Sugar Malabsorption
Due to Deficiencies of Disaccharidase Activities and of Monosaccharide Transport

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In many societies including our own, carbohydrates play a major part in the total calorie supply. According to the National Food survey figures (Greaves and Hollingsworth, 1964), the average daily diet of adults contains nearly 350 g. of this constituent. Diets of course vary with eating habits and social class, but the dietary carbohydrates are largely ingested as poly-, oligo-, and disaccharides. In the very young, however, the carbohydrate intake may consist almost entirely of disaccharides, though this phase is now getting progressively shorter. As the rapid decrease in breast-feeding has been followed by the early introduction of cereals into the cow’s milk formulae, even the infant of only a few weeks of age has also to digest polysaccharides.

The percentage of calories derived from carbohydrate increases from 40% in infancy to well over 50% later in life. The polysaccharides, starch and glycogen, are hydrolysed by salivary and pancreatic amylase to maltose and small quantities of isomaltose and glucose. The common disaccharides in our food are lactose and sucrose. The amount of lactose depends on the milk intake, as this is its main source. The human intestinal mucosa has therefore the task of absorbing large quantities of the disaccharides, maltose, isomaltose, sucrose, and lactose. For a long time surprisingly little attention was paid to this important absorptive function of the small intestine, but during recent years physiologists, biochemists, and paediatricians have discovered much of interest, and clinical observations have revealed a number of disorders associated with sugar malabsorption.

Physiology of Disaccharide Absorption

Until a few years ago it had been accepted that hydrolysis of the disaccharides into their component monosaccharides had to precede their absorption and entry into the further stages of metabolism, and that the disaccharidases, lactase, sucrase, and maltase, were secreted by unspecified cells of the intestinal mucosa into the lumen of the gut where the hydrolytic process took place. But studies in man during the past decade (Borgström, Dahlqvist, Lundh, and Sjövall, 1957; Dahlqvist and Borgström, 1961) demonstrated that disaccharidase activity in the intestinal lumen was extremely limited and did not account for the amount of carbohydrate absorbed. They further indicated that the majority of disaccharides were absorbed unhydrolysed and split intracellularly, a fact that accorded well with experimental findings (Cajorl, 1933; Fridhandler and Quastel, 1955).

The problem of localization of the sugar-splitting enzymes was brought nearer its solution by Miller and Crane (1961), who were able to separate the brush-border from the rest of the intestinal mucosa of the hamster, and found that the whole of the enzyme activity of the mucosa was accounted for by this layer. ß-galactosidase (lactase) activity had been localized in the microsomes of the rat intestinal mucosa by Doell and Kretchmer (1962), while Dahlqvist and Brun (1962), employing histochemical methods for the recognition of invertase and trehalase in various animal tissues, associated their activity with cytoplasmic granules. As yet there is no definite information concerning the possible relationship of the elements of fine structure of the microvillus with its absorptive and digestive functions. However, two related fractions have been obtained by density gradient centrifugation of tris-disrupted brush-borders from hamster intestinal mucosa, and have been identified as the microvillus cores and their surrounding membranous coats (Overton, Eichholz, and Crane, 1965; Eichholz and Crane, 1965).

Specificity of human intestinal disaccharidases. The belief that each enzyme has its corresponding specific substrate has been modified in so far as experimental and practical experience
has shown that synthetic sugars which have the same glycosidic linkage as naturally occurring products will be split by the same enzyme.

The following human intestinal disaccharidases have been identified by heat inactivation experiments (Dahlqvist, 1962; Dahlqvist, Auricchio, Semenza, and Prader, 1963), gel filtration on Sephadex and chromatography (Auricchio, Semenza, and Rubino, 1965c; Semenza, Auricchio, and Rubino, 1965a). The maltases or \(\alpha\)-glycosidases hydrolyse maltose, isomaltose, sucrose, and palatinose. Trehalase exerts its activity on trehalose, a rare disaccharide that occurs in certain mushrooms. The \(\beta\)-glycosidase lactase (\(\beta\)-galactosidase) attacks cellobiose, in addition to lactose. Cellobiose is a disaccharide resulting from the hydrolysis of cellulose, which consists of two molecules of glucose with a 1-4 \(\beta\) linkage similar to that which joins the glucose and galactose molecules in lactose (Fig. 1). Although cellobiose plays little part in human nutrition, since cellulose cannot be hydrolysed in the small intestine, the sugar can be used as an additional substrate to verify lactase activity. The presence of two intestinal lactases was demonstrated by Heilskov (1956) for the calf, and for the rat and rabbit by Doell and Kretchmer (1962), who found one lactase associated with the particulate fraction which hydrolysates two substrates, namely lactose and ortho-nitrophenyl-\(\beta\)-galactoside, while the soluble enzyme splits only the latter. Since ortho-nitrophenyl-\(\beta\)-galactoside is an artificial compound, the true function of the second enzyme is unknown. Two lactases have also been postulated for the human intestinal mucosa (Semenza et al., 1965a). These authors have been able to show that the two \(\beta\)-galactosidases in the mucosa of the human jejunum and ileum are not the result of an artefact, and that the ratio of cellobiose activity remains constant in relation to that of each of the lactases, further indicating that cellobiose and lactase activity are due to the same enzyme molecule. With regard to the multiplicity of human maltases, Dahlqvist (1964a) and Auricchio et al. (1965c) come to slightly different conclusions, and thus to somewhat differing nomenclature. Dahlqvist recognizes four maltases, while Auricchio and colleagues separate five (Table I).

