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Nutritional consequences of altered carbohydrate absorption in infancy and childhood

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For the breast-fed infant, which is now a rarity, but also for the bottle-fed baby, carbohydrates provide approximately 50% of the total calorie requirements. These are, initially at least, entirely disaccharides, namely lactose and sucrose. Later on when cereals are introduced into the diet another disaccharide, maltose, has an equally important role. The starch in the cereals is broken down by amylase to maltose and the latter by maltose-splitting enzymes to glucose which is then further metabolized. Thus the three most important disaccharides are lactose, sucrose and maltose. They are not hydrolysed in the intestinal lumen as had been believed for a long time, but are transported through the wall of the mucosal cells, and hydrolysis takes place inside these cells whence they pass as monosaccharides into the portal circulation. Dahlqvist & Borgström (1961) established these facts only during recent years, but they have to a large extent already been confirmed by a number of other workers. According to the Swedish workers, carbohydrase action is not uniformly distributed over the whole of the small intestines, but is mainly concentrated in the jejunum although some activity can also be found in the ileum.

Lactase activity seems to be located in the duodenum and in the proximal part of the jejunum. A personal observation supports this finding. A newborn infant who was operated on for an exomphalos and was also found to have an atresia of the ileum showed an excellent response to a lactose loading test.

Lactase activity in man, as well as in other mammals, is at a peak shortly after birth, and gradually decreases to its lowest level in the adult. It has been possible to demonstrate the presence of lactase activity and of other carbohydrase activities in the brush border of the intestinal mucosa and some reports have located them in the microsomes of the cells (Borgström & Dahlqvist, 1958; Doell & Kretchmer, 1962).

Sucrase activity is present in the distal jejunum and proximal ileum, and maltase activity can be demonstrated along the whole length of the jejunum and the proximal ileum.

Stimulated by reports of probably hereditary carbohydrase deficiencies, Dahlqvist (1962) attempted to determine the specificity of human intestinal disaccharidases by inactivation through heating at stepwise increased temperatures. It appeared that maltase activity is contributed by several different enzymes, one of which also hydrolyses isomaltose, though it is only about half as active against this substrate as against maltose. The fraction containing the sucrose-splitting enzyme activity also had a slight maltase activity. Lactase activity is specific for lactose (and cellobiose). One is therefore forced to the assumption that some of the disaccharidases act on more than one substrate and that certain substrates are hydrolysed by more than one enzyme.

During the past 5 years a great deal of attention has been focused on disorders of carbohydrate, and in particular disaccharide, absorption. It has been found that resulting disturbances may vary a great deal in gravity according to the extent of the enzyme deficiencies, the age of the patient affected and such environmental factors as the pattern of nutrition.

Holzel, Schwarz & Sutcliffe (1959) described the first of the disaccharidase deficiencies, namely that of lactase activity, in two breast-fed siblings. Since then our own observations include a further three children who were bottle-fed. The clinical picture that has emerged from our observations is a fairly characteristic one, although the state of malnutrition that arises may vary a great deal from case to case. It is likely to be more severe in the purely breast-fed baby, and in the infant on a cow's-milk formula if the sugar added to it is also lactose, as they are then unable to absorb the entire carbohydrate portion of their food. The number of proprietary milk preparations, particularly of the dried variety, that contain lactose as their only sugar complement is very large.

Affected babies tend to cry persistently, owing partly to hunger and partly to colicky pain, from which they frequently suffer (our last patient was referred to hospital as a suspected case of intussusception). Diarrhoea is one of the earliest signs to appear; the stools, ten to twelve in the 24 h, are frothy, sour-smelling and with a pH generally below 6. Excoriation of the buttocks is almost always present as a result of the irritation by the high content of organic acids in the stools.

There were no abnormal findings in the urine; lactose as such does not seem to penetrate the barrier of the intestinal mucosa, nor could it be discovered, except in minute quantities, in the stools. Most of the milk sugar is probably metabolized by the intestinal flora and only the fermentation products are detectable in the faeces. Random blood sugar estimations always gave low readings for as long as the patients received their carbohydrate in the form of lactose. The diagnosis of the abnormality

is not difficult provided one bears its possibility in mind after excluding the more common causes of malnutrition in infancy.

