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Intestinal Intolerance to Sugars in Children*

A Review

BY

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Intestinal intolerance to sugars is now well established as a cause of diarrhoea and failure to thrive in children. It is assuming increased importance now that it is realised that a variety of insults to the gut can lead to intolerance (*Advances in Paediatrics*, 1969), and secondly, because malnutrition may be both caused by and lead to sugar intolerance (Bowie, Brinkman and Hansen 1965). Sugar intolerance occurs in adults (mainly alactasia), but clinically it presents a different problem and will not be dealt with in this review.

BIOCHEMISTRY

The important monosaccharides in the human diet are glucose, galactose and fructose. Glucose and galactose are actively absorbed against a concentration gradient, and absorption can be blocked by phlorrhizin or the cyanide ion, implicating an enzyme or enzymes in their transport (Fisher and Parsons, 1949). Fructose on the other hand is absorbed by diffusion or facilitated diffusion (Holdsworth and Dawson, 1965) and is less dependant on an intact intestinal mucosa. This has important implications in the dietary management of sugar intolerance.

Lactose, maltose and sucrose are the most important disaccharides in the human diet. They are absorbed onto the brush border of the cells of the villous mucosa (Miller and Crane, 1961) where splitting into the constituent monosaccharides occurs. Separate enzymes for each sugar are probably involved, although the enzymes maltase and sucrase are very similar in their physical and chemical properties and may in fact be identical (Semenza, *et al.*, 1965). From the brush border, the monosaccharides are transported to the capillaries of the villi and thence to the blood stream. Disaccharide digestion was originally thought to occur within the intestinal lumen,

*Based on a lecture to the Mpilo Hospital Staff, Bulawayo on 17th December, 1970.

as disaccharidases are found in jejunal aspirate. However, they probably arrive there from the break-up of desquamating cells from the villi.

The brush border of the villous cells is susceptible to damage by numerous agents and when this occurs lactase is the enzyme most severely affected (Townley, 1966). Infants and children usually have high levels of lactase in the intestinal mucosa at biopsy and as they grow older this level falls. This may be due to a decrease in the substrate — that is, as they grow they drink less milk and the stimulus to the production of lactase falls, or it may be a normal physiological change. The fall in lactase levels in African children appears to be more marked than in European children, as one would expect if lack of substrate were involved (Clain, 1970). However, virtual absence of lactase is found in a significant number of African children beyond the age of five, and in adults, and this may be a racial characteristic (Cooke and Kajubi, 1966). Levels of maltase and sucrase remain fairly stationary throughout childhood.

CLINICAL SYMPTOMS

The symptoms of intestinal sugar intolerance are similar, whatever the aetiology. There is usually profuse explosive watery diarrhoea and abdominal distension. Failure to thrive is marked, and severe dehydration may occur. The buttocks may be severely excoriated due to the acid nature of the diarrhoea (see below). The stool may have an acid smell and if lactose intolerance is present, may smell of sour milk.

CLASSIFICATION

Table I

1. Primary			
An inherited lack of one or more enzymes			
A. Monosaccharide	—	Glucose Galactose	} Always together
B. Disaccharide	—	Lactose Maltose Sucrose	
2. Secondary			
After some insult to the intestinal mucosa			
A. Monosaccharide,			
B. Disaccharide — Lactose primarily involved, followed by sucrose/maltose.			
C. Mixed monosaccharide and disaccharide.			

Primary Monosaccharide Intolerance

Symptoms start at birth, with diarrhoea and failure to thrive. It is a rare condition, occurs in families, and is inherited as an autosomal recessive. Glucose and galactose are the sugars involved and intolerance to these two sugars always occurs together (Herbst *et al.*, 1969).

Secondary Monosaccharide Intolerance

Most of the diseases producing secondary disaccharide intolerance will also, if severe enough, affect monosaccharide absorption. See later, and Table II.

Primary Disaccharide Intolerance

Sucrose and isomaltose are the sugars most commonly implicated. Intolerance to these is always linked, possibly because the same enzyme is involved, or possibly because the *gene loci* for the production of the enzymes if, in fact, the enzymes are different, are very close together on the same chromosome. Breast-fed children with sucrose/isomaltose intolerance will do well until mixed feeding is started, or supplementary bottle feeds with cow's milk and sucrose are introduced. Bottle-fed babies will be symptomatic from birth if the main source of carbohydrate is sucrose, but asymptomatic if glucose is involved. An intelligent mother may notice that the introduction of sucrose has precipitated diarrhoea and spontaneously change to glucose. Similarly, older children quickly learn the foods which will precipitate abdominal discomfort and diarrhoea, and avoid them.