### TABLE I

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
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<tr>
<td>MalTase Ia (Ia)</td>
<td>Maltose</td>
<td>MalTase Ia (Ia)</td>
<td>Maltose</td>
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<tr>
<td>(isoMaltase palatinase)</td>
<td>Palatinose</td>
<td>(isoMaltase palatinase)</td>
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<tr>
<td>MalTase Ib (II)</td>
<td>Maltose</td>
<td>MalTase Ib (II)</td>
<td>Maltose</td>
</tr>
<tr>
<td>(sucrase; invertase)</td>
<td>Sucrose</td>
<td>MalTase Ib (II)</td>
<td>Sucrose</td>
</tr>
<tr>
<td>MalTase III (III)</td>
<td>Maltose</td>
<td>MalTase III (III)</td>
<td>Maltose</td>
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<tr>
<td>MalTase IV (IV)</td>
<td>Palatinose</td>
<td>MalTase IV (IV)</td>
<td>Palatinose</td>
</tr>
<tr>
<td>MalTase V (V)</td>
<td>Maltose</td>
<td>MalTase V (V)</td>
<td>Maltose</td>
</tr>
<tr>
<td>MalTase 6 (VI)</td>
<td>Palatinose</td>
<td>MalTase 6 (VI)</td>
<td>Palatinose</td>
</tr>
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Maltase 5 (in the latter classification) hydrolyses maltose, isomaltose, and palatinose, a synthetic sugar consisting of one molecule glucose and one molecule fructose in 1-6\(\alpha\) linkage. Since palatinose and isomaltose have the same glycosidic bond, they are split by the same disaccharidase (Fig. 2). Palatinose can therefore be used to demonstrate isomaltase activity (Auricchio, Prader, Mürset, and Witt, 1961) when isomaltose is in short supply (Fig. 2).

**FIG. 1.** — \(\beta\)-galactosidase hydrolys two disaccharides of different molecular composition but with the same glycosidic linkage.

**FIG. 2.** — Isomaltase hydrolys in addition to isomaltase palatinose, a synthetic disaccharide.

**Distribution of disaccharidases along the small intestine.** Comparison of a number of published animal and human investigations reveals the presence of species differences. In the rat, lactase activity is stronger in the middle part of the small intestine than in its proximal or distal regions, maltase activity is uniformly distributed, while sucrase (invertase) and isomaltase are strongest in the proximal areas. In the adult pig, the trehalase, lactase, and cellobiose activities are strongest in the proximal part, while the maltases are most active in the distal part (Dahlqvist, 1964a). In adult man, according to Auricchio, Rubino, and Mürset (1965a), enzyme assays on mucosal specimens obtained by peroral intestinal biopsy indicate that sucrase, isomaltase, and lactate are less active in the first part than in the remainder of the duodenum; in the upper jejunum and the last segments of the ileum.
disaccharidase activities are of the same order of magnitude. Taking the rate of absorption as a measure of disaccharidase activity, Gray and Ingelfinger (1965) found, with the aid of infusion experiments, that sucrose absorption was about twice as rapid in the human jejunum as in the ileum. Ingested sucrose was almost completely absorbed in the jejunum. In a study of 7 normal adults, 6 men and 1 woman, Newcomer and McGill (1966) carried out 6 to 13 peroral mucosal biopsies in each subject at various levels of the small intestine from the first part of the duodenum until well into the ileum. Lactase, sucrose, and maltase activities were determined; disaccharidase activity was low in the duodenum and ileum, while peak activity was found at variable points in the jejunum and proximal ileum.

**Foetal and neonatal intestinal disaccharidase activity.** The prenatal and postnatal development of disaccharidase activities is of importance not only for academic reasons, but also in connexion with the practical management of the very small premature infants. Lactosuria in the premature baby was recognized and explained half a century ago by the absence of lactase activity (Langstein and Meyer, 1914), the enzyme being functional in the full-term infant. An investigation of 32 human embryos, foetuses, and newborn infants (Auricchio et al., 1965a) revealed that the enzyme activities were distributed uniformly throughout the small intestine except in the duodenum and terminal ileum, where only trehalase remained high. All glycosidases were present by the third month of intrauterine life. All α-disaccharidases (namely the maltases and sucrase) reached a maximum during the sixth or seventh month of intrauterine life while the β-glycosidases, lactase and cellobiase, developed more slowly before birth and reached their peak at term. Premature infants had a low level of lactase activity which, however, rose rapidly in the postnatal period independent of milk intake. Dahlqvist and Lindberg (1966), who studied human foetuses between 11 and 23 weeks of intrauterine life, found invertase and isomaltase activities fully developed before the 11th week, trehalase between the 11th and 23rd week, while the maltases that act only on a maltose substrate could not be detected.

Foetal meconium had a high enzyme activity, probably originating from desquamated mucosal cells, but the meconium obtained shortly after birth from term infants was devoid of disaccharidases. Alkaline phosphatase, which seems to be more stable, was extremely active.

