Review article

Archives of Disease in Childhood, 1973, **48**, 331.

Sugar-induced diarrhoea in children

MICHAEL GRACEY* and VALERIE BURKE

From the Gastroenterological Research Unit, Princess Margaret Children's Medical Research Foundation, Perth, Western Australia

In recent years there has been a proliferation of knowledge about normal and abnormal digestion and absorption of carbohydrates. Many of these advances have been made since Anderson's comments about sugar intolerance in her review of intestinal malabsorption in childhood published in this journal in 1966, and since Holzel's review of the problem in 1967. This review is not intended as a comprehensive survey of the vast literature on this topic, but is an attempt to summarize current knowledge of disorders of carbohydrate digestion and absorption in children. Practical rather than theoretical aspects will be emphasized. Application of this knowledge promises to be of great benefit to children throughout the world because these disorders are common and potentially lethal, but eminently treatable.

Carbohydrates are of universal dietary importance since they supply about one-half of man's caloric needs. In poorer communities they constitute an even larger proportion of the diet. The major dietary carbohydrates, starch, lactose, and sucrose, are consumed in varying proportions according to custom and age. Lactose is, of course, relatively more important in infants and young children.

In health, starch is hydrolysed in the lumen of the gut by amylases to maltose (a disaccharide), maltotriose (a trisaccharide), and limit dextrins (oligosaccharides). As pointed out by Gray (1970) this is contrary to the still widely held notion that disaccharides and monosaccharides are the final products of the hydrolysis of starch. The hydrolytic products of starch digestion are then presented to the small intestinal epithelium where mucosal disaccharidases split them further to the monosaccharides glucose, galactose, and fructose. Glucose and galactose are then transported through the epithelial cell by an energy- and sodium-dependent active transport process. This has been reviewed by Crane (1968). It has been

shown recently that the intestinal transport of fructose is also an active process, but probably separate from that used by the other important dietary monosaccharides (Gracey, Burke, and Oshin, 1972).

Types of carbohydrate malabsorption

Breakdown of starch is rapid even where amylase deficiency exists in pancreatic insufficiency and no definite clinical syndrome of carbohydrate malabsorption due to amylase deficiency is recognized. On the other hand, symptoms may occur when intestinal disaccharidase activity is deficient or monosaccharide transport is impaired. Several clinical syndromes of sugar malabsorption in childhood have now been identified. These are classified in the Table.

TABLE

Types of carbohydrate malabsorption in children

Type	Reduced disaccharidase activity	Impaired monosaccharide transport
Primary	Sucrase-isomaltase deficiency Lactase deficiency	Glucose-galactose malabsorption
Secondary	Lactase deficiency Lactase deficiency with deficiency of other disaccharidases	Temporary monosaccharide malabsorption

Symptoms of sugar intolerance

The predominant symptom of sugar intolerance in children is diarrhoea which may be very severe and life-threatening in infants and young children. Diarrhoea results from the osmotic attraction of large volumes of water to the undigested or malabsorbed sugar within the lumen of the small bowel (Torres-Pinedo, Rivera, and Fernandez, 1966). Acid metabolites produced in the large bowel by

*Adolph Basser Research Fellow of the Royal Australasian College of Physicians.

bacterial fermentation contribute to diarrhoea by further increasing osmolarity and reducing pH, thereby impairing the colonic absorption of water (Christopher and Bayless, 1971). Bacterial activity in the large bowel also produces CO₂, so that these patients characteristically pass large amounts of flatus and frequent fluid stools of low pH.

Diarrhoea is often so profuse that the stools contain no recognizable solid material and become rapidly soaked into the infant's napkin and are mistaken for urine. When occurring in a newborn baby, the diagnosis of rectovesical fistula may even be entertained (Meeuwisse and Melin, 1969). Sugar malabsorption should be suspected in any acutely ill and dehydrated child; digital examination of the rectum in such circumstances will cause the passage of fluid stool containing excessive amounts of sugar and so allow the diagnosis to be made. In older children the clinical pattern resembles that in adults where bloating, flatulence, and abdominal cramps are more usual and severe diarrhoea is rare.