Primary lactase deficiency is rarer than sucrose/isomaltase deficiency and presents at birth. There appears to be a varying racial incidence of the condition, as Cooke & Kajubi (1966) have shown in Uganda.

Secondary Disaccharide Intolerance

A large number of diseases has been found which can give rise to a secondary disaccharide intolerance.

Table II

Post Diarrhoea States	Small bowel resection
a. Virus	Ulcerative colitis
b. Bacterial	T.B. Gut
Salmonella	Gastrectomy
Pathogenic E. Coli	Abeta lipoproteinaemia
c. "Non-specific"	(Acanthocytosis)
Gluten enteropathy	
Giardiasis	
Malnutrition	

Whether or not intolerance develops would seem to depend on several factors:

1. The magnitude of damage to the cells with brush borders.
2. Whether or not cellular regrowth and migration can keep pace with the continuing damage.
3. The area over which damage has occurred; and

4. Whether or not there has been a decrease in actual surface area of the gut — by resection, or by villous atrophy.

In most diseases causing intolerance, more than one of these factors is involved; for example, in gluten enteropathy the villi become severely atrophied, reducing the surface area for absorption. In addition the mucosal cells are damaged along with their brush borders. If the disease has progressed to the stage where the child is malnourished, then cellular regrowth may be depressed.

Similarly in malnutrition, initial damage to the mucosal cells may be brought about by a bacterial infection, but because of malnutrition, the mucosal surface of the gut may never be adequately repaired. The mucosal cells are replaced in normal children once in 3-6 days, the cells migrating from the intervillous crypts, along the villi, to be shed from the tips of the villi (Creamer, 1966). In protein-deficient monkeys, the rate of migration of these cells is markedly decreased (Deo and Ramalingaswami, 1965). In addition, the mitotic rate for cells in the intervillous crypts is reduced in malnourished children (Brunser, 1966). The end result histologically resembles the picture in gluten enteropathy.

Diarrhoea

Diarrhoea due to sugar intolerance is caused by an interaction of several factors. Unsplit sugars remaining in the intestinal lumen are fermented by bacteria, with the production of lactic and other acids. These are irritant to the mucosa and produce intestinal hurry. Secondly the bacterial flora may change, and thirdly, the unsplit sugars and fermentation products from the sugars act through the osmotic pressure they exert, to keep water within the gut lumen. If intestinal hurry and diarrhoea are severe, monosaccharides may appear in the stool, when, in fact, no true intolerance to them exists.

DIAGNOSIS

Three very simple screening tests are available, and are applicable to all forms of suspected intolerance.

1. The stool pH as estimated with Universal indicator. A pH below 5.5 is significant.
2. Stool test for reducing substances. This is carried out in the same way as testing urine for glucose. Five drops of liquid stool are added to 10 drops of water, and a Clinitest tablet placed in the test tube. More than half per cent. reducing substances is significant. If sucrose intolerance is suspected, the stool must be boiled with

a few drops of N. hydrochloric acid and the test repeated after neutralisation of excess HCl.

3. Test stool for glucose by the glucose-oxidase method (Clinistix). This will show specifically whether glucose is present or absent. If none is present but reducing substances are, then the intolerance is almost certainly to disaccharides alone. Stool chromatography will identify the individual sugars present, but takes at least 24 hours to complete.

Oral tolerance tests using individual sugars (2G per kg) are comparatively straight forward, and give more valuable information if chromatography is performed on the stool passed an hour or two after the oral dose of sugar. Normally the blood glucose should rise 25-30 mg an hour after the ingestion of sugar. If a disaccharide tolerance test is abnormal, the tolerance test may be repeated using the constituent monosaccharides to rule out monosaccharide intolerance as a cause of apparent intolerance to a disaccharide. During the tests, a careful watch must be kept on the child for abdominal distension, vomiting and diarrhoea, which although helping in the diagnosis, may lead to a rapid deterioration in the child's condition.