In some mammals such as rats, pigs, and cows, lactase activity is highest in the newborn and decreases gradually to its lowest level in the adult specimen. In other animals such as mice, rabbits, and guinea-pigs, the β-galactosidase activity may decrease at different rates in the jejunum and ileum (Koldovsky, Heringová, Jirsová, Chytil, and Hošková, 1966) according to the pH. In rats and pigs, sucrase (invertase) activity is not evident at birth, but develops later. Injections of hydrocortisone into young rats caused invertase activity in the small intestine to appear at an earlier stage than normal (Doell and Kretchmer, 1964). This was further supported by immunochemical studies with a fluorescent antibody technique (Doell, Rosen, and Kretchmer, 1965). In man, lactase activity remains at a high level provided it is not altered by external factors.

**Sugar Transport**

Assuming the disaccharide-splitting enzymes to be intracellular, the means by which sugars enter the mucosal cells is still obscure. This could be by diffusion, if for instance rapid hydrolysis of the disaccharide within the cell maintained a gradient between it and the intraluminal medium. For glucose and galactose there also exists an active carrier system. Actively transported sugars, i.e. those transported against a concentration gradient, possess certain structural features in common, a pyranose ring, an oxygen bridge between C1 and C5, and a free -OH group at C2.

A further essential requisite is the presence of sodium ions on the membrane of the mucosal cell. Substitution of lithium, magnesium, or choline for sodium prevents active transport. The driving force is regarded as a form of biological pump, with adenosine triphosphate (ATP) providing the immediate energy source. Ouabain, phlorizin, and 2 : 4-dinitrophenol inhibit the absorption of glucose and galactose. It has been suggested that ouabain acts by virtue of its property of disturbing tissue electrolyte metabolism (Davenport, 1966).

Littman and Hammond (1965) have proposed that sugars enter the intestinal cell by means of a ternary sugar-Na-carrier complex. This carrier would possess two specific binding sites, one for the substrate and one for Na⁺. The rate of sugar transport seems to be dependent on the difference between intracellular and extracellular Na concentrations, and the driving force is derived from the Na concentration gradient, which is maintained by an ouabain-sensitive mechanism. Czaky's hypothesis, however, suggests that it is the energy yielding system which requires intracellular Na for its activation and which is inhibited by the cardiac glycosides. The pump part is then an ATP-
Adenosine triphosphatase-sodium complex with a specific carrier for sugar. According to Semenza, Tosi, Valtotton-Delachaux, and Mulhaupt (1964), human intestinal sucrase is also activated by Na, and a mechanism similar to that of glucose absorption might be responsible for the transport of sucrose.

Actively transported sugars move far faster than a sugar such as fructose which crosses the cell membrane by diffusion.

Disturbances of the transport mechanism have recently been implicated in the pathogenesis of serious metabolic disorders in infancy.

Deficient Lactase Activity

Among the disaccharidase deficiencies, diminished or absent, lactase activity is the most important. The congenital and probably hereditary type is rare in childhood, but the acquired type has been found associated with a large number of unrelated gastrointestinal disorders. Lactase seems to be by far the most sensitive of sugar-splitting enzymes in the brush-border of the small intestinal mucosa. Maybe because of its spatial localization it is both more easily damaged than the other disaccharidases, and takes longer to recover function if the injury is reversible.

Congenital alactasia (hypolactasia). The first observation of primary, congenital, and most likely hereditary, deficient lactose absorption in two sibs was made by Holzel, Schwarz, and Sutcliffe (1959), who introduced the lactose tolerance test as circumstantial evidence for lactase activity; following a lactose loading dose the rise of the blood glucose level was small compared with that after a glucose-galactose load. 18 cases have subsequently been recorded, of which 15 have been boys and 3 girls (Weijers, van de Kamer, Dicke, and Ijsseling, 1961; Holzel, 1962, 1965; Thornton, Burkinshaw, and Kawerau, 1962; Davidson, Sobel, Kugler, and Prader, 1964; Durand and La medica, 1962; Lifshitz, 1966; Launiala, Kuitunen, and Visakorpi, 1966).

Familial incidence and genetic factors. Three pairs of sibs were found with the condition, but there have been no cases with consanguineous parents.

Clinical picture. Diarrhoea, as in all the disaccharidase malabsorptions, is the main feature, and starts within a few days after birth as soon as milk feeding is well established. Since the lactose content of the food is the factor determining the severity of the alimentary tract manifestations, these are likely to be more severe in the infant at the breast or on cow’s milk formulae enriched with lactose. Deficient hydrolysis of the sugar leads to its retention in the gut and to an influx of large quantities of water to balance the increase in osmotic pressure.

Bacterial fermentation of the unabsorbed lactose produces appreciable quantities of short-chain fatty acids, which account for the low pH of the sour smelling, frothy, loose, or watery stools. Intestinal colics and extensive excoriation of the buttocks add to the clinical features to form a fairly characteristic picture.

Since the patients with primary lactase deficiency (hypolactasia or alactasia) are young infants, in only a few cases has the diagnosis been supported by estimation of β-galactosidase activity in peroral biopsy specimens of intestinal mucosa (Davidson et al., 1964; Lifshitz, 1966; Launiala et al., 1966).