Diagnosis. The diagnosis of sugar intolerance in childhood is relatively simple. A careful assessment of the symptoms and the dietary history should raise the suspicion of sugar-induced diarrhoea which can then be documented as discussed below.

The Clinitest* method (Kerry and Anderson, 1964) is simple and reliable if done adequately, and estimates the amount of reducing substances in the stool. Normally, there are only traces of sugar in the stools of infants and children, and more than 0.5% is excessive. This method has the advantage of being convenient and is appropriate for immediate testing of the stools in the ward, consulting room, or even under field conditions. However, it must be stressed that the fluid part of the stool must be collected for testing and that the test be performed promptly to prevent bacterial degradation of carbohydrate present. Sucrose is not a reducing substance and will not be detected by this method; prior hydrolysis of the specimen with HCl is necessary if sucrose malabsorption is suspected. Adults with proven disaccharidase deficiency excrete only very small amounts of sugar in their stools (McMichael, Webb, and Dawson, 1965) so the Clinitest method is not reliable in such patients.

The total amount of reducing substances in the stool can be estimated and the individual sugars excreted in the stools can be identified by paper chromatography, but this information is not essential for adequate diagnosis and management.

Similarly, quantitative assay of stool lactic acid excretion is unnecessary.

Other tests of intestinal sugar absorption are available. These are used widely in adults but are not generally needed in children. They should be of benefit if the diagnosis of sugar intolerance is in doubt or if a congenital form of malabsorption implying long-term treatment is suspected. They are more appropriate to the investigation of older children.

Sugar tolerance tests may be useful in older patients when sugar intolerance is suspected but diarrhoea is not present at the time. Serial blood glucose levels are estimated after a loading dose of 1 to 2 g/kg of the suspected sugar and, normally, a rise of 30 mg/100 ml occurs within 2 hours. Abdominal symptoms and, in young patients, the subsequent passage of fluid, sugar-containing stools occur if clinically significant sugar intolerance exists. The response to different sugars may help distinguish different forms of sugar intolerance, for example a normal response to fructose but impaired responses to glucose and galactose in patients with glucose-galactose malabsorption.

The barium-lactose meal has been adapted for use in children by adjusting the dose of barium and lactose given according to the patient's age and weight (McNeish and Sweet, 1968). The rapid passage of the dye through abnormally dilated loops of small bowel correlates with other evidence of sugar intolerance. This method may be helpful in older patients but is rarely necessary in infants and small children.

Direct estimation of mucosal enzyme activity is rarely indicated in the diagnosis of sugar intolerance in children. Secondary lactase deficiency is by far the commonest type seen, and its clinical and pathological features are now firmly established (see below). Consequently, a confident diagnosis can usually now be made on the clinical features, the demonstration of excessive amounts of reducing substances in the stools by the Clinitest method, and the subsequent prompt response to removal of lactose from the diet. Not only is biopsy and enzyme assay unnecessary in such patients, but it exposes them to unjustifiable risks. Furthermore, the mere demonstration of depressed enzyme activity in a tiny piece of mucosa from the upper gut does not necessarily mean *sugar intolerance*, a clinical concept implying the production of symptoms after ingestion of the offending sugar (Townley, 1966). These remarks apply particularly to disorders such as coeliac disease where the morphological changes are known to be most marked in the proximal intestine (Rubin *et al.*, 1960). Disacchari-

*Clinitest, Ames Company, U.S.A.

dase assays should be reserved for cases in which the diagnosis is causing doubt and concern or where a life-long congenital disorder such as sucrase-isomaltase deficiency is suspected.

Tests of sugar uptake by biopsy specimens of small bowel tissue are, at present, appropriate for research rather than routine diagnosis. They have been used to show impaired uptake of glucose and galactose in glucose-galactose malabsorption (Elsas *et al.*, 1970) and may eventually be applied more widely for diagnostic purposes.

