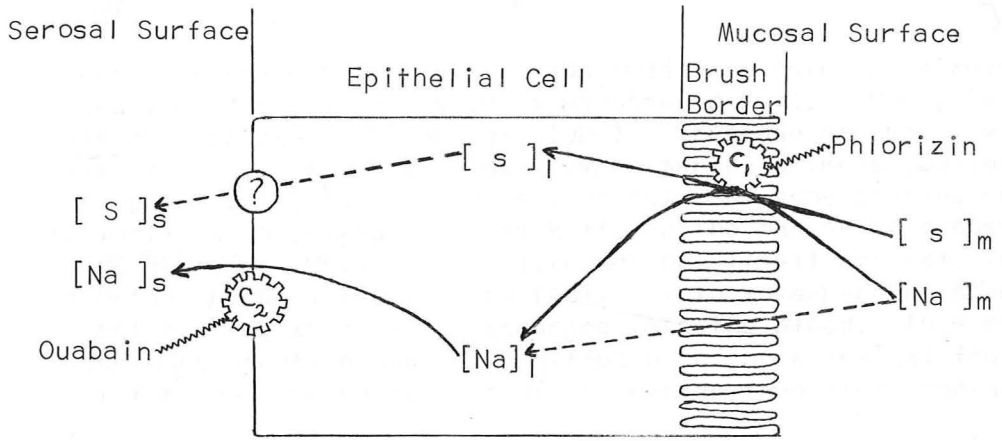
d-glucose

b) Structural Requirements for Active Transport
   1) 6 carbon sugar
   2) OH at carbon 2 with glucose configuration
   3) d-pyranose ring (6 membered)

Active Transport	Not Transported
d-glucose	L-glucose
d-galactose	mannose (D or L)
3-O-methyl-d-glucose	pentoses
	d-fructose

Mannose differs from glucose only in configuration of OH at C-2. Fructose differs in a number of ways, most notably in having a 5-membered ring. Actively transported sugars show mutual competitive inhibition, indicating a common pathway of absorption. Passively absorbed sugars do not inhibit active transport.

c) Mechanism of Active Sugar Absorption



A Hypothetical Model of the Na-sugar interaction in distal rabbit ileum

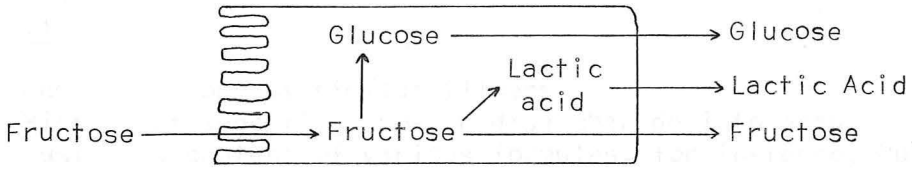
Rislis and Quastel (Effects of cations on sugar absorption, Canad. J. Biochem. 36:347, 1958) have shown that active glucose transport is dependent on sodium. Transport stops completely if sodium is completely removed. This has now been confirmed by many others.

Csáky has shown that if the sodium pump is blocked by ouabain, sugar transport is blocked (Effect of digitalis on active intestinal sugar transport, Am. J. Physiol. 200:459, 1961).

Conversely, glucose stimulates the active sodium transport. This has been most recently reviewed and studied by Schultz and Zalusky (Ion transport in rabbit ileum, J. Gen. Physiol. 47:1043, 1964). They found that active sugar transport <u>per se</u> stimulated active sodium transport from mucosa to serosa. 3-methyl-glucose, which is actively transported but not metabolized, stimulated sodium transport as well as glucose. Fructose did not.

The luminal pump in brush border is thought to carry a sugar-Na complex into the cell, where dissociation occurs. The Na is actively pumped out of the cell, keeping the cellular concentration of sodium low, and intracellular sugar diffuses out of the basal membrane. In the absence of sugar, sodium can only diffuse through the luminal border of the cell. In the absence of Na, sugar transport stops.

Fructose Absorption



Fructose is not actively transported. It is absorbed at a rate in between that of d-glucose and the slowly absorbed sugars such as mannose and xylose (Cori, The rate of absorption of hexoses and pentoses, JBC 66:691, 1925). Fructose can be converted to glucose in the intestinal cell, at least in many experimental animals (Bollman and Mann, Am. J. Physiol. 96:683, 1931). The intestinal cells of some species are able to convert fructose to lactic acid (Kiyasu and Chaikoff, On the manner of transport of absorbed fructose, JBC 224:935, 1957). Thus, although not itself actively transported, fructose may be converted in the intestinal epithelium into two separate metabolic products, glucose and lactic acid, which are discharged into the blood. This may decrease intracellular fructose concentration and favor diffusion of more luminal fructose into the cell, and account for its more rapid rate of absorption than other non-actively transported sugars.