Lactase deficiency in the adult. A syndrome not unlike that seen in young infants with deficient lactase activity was first described in adults by Haemmerli, Kistler, Ammann, Auricchio, and Prader (1963), Haemmerli, Kistler, Ammann, Marthaler, Semenza, Auricchio, and Prader (1965), and Auricchio, Rubino, Landolt, Semenza, and Prader (1963b). They recognized that lactose malabsorption was the basis of the clinical manifestations of milk intolerance previously diagnosed in a number of patients who, two hours after milk ingestion, developed abdominal colic, flatulence, and watery diarrhoea. Removal of lactose from the diet brought them rapid relief. Enzyme studies of intestinal biopsy specimens proved the absence of lactase activity in an otherwise morphologically normal mucosa. These observations have been confirmed by Cuatrecasas, Lockwood, and Caldwell (1965), Dunphy, Littman, Hammond, Forstner, Dahlqvist, and Crane (1965), Peternel (1965), and McMichael, Webb, and Dawson (1965).

It has been pointed out, however, that not all adults with deficient lactase activity had clinical manifestations when given lactose. Nor did its removal alleviate symptoms in other patients who despite normal lactase could not take milk without discomfort. Since signs of milk intolerance had not been evident during early childhood, it was postulated that the lactase-deficient patients had acquired the defect later in life. There are, however, few observations that would allow a rational interpretation of pathogenetic factors occurring in older children or adults. A large number of diseases of the alimentary tract have now
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have been found to be accompanied by reduced or impaired disaccharidase activity, but in general these have been associated with inflammatory or trophic changes in the intestinal mucosa, usually reversible with improvement of the primary condition. A decrease in lactase activity from birth to the end of the suckling period, and continuing to a low level in the adult, has been observed in various animals, i.e. the pig, calf, rabbit, and rat, and to some extent in the cat and dog. This, however, does not apply to the human species (see above), nor is there any support for the concept that feeding large amounts of lactose may lead to an increase of lactase activity, as reported in rats (Girardet, 1965; Cuatrecasas et al., 1965). Genetic aspects have therefore been scrutinized more closely and their significance stressed.

Racial factors. Of the 41 American Negroes studied by Cuatrecasas et al. (1965), 30 were lactose non-absorbers. This high incidence of lactase deficiency in the American Negro induced Cook and Kajubi (1966) to examine its tribal distribution in Uganda. They found lactase deficiency to be common in Baganda children and adults, and also among members of other Bantu tribes. Patients with Hamitic ancestry from Rwanda and Ankole had much higher levels of activity. Tribal cultures and habits may have been influenced by lactase levels, since the Hamites studied were cattle owners and lived mainly on milk, whereas the Baganda are an agricultural society who lived mainly on a vegetable diet. The incidence of lactase deficiency in the American Negro was further studied by Bayless and Rosenzweig (1966) with 40 healthy, well-nourished volunteers. 70% of the Negroes had low levels of activity, compared with 5% of the Caucasians. McMichael et al. (1965, 1966), referring to a personal communication by Moskoutis regarding the great frequency of lactase deficiency among Greeks, point out that 15 out of 17 Greek Cypriots living in London whose lactose tolerance was tested also had lactase deficiency. The experience of Jeejeebhoy, Desai, and Verghese (1964) with patients suffering from sprue indicates that deficient lactase activity is not uncommon in the Indian population, though this relates to special circumstances. Its occurrence as a post-gastrectomy complication transcends racial limits and has mainly been reported in Caucasians (Hoof, van Hauwaert, de Laey, and Adriaenssens, 1963; Plotkin and Isselbacher, 1964).

Familial lactose intolerance. Discussions of the published material on lactose malabsorption often make reference to a syndrome first described by Durand in 1958 under the title of ‘Lattosuria idiopathica in una paziente con diarrea cronica ed acidosi’. He published the biochemical data of the case in greater detail in 1959. The two papers contain the case history of a 13-month-old girl of consanguineous parents who had recurrent episodes of diarrhoea from the first few days of life, accompanied by a heavy lactosuria, minor degrees of proteinuria, renal acidosis, failure to thrive, and eventual death at the age of 15 months. Necropsy showed an atrophic enteritis with degenerative atrophic changes in adrenals, liver, and convoluted tubules in the kidney. Among other explanations Durand suggested the possibility of an intestinal lactase deficiency as the cause of the disease. Darling, Mortensen, and Søndergaard (1960) published records of two related infants suffering from diarrhoea, vomiting, and failure to thrive, associated with lactosuria and aminoaciduria, with death at a few weeks of age. Short periods of lactose-free diet had led to the disappearance of the mellituria, but did not seem to influence the course appreciably. A case of congenital lactose intolerance in a 2-year-old child with lactosuria, renal acidosis, increase in blood urea, vomiting, and failure to thrive, was recognized by Fois, Vedovini, and Marinello (1961): recovery followed a lactose-free regimen. Congenital lactosuria occurring as a familial fatal disease in 3 sibs (Jeune, Charrat, Cotte, Fournier, and Hermier, 1960) illustrates its gravity. A lactose-free diet ensured recovery in a number of cases (Fois et al., 1961; Inall and Burkinshaw, 1960; Holzel, Mereu, and Thomson, 1962).

It has been suggested that this disorder is a more severe form of deficient lactase activity and lactose malabsorption, but our studies lead to the view that congenital (familial) lactose intolerance is an entirely different clinical and pathological entity, with a separate pathogenesis, pathophysiology, and prognosis. There may be some similarity in symptomatology, since a temporary reduction of lactase activity may be part of some process interfering with the more general absorptive functions and an increased permeability of the small intestinal mucosa. The associated sucrosuria, glucosuria, and steatorrhoea are in keeping with such a view. The gastrointestinal manifestations are mainly vomiting and only to a lesser extent diarrhoea; renal involvement can be deduced from the presence of acidosis, aminoaciduria, mellituria, and a rise in blood urea. Haemorrhagic complications are not unusual in the untreated patient whose condition is precarious.