The ultimate test for the diagnosis of sugar intolerance is the clinical response to removal of the suspected sugar from the diet. If the diagnosis is correct there will be a prompt improvement in the symptoms and the nature of the stools passed, followed by a rapid weight gain; if not, the diagnosis should be reconsidered.

Treatment

In all types of sugar-induced diarrhoea the treatment depends on removal of the offending sugar from the diet. Long-term dietary restriction is needed in the congenital forms of sugar intolerance, while exclusion of the sugar for a temporary but variable time is indicated in secondary sugar intolerance. This will be considered in discussion of the individual types.

The secondary types of sugar-induced diarrhoea are far more frequent than the primary forms and so will be discussed first.

Secondary disaccharidase deficiency. The disaccharidases are found in the brush border lining the luminal surface of the intestinal epithelium (Miller and Crane, 1961) and therefore are liable to be affected in any disorder in which the intestinal mucosa is damaged. Examples of this include gastroenteritis, coeliac disease, parasitic infestations, and protein-calorie malnutrition. Because lactase is the last enzyme to reach mature levels during fetal development (Sunshine and Kretschmer, 1964), prematurity is an important predisposing factor, making the risk of lactase deficiency high in outbreaks of diarrhoea in nurseries for the newborn. Normally, lactase is present in lower concentrations than the other brush border disaccharidases (Dahlqvist, 1964); it is also the last to recover completely after mucosal damage (Plotkin and Isselbacher, 1964). Consequently, lactase deficiency is the most important type of secondary disaccharidase deficiency. Sucrase deficiency of clinical importance may occur simultaneously but never exists as an isolated, secondary phenomenon.

In our experience, the commonest situation in which secondary lactase deficiency occurs is in infants and toddlers after gastroenteritis. During recovery from the initial illness the patient develops watery diarrhoea which is often yellowish and frothy when normal lactose-containing feeds are being introduced. The stools are acid and contain excessive amounts of reducing substances. The substitution of a lactose-free feed* will result in marked improvement in the stools over the next 24 hours and a rapid weight gain (Fig.). However,

FIG.—Weight chart of an Australian aboriginal infant with secondary lactase deficiency, showing rapid response to a lactose-free diet.

a complete recovery of lactase activity and the ability to tolerate dietary lactose may take some weeks or months to occur. Relapses after the reintroduction of lactose into the diet over this time should, therefore, be managed by further exclusion of dietary lactose. It must be borne in mind, of course, that patients with cow's milk protein allergy will respond in the same way since lactose-free diets are usually free of milk-protein as well. These patients can be differentiated by their responses to separate milk protein fractions and lactose (Freier and Kletter, 1972).

Temporary histological changes and generalized depression of disaccharidase activity occur in secondary lactose intolerance, but these are not specific and are not needed to reach the diagnosis. The current fashion for early introduction of solids into the infant's diet in our community has led to earlier presentation of coeliac disease with watery stools and secondary lactose intolerance (Anderson,

*E.g. Nutramigen, Mead Johnson; Galactomin, Trufood; Low Lactose Milk Food, Cow and Gate.

Gracey, and Burke, 1972). This can be difficult to distinguish from the pattern of lactose intolerance secondary to gastroenteritis, and the nonspecific nature of the histological changes limits the value of biopsy in this situation. Occasionally, the use of a combined sugar- and gluten-free diet for some months is indicated in these patients before the definitive diagnosis can be made.

Secondary disaccharidase deficiency is not uncommon in infants after surgery on the gastrointestinal tract, particularly after the relief of large bowel obstruction in the neonatal period (Burke and Anderson, 1966). This should be suspected in patients with poor weight gain after operation, particularly if continued leakage of fluid from the stoma leads to excoriation of the surrounding skin. An important point to appreciate in management is that intolerance to both lactose and sucrose is common in these patients.