The surest way of diagnosing a disaccharidase deficiency is to perform a jejunal biopsy and estimate the levels of each enzyme in the jejunal mucosa. Oral tolerance tests and jejunal biopsy should not be performed on seriously ill children, and are best delayed until a week or two after admission.

TREATMENT

When a child is too ill for specific tests to be carried out, but screening shows sugar intolerance to be present, there should be complete elimination from the diet of all sugars except fructose. After improvement, the diet may be modified in accordance with the more specific tests. Most of the diets consist of a non-milk source of protein (Casilan, Nutramagen, Soya) to which must be added carbohydrate (monosaccharides in the case of disaccharide intolerance, or fructose in the case of glucose/galactose intolerance), and fat (as sweet oil, peanut oil, or medium chain triglycerides) to provide calories. These purely artificial diets may lead to electrolyte imbalance and supplements of sodium, potassium, zinc, molybdenum, magnesium, iodine, cobalt, copper and iron may be necessary (Clayton, 1966). Similarly, full doses of vitamin supplements must be given, including vitamin K, from the first few days of treatment.

When treating children with sugar intolerance it must be remembered that antibiotic and vitamin

syrups are often made up in a base of sucrose or lactose and may be responsible for relapses.

THE CLINICAL IMPORTANCE OF SUGAR INTOLERANCE

Stool pH and estimation of reducing substances in the liquid stool should be part of the investigation of every child with failure to thrive or diarrhoea.

COELIAC DISEASE

Lactose intolerance is so frequently associated with coeliac disease that elimination of milk and its products should be routine in all children seriously ill with this disease. Milk can usually be re-introduced after 2-3 months.

POST DIARRHOEAL STATES

Monosaccharide intolerance and especially disaccharide intolerance are fairly common after attacks of diarrhoea on an infective basis; and most common after pathogenic *E. coli* infection in infants under one year. Intolerance should be suspected if profuse diarrhoea continues and the infant continues to lose weight. Appropriate elimination diets often bring dramatic improvement, although the intolerance may last up to three months after the precipitating illness.

MALNUTRITION

The association between malnutrition and atrophic changes in the gut has been mentioned. A vicious circle is readily set up where milk feeding produces diarrhoea, which in turn gives rise to further gut damage and worsening of the diarrhoea and malnutrition. The frequent association of kwashiorkor with lactose intolerance explains why milk feeding may precipitate profuse diarrhoea within 24 hours of admission to hospital in such cases, and also the failure of so many supplementary milk feeding schemes. In parts of East Africa, dried skimmed milk is known as the food which produces diarrhoea. Intolerance to sucrose, maltose and to the monosaccharides is also well recognised in malnourished children, although not as commonly as to lactose (Wharton, *et al.*, 1968, and Chandra, *et al.*, 1968).

All children admitted with malnutrition, most of whom, incidentally, have diarrhoea, should have screening tests performed on their stool 24-48 hours after admission (to allow for some sugar loading). In our experience, a number of children will have positive tests, but without profuse life-threatening diarrhoea. In these children we continue the usual regime of feeding based on skimmed milk, and repeat the stool test after 5-7 days. In most, the evidence of intolerance will have gone. Presumably, the intestinal mucosa has regrown. In a few cases, diarrhoea will continue or worsen with milk feeds, and stool screening

will continue to show sugars. In these children a diet eliminating lactose should be tried (Casilan plus sucrose) and if diarrhoea still persists, all disaccharides should be eliminated (Casilan/glucose diet). If sugars are still present in the stool on this latter diet, Casilan/fructose feeding should be tried, but with monosaccharide intolerance, the outlook in kwashiorkor is extremely grave (Wharton, 1968).

Anderson (1970) has suggested that complete elimination of milk from the initial diet of children with kwashiorkor will not only lessen diarrhoea but shorten the time each child needs hospital care — thus reducing the cost of admission. Elimination diets are more expensive than normal diets, but in our experience the majority of Rhodesian African children with kwashiorkor have only a transient intolerance to sugar and we still feel initial treatment on traditional lines with fortified milk to be justified.

SUMMARY

Sugar intolerance should be suspected in any child with diarrhoea. Two simple tests of the stool are described, which can confirm or rule out this suspicion. Congenital and acquired intolerance are discussed and some guidance is given to their dietary management.

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