The following example may illustrate the problem:

E.L. was born on 24 April 1961, the youngest of three siblings. His birth weight was $8\frac{1}{2}$ lb. Delivery after an uneventful pregnancy was normal. His mother was unable to feed him and he was put on a formula of reconstituted dried cow's milk with a lactose content of 7.1%. At the age of 5 weeks he was referred to hospital because of a severe state of malnutrition, persistent vomiting, diarrhoea and grossly excoriated buttocks. He was then 2 lb below his birth weight. His stools were noticed to be frothy and sour smelling and for as long as he remained on the formula prescribed at home his weight did not increase although his food intake provided approximately 100 kcal/lb body-weight daily—far in excess of his requirement. However, as soon as sucrose was added to his feeds he began gaining weight, but ceased when the sucrose was omitted. When sucrose and cereals were added once more his progress became satisfactory. A glucose loading test was normal but a lactose absorption test produced only a negligible rise in blood sugar. A glucose–galactose mixture, however, led to a satisfactory increase of the blood sugar levels.

These observations strongly suggest the absence of lactase activity and the child's inability to utilize this disaccharide. The state of malnutrition is the result of the calorie deficit that arises when the carbohydrate component in the food is lactose only. The other clinical manifestations are the direct consequences of the failure of lactose hydrolysis. Similar cases have been recorded by Weijers, van de Kamer, Dicke & Ijsseling (1961) in Holland and by Lifshitz & Holman (1964) in the United States. In the latter case the congenital deficiency of lactase activity was combined with other disaccharidase deficiencies.

Von Haemmerli, Kistler, Ammann, Auricchio & Prader (1963) have recently published a study on acquired deficiency of lactase activity in the mucosa of the small intestine of twenty-three adults which presented as a form of milk intolerance. The authors were able to substantiate their clinical findings by carbohydrate tolerance tests and determination of disaccharidase activity in jejunal biopsies. Their patients tolerated milk well as children but not in later life when it led to severe abdominal pain, abdominal distension and diarrhoea, the severity of the symptoms depending on the quantity of milk ingested—thus not unlike the picture we first described in early infancy. Most of these patients had been regarded as suffering from milk allergies.

Durand (1958) reported a case of idiopathic lactosuria associated with severe general disturbances and ending fatally. Since then a number of cases have appeared in the medical literature under a variety of titles such as lactosuria and aminoaciduria (Darling, Mortensen & Søndergaard, 1960), congenital lactosuria (Jeune, Charrat, Cotte, Fournier & Hermier, 1960), congenital lactose intolerance (Fois, Vedovini & Marinello, 1960).

A summary of the clinical data gives the following picture. The disease begins in the neonatal period, irrespective of breast- or bottle-feeding, with diarrhoea, vomiting, refusal of feeds and ensuing malnutrition. Haemorrhagic manifestations may appear. Renal disturbances such as renal acidosis, hypercalcaemia, proteinuria,

increase in blood urea have been observed in addition to the common characteristic lactosuria, which occasionally may be associated with sucrosuria or glycosuria. Genetic factors may play a part.

Our own patient (Holzel, Mereu & Thomson, 1962), who had been fed on a reconstituted dried-milk formula, developed diarrhoea at the age of 4 weeks, followed by profuse vomiting, abdominal distension and wasting. After exclusion of the more common disorders it was discovered that he had a considerable lactosuria; on a lactose-free diet he progressed amazingly well. After a 10-day interval 1% of lactose was added to his lactose-free food and immediate relapse occurred. Improvement followed again on lactose withdrawal. It has been suggested that this condition is also due to deficient lactase activity. However, we find little to support such a hypothesis. We feel that the fact that relatively very small amounts of lactose can precipitate a deleterious state of affairs in the patient can only be explained on the basis of some toxic effect of lactose, by an as yet unknown mechanism, on the intestinal mucosa and maybe also on other organs, whereas the form of lactase deficiency previously discussed leads to wasting because of the calorie deficit and intestinal manifestations as a result of bacterial fermentation.