Lactase deficiency is common in children of poorer communities. There is evidence suggesting that genetic factors are important in its high incidence in certain ethnic groups, such as Ugandans (Cook and Kajubi, 1966) and Orientals (Chung and McGill, 1968). However, environmental factors, particularly malnutrition and repeated intestinal infections and infestations, are also important in these communities; and our own observations (unpublished) indicate that lactase deficiency in young Australian aborigines is often temporary, in contrast to previous opinion that it was probably a racial trait (Maxwell and Elliott, 1969; Alpers and Isselbacher, 1970). The alternative possibility remains, of course, that populations such as these tend to have decreasing lactase levels with increasing age and this tendency is hastened by malnutrition, parasitic infestations, and infectious diarrhoea.

Temporary monosaccharide malabsorption.

This has been recognized only recently (Burke and Danks, 1966) but has subsequently been seen in various countries and is probably not uncommon. It appears to occur in three main groups: after gastroenteritis in infants (Burke and Danks, 1966), after operations on the upper small bowel in infants (Burke and Anderson, 1966), and in malnourished infants and children (Lifshitz, Coello-Ramirez, and Gutierrez-Topete, 1970; Walker and Harry, 1972). These patients are often desperately ill and the prognosis is grave unless the diagnosis is made promptly and effective therapy begun without delay.

The clinical features resemble those of secondary disaccharidase deficiency. The main symptom is

diarrhoea which often develops when a lactose-containing formula is introduced after an episode of gastroenteritis. Unlike patients with disaccharidase deficiency, however, diarrhoea containing excessive amounts of sugar will continue if a disaccharide-free formula containing monosaccharides is then used, because these patients are unable to absorb any carbohydrates including the simple sugars, glucose, galactose, and fructose. The diagnosis should be suspected in any child or infant with severe diarrhoea, even before a disaccharide-free diet has been tried. Metabolic acidosis is another feature of the clinical picture (Burke and Danks, 1966), and hypoglycaemia is a frequent and potentially lethal complication in malnourished patients with temporary monosaccharide malabsorption (Lifshitz *et al.*, 1970).

Intravenous feeding is usually needed initially to correct dehydration and electrolyte disturbances. Completely carbohydrate-free feeds* can be started when the patient's condition permits. A combination of 2.5% casein and 3.4% butter fat emulsified with bile salts and with added vitamins has been used with success (Burke and Danks, 1966). Further dietary information is given by Harries and Francis (1968). Diluted cow's milk can usually be introduced gradually into the diet. Recovery may occur within a couple of weeks but may take several months.

The pathogenesis of this condition is not fully understood. Burke and Danks (1966) showed that damage to the small bowel epithelium was not responsible and that disaccharidase activity was normal. An overgrowth of bacteria in the proximal small bowel has been reported from recent studies (Gracey, Burke, and Anderson, 1969; Lifshitz *et al.*, 1970). It seems likely that the deconjugation of bile salts by organisms not normally resident in the lumen of the gut produces interference with intestinal transport of monosaccharides (Gracey *et al.*, 1971). In malnourished children with this disorder, it is probable that multiple, interrelated factors are operative.

Primary disaccharide deficiency.

Sucrase-isomaltase deficiency. This is a rare, congenital disorder transmitted as an autosomal recessive (Kerry and Townley, 1965) in which there is a life-long deficiency of sucrase. Symptoms appear only after introduction of cane sugar into the diet, usually at the age of 2 to 3 months.

The clinical features depend on the age of the patient, the amount of cane sugar in the diet, and

*E.g. CHO-free, Borden, U.S.A.; CF1, Nestle, Australia.

whether the patient is homozygous or heterozygous for the condition. Diarrhoea is most severe in homozygotes under the age of 6 months who have a formula sweetened with cane sugar. Diarrhoea is usually mild in adults and older children, and complaints of bloating and abdominal discomfort are common. Presentation may occasionally be delayed beyond adolescence (Neale, Clark, and Levin, 1965). Diarrhoea is rare in heterozygotes after infancy unless very large amounts of sucrose are ingested.