Summary of Primary Monosaccharide Malabsorption

The active transport process for sugars in the human small intestine can be absent on a congenital basis. A similar renal tubular defect is also present.

In these patients, d-glucose, d-galactose and 3-methyl-glucose are absorbed slowly, only by passive diffusion, at a rate about equal to that of mannose and L-glucose. The diarrhea is probably caused by the osmotic effect of unabsorbed monosaccharides.

Fructose, although not actively transported, is absorbed more rapidly, possibly because of intracellular conversion to glucose and lactic acid. Were it not for this more rapid absorption rate of fructose, life would not be possible for children with severe deficiency of active transport.

Milder defects may go unrecognized in children and persist to adult life.

Whether R.G. will "outgrow" her defect is unknown.

Orally ingested electrolytes are tolerated in spite of absence of active sugar transport.

Diagnosis of Monosaccharide and Disaccharide Malabsorption

Suspect If:

1. Family history of similar illness
2. History of specific mono- or disaccharide intolerance. In infants, must know content of various formulas, for instance, Nutramigen contains no lactose but 40% sucrose; Sobee has only 10% sucrose, etc.
3. Diarrheal stool has low pH

Indirect Tests:

1. Elimination diets

2. Oral tolerance tests: Unfortunately, disaccharide tolerance tests may be flat in normal people - as often as 30%, according to Plotkin (Gastroenterology 46:287, 1964). A normal test of more value than a negative one. Intraduodenal administration of test sugars may make tolerance tests more reliable.
   If diarrhea occurs with a flat curve, suspicion of intolerance is greatly increased.

3. Stool pH: Normally 6.8-7.2
   Stool pH may fall to 4.5 with sugar malabsorption, but also may be low with any of the malabsorption syndromes where unabsorbed carbohydrate comes in contact with bacteria.
   a. Gryboski, et al. A study of fecal sugars by high voltage electrophoresis. Gastroenterology 47:26, 1964.
   b. Kern, et al. Proc. of Central Soc. for Clin. Res. 37:45, 1964.

4. Fecal lactic acid
   a. Weijers, et al. Diarrhea caused by sugar splitting enzymes. Lancet 2:296, Aug. 6, 1960.
   b. Kern, et al. Proc. of Central Soc. for Clin. Res. 37:45, 1964.

   Normal 32 mg. per day ± 22 mg.

   May be very high, up to 4 gm. per day, in sugar malabsorption, but also may be very high in the other malabsorption syndromes.
   Therefore, high stool lactic acid is fairly specific for primary sugar malabsorption only if the patient does not have a generalized malabsorption syndrome.

5. Assay of fecal sugars: Value not definitely known at this time
   a. Weijers, et al. (Acta Paediatrica 51:371, 1962) state that patients with disaccharide intolerance excrete the offending disaccharide in stool 24 to 48 hours after its ingestion and imply that this does not happen in normal persons.
   b. Durand, et al. (Diagnosis of carbohydrate intolerance diarrhea by stool chromatography, Lancet 2:374, 1961) report no sugars in stool from 20 children with "non-metabolic diarrhea".

c. Ford and Hayworth (The fecal excretion of sugars in children, J. Pediatrics 63:988, 1963) describe mono- or disaccharides in 26 of 32 stools from children with acute diarrhea and in 33 of 39 stools from infants and children without evidence of intestinal disease.
d. Gryboski, Zillis and Hou Ma (A study of fecal sugars by high voltage electrophoresis, Gastroenterology 47:26, 1964) found very small amounts of mono- and disaccharides in normal stools from children and adults. Diarrheal stools not reported.

Direct Tests:

Mucosal Content of Disaccharidase Enzymes

1. Dahlquist, A. A method for assay of intestinal disaccharidase. Analyt. Biochem. 7:18, 1964.
2. Anderson, C. M. Intestinal sucrase and isomaltase deficiency in two siblings. Pediatrics 31:1003, 1963.
3. Plotkin, et al. New Eng. J. Med. 271:1033, 1964.

Evaluation and specificity of mucosal assay is difficult at this time, although apparent success has been attained by above authors.

Must rule out sprue and other generalized diseases of intestinal mucosa by mucosal biopsy, etc., before diagnosis of primary malabsorption can be definitely made.