The disease is self-limiting, and tolerance for lactose may return 6-18 months after the onset.
Too early resumption of milk feeding may end in catastrophe.

The reasons for regarding 'familial lactose intolerance' as a separate entity are: (1) difference in clinical pattern; (2) the presence of lactosuria which is absent in even the severe forms of deficient lactase activity; (3) the satisfactory rise in blood glucose levels following lactose-loading doses during the active phase of the disease (Darling et al., 1960; Fois et al., 1961; Holzel et al., 1962); (4) the return to normal lactose absorption after brief periods of lactose-free diet, with exacerbation of lactose intolerance if lactose feeding continues; (5) the self-limiting nature of the disorder, hardly compatible with a hereditary enzyme defect; and (6) lactase activity demonstrated to be normal after recovery (Holzel, 1967).

**Primary Sucrase-Isomaltase Deficiency**

The description by Weijers et al. (1961) of a diarrhoeal disorder in children due to sucrose malabsorption was soon followed by others. Prader, Auricchio, and Mürset (1961), Delaître, Fonty, Varlet, and Fourrier (1961), Auricchio et al. (1961), Auricchio, Dahlqvist, Mürset, and Prader (1962), and Auricchio, Dahlqvist, Mürset, and Prader (1963a), Auricchio, Rubin, Prader, Rey, Jos, Frézal, and Davidson (1965b) demonstrated the simultaneous occurrence of isomaltase deficiency in their patients, and this was confirmed by investigators in different parts of the globe (Anderson, Messer, Townley, and Freeman, 1963; Rey, Frézal, Jos, Bauche, and Lamy, 1963; Burgess, Levin, Mahalanabis, and Tonge, 1964; Launila, Perheentupa, Visakorpi, and Hallman, 1964; Nordio and La medica, 1964; Sonntag, Brill, Troyer, Welsh, Semenza, and Prader, 1964; Townley, Khaw, and Shwachman, 1965; Semenza, Auricchio, Rubin, Prader, and Welsh, 1965b).

In recent reviews of the condition, the number of published cases has been given as 40 by Townley (1966), while Prader and Auricchio (1965) know of 63 cases, 34 male and 29 female, among them only 5 adults.

**Genetics.** The mode of inheritance has yet to be established. A dominant trait was initially suggested (Auricchio et al., 1961), but a recessive disorder seems probable, since there are at least 10 records of affected sibs and 2 of consanguineous parents (Prader and Auricchio, 1965). One of the difficulties in establishing the recessive nature of the condition is the recognition of the heterozygote. Kerry and Townley (1965) decided to use the quantitative assay of disaccharidase in small bowel biopsy specimens for the detection of the carrier of the abnormal gene. Four families, each with a child suffering from sucrose-isomaltose absorption, were submitted to peroral intestinal biopsies, and the values of the disaccharidase assay were compared with those obtained in a group of normal adults and children. All the parents of the affected children had intestinal sucrase and isomaltase levels below the average found in the control group. When the levels of the enzymes were expressed as ratios to lactose they differed significantly from the control group. The authors therefore concluded that sucrose-isomaltase deficiency was a recessively-transmitted disorder.

A special problem in this hereditary condition is the constant association of two enzyme defects. According to Dahlqvist (1962) the two activities are attributable to separate enzymes. To reconcile the available facts with the 'one gene one enzyme hypothesis', is somewhat puzzling. However, if it be assumed that one defective structural element may possess two active side chains for different substrates this would readily explain the data (Launila et al., 1964).

**Clinical features.** Diarrhoea, the most constant symptom in all the sugar malabsorption syndromes, follows the introduction of sucrose and starch into the infant's diet. In the breast-fed infant this is likely to be at a later date than in the bottle-fed one. Though many of the commercially prepared baby foods contain only lactose, starch is now being offered at an increasingly early age. The persistence of the fermentative diarrhoea is accompanied by a failure to thrive, which is never as marked as in the cases with lactase deficiency. Some patients manifest also minor degrees of steatorrhoea (Nordio, La medica, and Vignolo, 1961; Anderson et al., 1963; François, Frederich, Vicens-Calvet, Bertrand, and Ruutton-Uglieno, 1963; Rey et al., 1963; Gorouben, Bedu, Le balle, Grumbach, Yonger, Weill, and Kaplan, 1963; Burgess et al., 1964; Lifshitz and Holman, 1964). Spontaneous improvement has been known to occur (Auricchio et al., 1961), but in the vast majority of patients dietary adjustment, such as the replacement of sucrose and starch by glucose, is enough to bring about lasting improvement.

**Diagnosis of Disaccharidase Deficiencies**

This should be considered whenever there is a history of diarrhoea, with onset in early infancy. Marked malnutrition will only be encountered in the more severe forms and is more likely to be the result of lactase deficiency than of defective sucrase and isomaltase activity. The frothy appearance of the
stools and their sour smell may arouse the first suspicion of such a disorder.