The patient may often be suspected of having secondary disaccharidase deficiency and will, of course, respond to the removal of all disaccharides from the diet. Diarrhoea will recur, however, when dietary sucrose is reintroduced but lactose will be tolerated without difficulty. A carefully taken dietary and clinical history should alert one to the diagnosis; the family history may also be helpful. In older children the diagnosis may be more elusive as the diarrhoea is not so severe and the clinical features may be more suggestive of coeliac disease; mild steatorrhoea sometimes occurs.

This condition requires prolonged dietary management and the diagnosis must be clinched by means of quantitative small intestinal disaccharidase assay. There is depression of sucrase and isomaltase activities with some depression of maltase levels. The mucosa is histologically normal.

Sucrose must be removed from the diet for at least the first year of life. However, variable amounts can be tolerated in later life and patients usually adjust their intake according to the production of symptoms.

Congenital lactase deficiency. While lactase deficiency in the adult is very common, particularly in certain racial groups such as Orientals (Chung and McGill, 1968), congenital lactase deficiency appears to be rare. There is considerable controversy about the pathogenesis of the adult form (Kretchmer, 1971; Neale, 1971; Rosensweig, 1971), but it is clear that this disorder appears some time after weaning. On the other hand, congenital deficiency of the enzyme implies a permanent condition, present from birth.

In the late 1950s there were several reports of diarrhoea in infants after starting milk feeds due to malabsorption of lactose. Primary lactase deficiency was presumed in these cases (Holzel, Schwarz, and Sutcliffe, 1959) but these early studies lacked the advantage of serial disaccharidase assays. Some reports in the 1960s were suggestive of lactase deficiency from birth, but they did not absolutely exclude prolonged, secondary lactase

deficiency which we now know is relatively common. A recent report (Levin *et al.*, 1970) has at last documented, without any real doubt, the diagnosis of congenital lactase deficiency in an infant first investigated at the age of 3 days and then observed for longer than 2 years. These authors illustrate the difficulties involved in adequate documentation of this rare disorder.

Congenital monosaccharide malabsorption.

Glucose-galactose malabsorption. This is a very rare autosomal recessive hereditary disorder in which there is an inability to tolerate the dietary monosaccharides, glucose and galactose (Laplane *et al.*, 1962; Lindquist, Meeuwisse, and Melin, 1962). The defect involves the intestinal transport of these sugars, while the transport of other small molecules including fructose, amino acids, and electrolytes appears normal. Renal tubular reabsorption of glucose is also slightly defective so glycosuria may occur (Meeuwisse, 1970).

Patients develop diarrhoea within a few days of birth and rapidly become dehydrated. These patients have impaired blood glucose responses after oral loads of glucose, galactose, or lactose. They are, therefore, different from patients with isolated lactase deficiency who are able to tolerate glucose and galactose but not the disaccharide, lactose. In infants, the abnormal blood glucose response to glucose or galactose will be accompanied by the production of fluid diarrhoea with excessive amounts of sugar in the stools. When fructose is used as the sole dietary source of carbohydrate, the diarrhoea ceases abruptly. This confirms the diagnosis and, of course, distinguishes it from the secondary form of monosaccharide malabsorption mentioned earlier where all dietary sugars, including fructose, cannot be absorbed. Small intestinal histology and disaccharidase activity are normal, but this information is not needed to make an accurate diagnosis in infancy. If available, substrate transport studies (Elsas *et al.*, 1970) will show impaired uptake of glucose and galactose by biopsy specimens of small bowel, while the uptake of fructose, which is transported by a different transport pathway (Gracey *et al.*, 1972), is normal.

The defect in glucose-galactose malabsorption is permanent and necessitates long-term dietary restriction. Infants require a feeding formula in which fructose is the only source of carbohydrate.* The prognosis is good if the correct diagnosis is made and treatment begun early.

