Disaccharidase deficiency in man

A. M. DAWSON

St Bartholomew's Hospital, London, E.C.1

IT IS STILL commonly taught in physiological textbooks that carbohydrates are completely digested in the lumen of the bowel by the action of pancreatic juices and the succus entericus. This is untrue and in fact the enzymes of the succus entericus probably represent desquamated intestinal cells and are not present in sufficient quantity to be of physiological significance, while the final stage of digestion takes place on or in the intestinal mucosa; this was realized at the turn of the century by Weymouth Reid. A scheme of sugar digestion and absorption is shown in Fig. 1. Starch comprises straight chains of repeating units of glucose (1-4 linkage—amylose) or branched chains (1-4 1-6 linkage—amylopectin). Under the action of pancreatic amylase maltose, maltotriose (1-4 glucose-glucoside with 3 glucose units) and isomaltose (1-6 glucose-glucoside) are formed. The other main dietary disaccharides are lactose (galactose plus glucose) and sucrose (fructose plus glucose).

There are four main groups of enzymes in the brush-border of the mucosal cell which split the dietary disaccharides; once split, the constituent monosaccharides are pumped across the mucosal cell by a specialized mechanism.

It is a good rule in clinical medicine that if an enzyme is present and it is not necessary for life, then some members of the population will be deficient and on occasions this may give rise to symptoms and so it was realized that a group of children who fail to thrive, have acid, fermentative stools with diarrhoea and are cured by withdrawal of the offending disaccharide from the diet are suffering from such a deficiency. This was first well documented by Weijers *et al.* (1961) who described a child who was unable to tolerate sucrose or starch but could tolerate lactose. This child, in fact, was suffering from the condition of sucrase-isomaltase deficiency and it would seem from this and other studies (Burgess *et al.*, 1964; Auricchio *et al.*, 1965a) that a defici-

Fig. 1. Scheme for digestion and absorption of carbohydrate.

iciency of both these enzymes always goes hand-in-hand. Furthermore, if one separates solubilized fractions of intestinal cells the activity of sucrase and isomaltase have similar mobility on a Sephadex column (Auricchio, Semenza & Rubino, 1965b). It is thus considered that these two enzymatic activities are both present on a single protein, for it is usual to assume that one gene controls the synthesis of one protein. This condition is a recessive one, and Kerry & Townley (1965) have shown that the parents of such children both have a reduced amount of isomaltase and sucrase in biopsy specimens of small bowel. Other children may have similar symptoms due to lactase deficiency and their diarrhoea is caused by their inability to absorb mild sugar, lactose; when milk is withdrawn from their diet symptoms improve (Holzel, Schwarz & Sutcliffe, 1959).

Besides these rather uncommon congenital defects it would seem that quite a large proportion of the adult population are unable to absorb lactose. Indeed, in a series of small-bowel biopsies on sixty-seven patients in which this enzyme was estimated and in which the biopsies were performed for either unexplained diarrhoea or other nutritional disturbances, twenty were found to be lactase-deficient (McMichael, Webb & Dawson, 1966). It may be seen from the scattergram in Fig. 2 that there are two distinct populations with regard to lactase activity. Furthermore, it should be noticed that the distribution of this

activity is on a log and not normal scale. That this was an isolated deficiency is shown by the fact that the maltase activity in these biopsies was comparable in the hypolactasic and normolactasic groups. This low mucosal lactase has functional significance. This can be shown by doing lactose-tolerance curves, when the rise in blood sugar is lower than in normal people, by direct tests of sugar absorption, using a perfusion technique (McMichael, Webb & Dawson, 1967) and also noting that during a lactose-tolerance test many patients will have cramping abdominal pain and diarrhoea due to the osmotic action of the unabsorbed sugar. It will be noted that there is some lactase activity in the mucosa of the hypolactasic group, but this may well be due to a β -galactosidase which has a higher affinity for other galactosides rather than lactose and resides within the cell sap rather than on the brush border (Zoppi *et al.*, 1966).