Weijers *et al.* (1961) described three cases with chronic diarrhoea, two of whom were suffering from deficiency of invertase activity and one from deficiency of invertase and maltase activities. Sucrose in their diet led to thin, foamy diarrhoea with abdominal distension and some degree of malnutrition. The faeces contained large quantities of lactic acid and volatile fatty acids. Shortly afterwards Prader, Auricchio & Mürset (1961) were able to confirm the Dutch workers' findings relating to disaccharidase deficiency causing chronic diarrhoea but furthermore they were able to show (Auricchio, Dahlqvist, Mürset & Prader, 1963) that the deficiency of sucrase activity in their four cases was linked with an isomaltose malabsorption. This discovery was based on their observation that the ingestion of starch or dextrins induced relatively mild attacks of diarrhoea in patients who were seemingly only suffering from lack of sucrase activity. Isomaltose contains a 1:6 glucosidic linkage. Nordio, La Medica & Vignolo (1961), Anderson, Messer, Townley & Freeman (1963) and Lifshitz & Holman (1964) reported further cases. If one assumes a hereditary basis for these disorders, it is at present difficult to understand how more than one enzyme can be involved, as known inborn errors of metabolism are caused by the abnormal or absent activity of a single enzyme.

There is no doubt that in addition to these primary and probably hereditary carbohydrase or disaccharidase deficiencies a variety of noxious agents can injure the cells of the brush border of the intestinal mucosa and thus induce disaccharidase deficiencies and disaccharide malabsorption.

We had opportunity to observe such acquired absorptive disorders and were surprised by the severity of these conditions which might well have led to death from malnutrition had they not been recognized in time. The acquired enzyme deficiencies may be temporary or permanent. They generally involve several of the carbohydrases at the same time.

The following is an illustrative case history:

P.McL., a male infant born on 23 July 1961, was admitted to hospital at the age of 2 months with diarrhoea and vomiting. He had been treated with antibiotics for a fortnight by the family physician because of a respiratory tract infection. The pneumonia cleared in hospital, but vomiting persisted and his condition deteriorated to a state of stupor. For several weeks his weight remained stationary. Routine laboratory investigations were negative. During metabolic studies it was found that he did not absorb lactose; glucose was added to the milk but with little effect. Sucrose and maltose absorption too seemed grossly deficient. Estimation of fat in the stools showed a moderate degree of steatorrhoea, and xylose excretion in the urine after a test dose was in the region of 3%. On the basis of the disaccharide absorption tests, sucrose and starch were now eliminated from the child's diet and replaced by monosaccharides, mainly glucose. From then onward he showed definite but slow improvement. He became a happy, smiling infant. When from the age of $3\frac{1}{2}$ months dried yeast was added to his feeds and starch reintroduced he progressed by leaps and bounds. The steatorrhoea disappeared, there was no vomiting or diarrhoea. When we were able to obtain sources of sucrase activity as well as amyloglucosidase and dispensed with the administration of yeast, he was gaining weight at the rate of 1 lb a week. A characteristic feature throughout the whole illness was a marked loss of muscular tone which only returned very gradually.

The next case presents an entirely different facet of the same problem. It demonstrates that the carbohydrate malabsorption can be induced or precipitated by a protozoal infection.

A.G., aged 4 months, was admitted to hospital because of an acute respiratory infection. Her weight was 6 lb 4 oz, only 2 oz above her birth weight. On inquiry the mother stated that the child had not been thriving for some time in spite of the utmost care—but there were seven more children to be looked after and she herself had to go out to work.

The baby presented a picture of severe malnutrition with some abdominal distension. Routine investigations were unhelpful; there was no steatorrhoea but the stools were offensive and intermittently the infant had episodes of diarrhoea and vomiting.

During the spontaneous remissions she did not show any striking improvement and she did not gain weight. After a number of attempts at explanation a heavy infestation with *Giardia lamblia* was established. Although it cleared with mepacrine and no cysts could be detected in the faeces or duodenal juice, she made little progress. Among further investigations disaccharide absorption was also explored and to our surprise she did not seem to be able to absorb sucrose, maltose or lactose. With the administration first of yeast and then of bimyconase (sucrase × amyloglucosidase) she made extremely rapid progress.