*E.g. Galactomin 19, Trufood.

As these patients grow up, their tolerance for dietary carbohydrates improves so that older children and adults are able to include amounts of milk, sugar, and starch in their diet depending on the severity of the symptoms produced.

REFERENCES

- Alpers, D. H., and Isselbacher, K. J. (1970). Disaccharidase deficiency. In *Advances in Metabolic Disorders*, Vol. 4, p. 75. Ed. by R. Levine. Academic Press, New York.
- Anderson, C. M. (1966). Intestinal malabsorption in childhood. *Archives of Disease in Childhood*, **41**, 571.
- Anderson, C. M., Gracey, M., and Burke, V. (1972). Coeliac disease. Some still controversial aspects. *Archives of Disease in Childhood*, **47**, 292.
- Burke, V., and Anderson, C. M. (1966). Sugar intolerance as a cause of protracted diarrhoea following surgery of the gastrointestinal tract in neonates. *Australian Paediatric Journal*, **2**, 219.
- Burke, V., and Danks, D. M. (1966). Monosaccharide malabsorption in young infants. *Lancet*, **1**, 1177.
- Christopher, N. L., and Bayless, T. M. (1971). Role of the small bowel and colon in lactose-induced diarrhea. *Gastroenterology*, **60**, 845.
- Chung, M. H., and McGill, D. B. (1968). Lactase deficiency in Orientals. *Gastroenterology*, **54**, 225.
- Cook, G. C., and Kajubi, S. K. (1966). Tribal incidence of lactase deficiency in Uganda. *Lancet*, **1**, 725.
- Crane, R. K. (1968). Absorption of sugars. In *Handbook of Physiology, Section 6, Alimentary Canal, Volume III. Intestinal Absorption*, p. 1323. Ed. by C. F. Code. American Physiological Society, Washington D.C.
- Dahlqvist, A. (1964). Method for assay of intestinal disaccharidases. *Analytical Biochemistry*, **7**, 18.
- Elsas, L. J., Hillman, R. E., Patterson, J. H., and Rosenberg, L. E. (1970). Renal and intestinal hexose transport in familial glucose-galactose malabsorption. *Journal of Clinical Investigation*, **49**, 576.
- Freier, S., and Kletter, B. (1972). Clinical and immunological aspects of milk protein intolerance. *Australian Paediatric Journal*, **8**, 140.
- Gracey, M., Burke, V., and Anderson, C. M. (1969). Association of monosaccharide malabsorption with abnormal small-intestinal flora. *Lancet*, **2**, 384.
- Gracey, M., Burke, V., and Oshin, A. (1972). Active intestinal transport of D-fructose. *Biochimica et Biophysica Acta*, **286**, 397.
- Gracey, M., Burke, V., Oshin, A., Barker, J., and Glasgow, E. F. (1971). Bacteria, bile salts, and intestinal monosaccharide malabsorption. *Gut*, **12**, 683.
- Gray, G. M., (1970). Carbohydrate digestion and absorption. *Gastroenterology*, **58**, 96.
- Harries, J. T., and Francis, D. E. M. (1968). Temporary monosaccharide intolerance. *Acta Paediatrica Scandinavica*, **57**, 505.
- Holzel, A. (1967). Sugar malabsorption due to deficiencies of disaccharidase activities and of monosaccharide transport. *Archives of Disease in Childhood*, **42**, 341.
- Holzel, A., Schwarz, V., and Sutcliffe, K. W. (1959). Defective lactose absorption causing malnutrition in infancy. *Lancet*, **1**, 1126.
- Kerry, K. R., and Anderson, C. M. (1964). A ward test for sugar in faeces. *Lancet*, **1**, 981.
- Kerry, K. R., and Townley, R. R. W. (1965). Genetic aspects of intestinal sucrase-isomaltase deficiency. *Australian Paediatric Journal*, **1**, 223.
- Kretchmer, N. (1971). Lactose and lactase—a histological perspective. *Gastroenterology*, **61**, 805.