Faecal pH. The faecal pH can be used as a screening test, but is not very reliable since it may also be lowered in infective forms of gastro-enteritis, and may occasionally be normal. In serial stool examination on several adult patients with hypolactasia, McMichael et al. (1965) found that the pH fluctuated, and that not even after lactose administration was a low value registered. Values were similar to those found in 14 control patients, and in no patient was a random pH of less than 5.7 recorded. However, in infants on cows' milk feeds the stool has a pH between 6.5 and 7.5, while in the fermentative diarrhoeas it is below 6 and sometimes closer to 5.

Lactic acid in faeces. Since the fall in pH is the result of the formation of large quantities of low molecular weight organic acids, the estimation of lactic acid has been recommended as a useful test. Lactic acid can be determined by enzymatic or chemical methods; a simple technique has been developed by Clarke and Podmore (1966).

Although increase in lactic acid excretion may occur in other forms of diarrhoea, and cannot therefore be regarded as specific, a healthy child on a normal diet rarely excretes more than 35 mg. lactic acid per 24 hours. By contrast, in a fermentative diarrhoea several grammes may be excreted in the course of 24 hours (Weijers and van de Kamer, 1964), and the finding of more than 50 mg. lactic acid in a random sample of 100 g. faeces can be taken to indicate excess fermentation.

Determination of the total content of low molecular weight volatile fatty acids (Weijers and van der Kamer, 1964) provides no more reliable evidence than the tests mentioned; no increase was found in lactase-deficient adults (McMichael et al., 1965).

Sugar-loading tests. If carried out in the absence of diarrhoea, these tests are extremely useful in the assessment of disaccharidase activity. The recommended dose of sugar administered orally is 2 g./kg. body weight or 50 g./m.2 body surface area. It makes little difference which of the two standards one accepts, provided it is maintained. It seems advisable to precede the test for a few days with a diet rich in carbohydrates. Since absorption is influenced by a variety of factors besides disaccharidase activity, as for instance the rate of gastric emptying, the standard use of a 10% solution of the required sugar is probably wise (Girardet, 1965).

In some adults slow gastric emptying may lead to a flat lactose tolerance curve, and Kern and Struthers (1966) found that in these cases the intraduodenal administration of 30 g. lactose in 300 ml. water in 30 minutes caused a normal rise of blood glucose. Peternel (1965), in evaluating the oral lactose tolerance test as a screening test, found a good correlation between an increase in blood glucose greater than 20 mg./100 ml. above the fasting level, with normal lactase activity. Girardet and Richterich (1962) failed to obtain a rise in glucose blood levels in some healthy adults after lactose loading, and this may occasionally happen. In our experience, lactose tolerance tests can be usefully employed if their results are reproducible. To a large measure, this applies also to other disaccharide loading tests, in particular to sucrose tolerance tests. An increase of blood glucose of more than 30 mg./100 ml. above fasting level at any point of the tolerance curve may be regarded as an indication of normal disaccharidase activity, values that do not exceed 20 mg. usually denoting impaired absorption. An increase of 20-30 mg./100 ml. above fasting level is of doubtful significance.

It is important to carry out control tests with the corresponding component monosaccharides mixed in equal parts to eliminate disturbances with similar symptomatology but different pathogenesis, such as the glucose-galactose malabsorption syndromes, or conditions associated with a gross general reduction of small intestinal absorptive capacity. Congenital monosaccharide malabsorption has not been reported in adults and the control tests have therefore less significance. Fat balance studies, xylose excretion, etc. have to be employed to exclude disaccharide deficiencies secondary to other causes of malabsorption (Anderson, 1966).

Sugar excretion in the urine. Excluding the minute quantities that occur physiologically, this is not raised in the primary disaccharidase deficiencies, but is present to an appreciable degree in lactose intolerance (see above). The faeces, however, may contain increased amounts of the disaccharide or, under special bacteriological conditions, also the monosaccharides. Chromatographic demonstration of the sugars in the faeces and urine may prove a valuable diagnostic aid. Application of the 'clini-test' to the liquid part of the motions was suggested as a helpful screening procedure in cases suspected of disaccharide malabsorption by Burke, Kerry, and Anderson (1965).

Radiological diagnosis. Recently an attempt has been made to exploit radiography in the recognition of sugar malabsorption, by utilizing a suspen-
sion of micropaque barium sulphate with 25 g. of lactose or other sugars, according to the suspected enzyme deficiency. Laws and Neale (1966) found characteristic changes: the small intestine appeared distended by dilute contrast medium; peristalsis was very active, the contrast medium reaching the transverse or descending colon within an hour; while the haustral pattern was strikingly prominent.

Quantitative biochemical assay of disaccharidases in peroral biopsy specimens of intestinal mucosa is regarded as the most reliable diagnostic means. The technique, difficulties, and limitations of peroral biopsy have been very fully discussed by Anderson (1966). Since only a tiny fraction of intestinal mucosa is examined, one may obtain entirely misleading information, particularly in disaccharidase deficiencies secondary to diseases of the small gut. In conditions where the proximal part is more heavily involved than the distal, one may be faced with the conflicting results of tolerance tests and enzyme assay, namely that disaccharide absorption may be taking place even in the seemingly complete absence of the sugar-splitting enzymes. Alternatively, a variety of agents may temporarily inhibit enzyme activity, but the resulting sugar malabsorption may be only one minor consequence of an underlying gross inflammatory process.