At the moment there is some considerable discussion over the possible aetiology of this hypolactasia. Initially it was considered to be an acquired lesion due to non-specific damage of the intestinal epithelium and has been found in association with a variety of gastro-intestinal and non-gastro-intestinal conditions (Hoofstede *et al.*, 1963; Jones, 1964; Struthers, Singleton & Kern, 1965). Certainly when the intestinal mucosa is damaged lactase is depressed to a greater degree than other disaccharidases, as shown by Plotkin & Isselbacher (1964) and McMichael *et al.* (1966), whose data are shown in Fig. 3. The ratio of maltase over lactase is shown in normal controls, in patients with so-called constitutional hypolactasia and in patients who have structurally abnormal biopsies either taken near their gastro-enterostomy stoma or patients with idiopathic steatorrhoea. It will be seen that the depression of lactase indeed is greater than maltase but that the order of depression is not comparable to the patients with hypolactasia and a morphologically normal biopsy. It seems more likely that hypolactasia is a genetic disturbance and that some people have a regression of lactase activity in their intestinal mucosa during childhood. A comparable state of affairs is found in many animal species (Fischer & Sutton, 1949). Evidence for this genetic effect was shown in studies on Greek Cypriot patients (Fig. 4): oral lactose-tolerance curves were performed on sixteen Greek Cypriot patients and it can be seen that the rise in blood sugar was comparable to that in a group of patients with biopsy-proven hypolactasia and much lower than the normal controls. Similarly, Cook & Kajubi (1966) have shown that there is a varying tribal incidence of

FIG. 2. Lactase (a) and maltase (b) activity in sixty patients with structurally normal biopsy (McMichael *et al.*, 1966). ●, Normal; ▲, alactasia.

hypolactasia in Uganda and in the U.S.A. Negro patients have a higher incidence of this deficiency than the white population (Bayless & Rosenweig, 1966). Clearly this is a different condition from babies with hypolactasia and failure to thrive and Cook (1967) has recently published crucial evidence to show that the neonatal values of lactase in the intestinal mucosa of populations who in adult life have a deficiency of this enzyme are normal, and furthermore by doing serial lactose-tolerance curves in different age groups in populations at random showed that hypolactasia appeared during childhood.

FIG. 3. Effect of mucosal damage on maltase/lactase activity in small gut biopsy.

Given that this defect is common, what is its clinical significance? It seems possible that some of the patients who complain that on taking milk they get diarrhoea, flatulence or cramping abdominal pain are in fact hypolactasic and their symptoms are due to the fermentation of unabsorbed lactose. However, the clinical impression is difficult to evaluate for many patients will claim that the symptoms come on with minute doses of milk and it is difficult to imagine that carbohydrate fermentation in such

FIG. 4. Blood sugar rise after 50 g oral lactose in Greek Cypriots compared with control and hypolactasic groups (McMichael *et al.*, 1966).

patients is important. It seems possible that most people would be able to tolerate the fermentation products of the unabsorbed sugar in their large bowel if it is in normal dietary quantities spread throughout the day. It may be noted that many children with isomaltase-sucrase deficiency as they grow up become relatively asymptomatic although they can tolerate a normal dietary intake of sucrose and although they do not develop any hydrolytic enzyme in their mucosa and so do not absorb the sugar in the small intestine. Theoretically it would be possible that if the bowel became more reactive (and obviously there is a variability in a standard population's response to a dose of purgative) symptoms may come about. Such changes in reactivity may occur in gastro-intestinal diseases and after gastro-intestinal surgery and it may explain why symptoms of lactose intolerance may occur in these conditions; that is, the deficiency of lactase has been present all the time but intolerance to lactose develops with the associated disease.

In summary, lactase deficiency in adults is a ubiquitous, genetically determined anomaly. It is tempting to speculate on the significance of the retention of lactase in certain genetic groups and the possible usefulness which it has in these

groups. It seems likely that it only on occasions causes symptoms and that this may be when the large bowel becomes more sensitive to the effects of unabsorbed sugar. It is this differing sensitivity of the large bowel rather than the defect in sugar absorption that warrants further study.

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