- Laplane, R., Polonovski, C., Etienne, M., Debray, P., Lods, J. C., and Pissarro, B. (1962). L'intolérance aux sucres à transfert intestinal actif. Ses rapports avec l'intolérance au lactose et le syndrome coeliaque. *Archives Françaises de Pédiatrie*, **19**, 895.
- Levin, B., Abraham, J. M., Burgess, E. A., and Wallis, P. G. (1970). Congenital lactose malabsorption. *Archives of Disease in Childhood*, **45**, 173.
- Lifshitz, F., Coello-Ramirez, P., and Gutierrez-Topete, G. (1970). Monosaccharide intolerance and hypoglycemia in infants with diarrhea. I. Clinical course of 23 infants. *Journal of Pediatrics*, **77**, 595.
- Lindquist, B., Meeuwisse, G., and Melin, K. (1962). Glucose-galactose malabsorption. *Lancet*, **2**, 666.
- McMichael, H. B., Webb, J., and Dawson, A. M. (1965). Lactase deficiency in adults. A cause of 'functional' diarrhoea. *Lancet*, **1**, 717.
- McNeish, A. S., and Sweet, E. M. (1968). Lactose intolerance in childhood coeliac disease. Assessment of its incidence and importance. *Archives of Disease in Childhood*, **43**, 433.
- Maxwell, G. M., and Elliott, R. B. (1969). The nutritional state of Australian Aboriginal children. *American Journal of Clinical Nutrition*, **22**, 716.
- Meeuwisse, G. W. (1970). Glucose-galactose malabsorption. Studies on renal glucosuria. *Helvetica Paediatrica Acta*, **25**, 13.
- Meeuwisse, G. W., and Melin, K. (1969). Studies in glucose-galactose malabsorption. A clinical study of 6 cases and a genetic study. *Acta Paediatrica Scandinavica*, **58**, Suppl. 188, 1.
- Miller, D., and Crane, R. K. (1961). The digestive function of the epithelium of the small intestine. II. Localization of disaccharide hydrolysis in the isolated brush border portion of intestinal epithelial cells. *Biochimica et Biophysica Acta*, **52**, 293.
- Neale, G. (1971). Disaccharidase deficiencies. *Journal of Clinical Pathology*, **24**, Suppl. (Royal College of Pathologists) 5, 22.
- Neale, G., Clark, M., and Levin, B. (1965). Intestinal sucrase deficiency presenting as sucrose intolerance in adult life. *British Medical Journal*, **2**, 1223.
- Plotkin, G. R., and Isselbacher, K. J. (1964). Secondary disaccharidase deficiency in adult celiac disease (nontropical sprue) and other malabsorption states. *New England Journal of Medicine*, **271**, 1033.
- Rosensweig, N. S. (1971). Adult lactase deficiency: genetic control or adaptive response? *Gastroenterology*, **60**, 464.
- Rubin, C. E., Brandborg, L. L., Phelps, P. C., and Taylor, H. C., Jr. (1960). Studies of celiac disease. I. The apparent identical and specific nature of the duodenal and proximal jejunal lesion in celiac disease and idiopathic sprue. *Gastroenterology*, **38**, 28.
- Sunshine, P., and Kretchmer, N. (1964). Studies of small intestine during development. III. Infantile diarrhea associated with intolerance to disaccharides. *Pediatrics*, **34**, 38.
- Torres-Pinedo, R., Rivera, C. L., and Fernandez, S. (1966). Studies on infant diarrhea. II. Absorption of glucose and net fluxes of water and sodium chloride in a segment of the jejunum. *Journal of Clinical Investigation*, **45**, 1916.
- Townley, R. R. W. (1966). Disaccharidase deficiency in infancy and childhood. *Pediatrics*, **38**, 127.
- Walker, A. C., and Harry, J. G. (1972). A survey of diarrhoeal disease in malnourished aboriginal children. *Medical Journal of Australia*, **1**, 904.