Prader and Auricchio (1965) give the following figures for the disaccharidase activities in the mucosa of the jejunum of the adult obtained by biopsy (Table II). The enzyme activity is expressed in units per g. protein; each unit splits one micromole substrate per minute.

**TABLE II**

**Disaccharide Activity in Jejunal Mucosa in Normal Adults (Prader and Auricchio, 1965)**

<table>
<thead>
<tr>
<th>Enzyme Activity (units/g. protein)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maltase</td>
<td>593</td>
<td>310-1120</td>
</tr>
<tr>
<td>Sucrase</td>
<td>173</td>
<td>70-325</td>
</tr>
<tr>
<td>Isomaltase</td>
<td>159</td>
<td>65-268</td>
</tr>
<tr>
<td>Lactase</td>
<td>107</td>
<td>39-258</td>
</tr>
<tr>
<td>Cellobiase</td>
<td>14</td>
<td>9-21</td>
</tr>
</tbody>
</table>

These authors also point out that though there is great variation in the absolute values of disaccharidase activity, the ratios between the various enzymes are constant with the exception of lactase activity. Maltase activity is three to four times higher than sucrase or isomaltase, and the latter about three to four times higher than lactase activity. Burke et al. (1965) gave the normal range of disaccharidase activity in jejunal mucosa in children (Table III).

**TABLE III**

**Disaccharide Activity (units/g. protein) in Jejunal Mucosa in Normal Children (Burke et al., 1965)**

<table>
<thead>
<tr>
<th>Enzyme Activity (units/g. protein)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactase</td>
<td>14-132</td>
<td>49-83</td>
</tr>
<tr>
<td>Sucrase</td>
<td>32-228</td>
<td>95-199</td>
</tr>
<tr>
<td>Isomaltase</td>
<td>31-177</td>
<td>89-187</td>
</tr>
<tr>
<td>Maltase</td>
<td>83-615</td>
<td>200-300</td>
</tr>
</tbody>
</table>

Burgess et al. (1964) expressed the unit of enzyme activity as equal to the hydrolysis in μmol of substrate/g. wet mucosa per minute; the values obtained in normal children are given in Table IV. Choosing the same standard, Holzel (1966) found the values ranging for lactase, 5-12; for maltase, 34-70; and for sucrase, 7-21. Recently Messer and Dahlqvist (1966) described a one-step ultramicro method for the assay of intestinal disaccharidases, which is more suitable for the small quantities of mucosa removed by peroral biopsy than the two-step method originally developed by Dahlqvist (1964a, b).

**TABLE IV**

**Disaccharide Activity (units/g. wet mucosa per minute) in Jejunal Mucosa in Normal Children (Burgess et al., 1964)**

<table>
<thead>
<tr>
<th>Enzyme Activity (units/g. protein)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactase</td>
<td>7-12</td>
<td>43-90</td>
</tr>
<tr>
<td>Maltase</td>
<td>12-20</td>
<td>17-4</td>
</tr>
</tbody>
</table>

**Acquired Disaccharide Malabsorption**

With the knowledge that the disaccharidases were located in the exposed position of the brush-border of the mucosal epithelium, intensive investigation of all those disorders associated with structural changes of the intestinal mucosa for sugar malabsorption has revealed a large number of secondary disaccharidase deficiencies, both in children and adults. Lactase was far more commonly deficient than other disaccharidases, particularly amongst adults. In children, reduced or absent activity related often to two or even three of the hydrolytic enzymes.

Secondary lactase deficiency in adults (Haemmerli et al., 1965) has been encountered following gastrojejunoostomy (Gryboski, Thayer, Gryboski, Gabrielson, and Spiro, 1963), bowel resection (Kern, Struthers, and Attwood, 1963), and various other affections of the gut. Combined disaccharidase deficiencies were common in coeliac disease of the adult (Plotkin and Isselbacher, 1964). In children,
the most striking form of deficient disaccharidase activity is associated with gluten-induced enteropathy (Holzel, 1964; Shmerling, Auricchio, Rubino, Hadorn, and Prader, 1964; Nordio, La medica, Vignolo, and Berio, 1965; Arthur, Clayton, Cottom, Seakins, and Platt, 1966; Lubos, Gerrard, and Buchan, 1967). Our studies and those of other workers agree on the fact that during the florid phase of the illness, when the surface structures of the small intestinal mucosa are considerably disorganized, disaccharide absorption is grossly impaired. Lactose tolerance is much more reduced than that of other disaccharides, and malabsorption of this sugar persists for much longer than that of the other common disaccharides. Patients with inadequate dietary control, and in relative well-being though with some delay in growth, have been able to absorb glucose at a normal rate but have shown flat disaccharide tolerance curves. It seems, therefore, that disaccharide loading tests can be used as a further tool in the assessment of absorptive recovery.

The occurrence of crises has in some of our coeliac patients been related to an increased intake of lactose. In one patient, enzyme assay of the intestinal mucosa specimen showed almost complete absence of lactase activity. A lactose- and gluten-free diet led to elimination of the crises and uninterrupted progress towards recovery. The routine imposition of lactose-, sucrose- and gluten-free diets (Arthur et al., 1966) on every child with coeliac disease may place an unnecessarily heavy burden on hospital and home, but where a gluten-free diet alone does not achieve the desired result, removal of the disaccharides may hasten recovery. The disacchariduria in these patients (Arthur et al., 1966) is more likely an expression of the severity of mucosal damage than an index of disaccharide intolerance (Prader, Shmerling, and Hadorn, 1966).