Re-examination of her absorptive capacity for disaccharides 6 months later showed almost complete recovery. In this case also muscular hypotonia was a very prominent feature.

It is a fair assumption that the disaccharide malabsorption was due to the *Giardia* infestation though the pathogenetic mechanism can so far only be a matter of speculation.

A further observation concerns another aspect of disaccharide malabsorption in which it is but a part of a more general disturbance of the absorptive function of the intestinal mucosa, as in the gluten-induced coeliac disease.

A 9-month-old infant was admitted to hospital with pyrexia, evidence of weight loss, severe muscular hypotonia, a high-pitched continual whine and some neck rigidity. However, laboratory investigations of urine, stools, blood and cerebrospinal fluid, and tuberculin tests, were all negative. Two days later he developed hyperpyrexia (107°F), photophobia, intense head retraction and was passing large, fluid, light-coloured stools.

After spontaneous remission for a month, a relapse seemed to be precipitated by an upper respiratory tract infection. This time not only was there marked muscular hypotonia but actual wasting of muscles of the neck, of the scapular region, of the deltoid biceps, triceps as well as the muscles of the thighs and buttocks. Tendon reflexes could just be elicited. Balance studies showed some degree of steatorrhoea, reduced xylose excretion in the urine after an oral test dose, a flat glucose tolerance curve and gross malabsorption of the three disaccharides. A diagnosis of coeliac disease was then entertained. Response to a gluten-free diet appeared dramatic with rapid increase in body-weight, return of normal muscle tone, improvement in his emotional status and gradual amelioration in disaccharide absorption.

Disaccharide malabsorption in coeliac disease has been suspected, in some ways implied, but not previously proven. We have since investigated a number of patients with coeliac disease and have found that disaccharide malabsorption is a constant nutritional aspect of the disease and seems to correspond with the degree of its severity.

Impairment of lactose and sucrose absorption was appreciably greater than that of maltose. This is not surprising if carbohydrase activity is considered in relation to the distribution of the mucosal lesions in steatorrhoea. Careddu, Giovannini & Cevini (1963) have shown that in cases of subacute enteritis, as well as in chronic forms of malnutrition of unknown aetiology, the disaccharides are often poorly absorbed. The disorder is temporary and disappears when the underlying illness improves.

Summary

Clinical studies in the field of disaccharide absorption have revealed a number of disorders which can be logically classified into:

(1) The primary (probably hereditary) enzyme deficiencies which involve lactase, sucrase and isomaltase activities. Deficiency of sucrase and isomaltase activities seems to occur linked together in the same individual; deficiency of lactase activity is found separately.

(2) The acquired forms may follow a variety of insults to the intestinal mucosa such as infections with viral, bacterial or protozoal agents, or injury by toxic substances. In the acquired disaccharide malabsorptions multiple enzyme deficiencies are more likely to be encountered, and therefore more serious sequelae, than in the primary hereditary types, although it is possible that a particular form of poison

may inhibit or inactivate selectively a single enzyme. It is probably not unreasonable to assume that disaccharide malabsorption as a cause of disease manifestation, such as chronic diarrhoea and malnutrition, certainly in childhood, is far more common than is suspected.

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The systemic influence of carbohydrates on teeth

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The fact that a symposium, organized by the American Dental Association in 1954, could be entirely devoted to 'the effect of sugars and other carbohydrates on the teeth' clearly indicates the extent of this subject and the necessity of restricting the present discussion to only one aspect. The less well established systemic or nutritional influence of carbohydrates on teeth has been chosen as it seems most in accord with the theme of this meeting. My intention is to assess, from the available experimental evidence, the relative importance of this influence in determining caries susceptibility.

Pre-eruptive influence of carbohydrates

Sognnaes (1948), in a study which is a landmark in experimental caries research, fed rats and hamsters on a purified, high-sucrose diet before and during the development of the molar teeth of their offspring, that is, during pregnancy and lactation. This resulted in a marked decrease in the caries resistance of these animals compared with others raised from dams on an unrefined stock diet. Less effect was observed when the high-sugar diet was given to the mothers during the lactation period only. Sognnaes & Shaw (1954) have confirmed these results and have also reported a similar pre-eruptive influence, operating before and after weaning, in the