**Giardiasis.** Lactose malabsorption in heavy infestation with *Giardia intestinalis* has been recorded by Durand (1964), Nordio, La medica, and Vignolo (1963), and Holzel (1967). Depression of lactase activity may occur as an isolated phenomenon, or as part of the more general reduction of disaccharide activity. Mucosal biopsy in our cases showed only minor degrees of inflammatory reaction with no major alteration in the mucosal pattern. Eradication of the infection was followed by very slow recovery of enzyme function.

**Gastro-enteritis.** Intolerance to milk following infective forms of gastro-enteritis was known to the paediatricians of the early decades of this century, but the protein and fat constituents were then regarded as causing the damage. Sunshine and Kretchmer (1964) and Burke et al. (1965) produced laboratory evidence that dietary lactose was the noxious factor in the persistent diarrhoea in these cases.

**Monosaccharide Malabsorption**

It is not unknown for the same important scientific observation to be made by independent scientific workers at the same time in different parts of the world. Preoccupation with similar topics of research is a common feature in the Western nations and probably more the result of modern means of communication than of the influence of a *genius mundi*.

It is nevertheless interesting to record that Lindquist, Meeuwisse, and Melin (1962) and Lindquist and Meeuwisse (1962) in Sweden recognized a new disorder of monosaccharide malabsorption more or less simultaneously with the French authors, Laplane, Polonovsky, Etienne, Debray, Lods, and Pissarro (1962). It was rightly named glucose-galactose malabsorption by Lindquist and his colleagues, who realized that basically it was probably due to some major disturbance of the absorptive mechanism, and they, as well as the French workers, assumed a congenital disturbance of the active transfer mechanism. Since then further cases have been published in Germany (Linnwehr, Schaumloffel, and Barthelmai, 1965), Australia (Anderson, Kerry, and Townley, 1965), U.S.A. (Schneider, Kinter, and Stirling, 1966; Marks, Norton, and Fordtran, 1966), and Belgium (Eggermont and Loeb, 1966). At least 11 well-documented cases prove the wide distribution of this inborn error of metabolism; familiarity with its clinical manifestation will in due course lead to a true assessment of its incidence.
Clinical picture. There is severe watery diarrhoea starting in the first week of life, leading to rapid and life-threatening dehydration. The faeces contain large quantities of sugars and lactic acid; the urine may also contain reducing substances in small amounts. The gravity of the condition varies; it may cause death in the untreated, or if less severe may produce a severe marasmus accompanied by chronic diarrhoea. The most telling feature is probably the almost instantaneous cessation of the explosive diarrhoea when oral feeds are stopped, only to start again if foods containing monosaccharides other than fructose or disaccharides are given, which by hydrolysis lead to the breakdown to monosaccharides. Familial incidence was observed by Lindquist et al. (1962), Laplane et al. (1962), and Anderson et al. (1965). Routine laboratory investigations of the faeces for pathogens are generally unhelpful. Slight steatorrhoea was observed in one patient only. A glucose or galactose loading test did not produce an adequate rise in blood glucose levels, in contrast to fructose which caused an increase of both glucose and fructose in the blood. Dehydration was associated with disturbances of electrolyte and nitrogen balance. Peroral biopsy specimen showed normal disaccharidase activity, and seemed structurally normal.

In view of the tolerance for fructose, with its different mode of absorption, it was a fair assumption that the active carrier system might be at fault, and a good deal of evidence has been brought forward in its support. Loading tests with 3-0-methylglucose (Anderson et al., 1965), a synthetic sugar with the requisite configuration for active transport, showed failure of absorption. The application of autoradiography to fresh specimens of intestinal mucosa with 14C-labelled galactose in a special medium, demonstrated the inability of the cells of the patient's mucosa to accumulate the galactose, while the uptake succeeded in the control specimen. Eggermont and Loeb (1966) tried to prove that glucose-galactose malabsorption was the result of a derangement of the sodium-dependent active transport. Meeuwisse and Dahlqvist (1966) obtained intestinal biopsy specimens from 2 patients with this disorder. The mucosa appeared normal on light microscopy. On incubation of the specimens with 14C-labelled glucose there was no greater accumulation of the sugar in the tissue than in the medium, while in control experiments glucose in the mucosa was 4 times as high as that in the medium. They are also of the opinion that the defect is in the glucose-galactose specific carrier.

In a special study with 14C-labelled sugars, Linneweh, Schaumlöffel, Graul, and Bode (1966) succeeded in determining the residual enzyme activity in their patient with monosaccharide malabsorption; it was 7·6% for glucose and 4·6% for galactose. Dietary treatment can be successfully carried out with a formula consisting of casein, corn oil, and fructose, with adequate vitamin complements. A rather ill-defined form of monosaccharide malabsorption of a transitory nature in young infants has recently been reported from Australia (Burke and Danks, 1966). Although these babies were thoroughly investigated, the results did not allow any aetiological or pathogenetic conclusions.

The rapidly expanding knowledge of the enzymatic mechanism involved in sugar absorption and its disturbances has by no means reached its limits, and no doubt further development will add to a better understanding of the physiological processes involved.

References


Sugar Malabsorption


