Disorders of carbohydrate digestion and absorption

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NORMAL DIGESTION AND ABSORPTION OF CARBOHYDRATES

The first stage of digestion and absorption of dietary carbohydrates is accomplished by the salivary and pancreatic α -amylases, mainly by the latter in the duodenum and jejunum, where the efficiency of its hydrolysis has been ascribed to the absorption of the enzyme onto the membrane on the surface of the microvilli where the reaction occurs, a phenomenon which has been called membrane or contact digestion (Ugolev, 1965).

The second stage involves the hydrolysis of disaccharides whether formed from polysaccharides (maltose) or ingested as sucrose and lactose which enter the small intestine largely unchanged. The disaccharidase activity of the intestinal juice is very small (Dahlqvist and Borgström, 1961) and the evidence is now conclusive that the specific disaccharidases are located in, or closely associated with, the intestinal mucosal cells (Eichholz and Crane, 1966). Experiments on isolates of the microvilli of the mucosa have confirmed that these contain most if not all the disaccharidase activity (Miller and Crane, 1961), and that the latter is associated with the plasma membrane of the microvillus (Eichholz, 1967; Eichholz and Crane, 1965). Using hamster intestine Johnston (1967) has identified sucrase and maltase in particles or knobs, 60 Å in diameter, covering the luminal surface of the plasma membrane.

The third stage is that of transport of the monosaccharide across the mucosal cell. Crane (1968a) has summarized the experimental evidence supporting the hypothesis that this is by mobile carrier systems situated in the plasma membrane. Hydrolysis precedes absorption and is closely integrated with it (Crane, 1968b) as shown in Figure 1. Glucose and galactose have the same specific system, their absorption being 'active', *ie*, against a concentration gradient, and probably dependent on the presence of sodium ions (Crane, 1968a). Glucose may also be transported by a pathway other than that shared with galactose (Newey, 1967). Fructose, however, is absorbed in direct proportion to its concentration (Holdsworth and Dawson, 1964), though the rapidity suggests that its diffusion is also facilitated by a 'carrier' (Crane, 1968b). Although the glucose

'carrier' has not been identified, the kinetics of the absorption process resemble those of an enzyme-substrate reaction (Crane, 1968b; Matthews, 1968).

FIG. 1. Diagrammatic representation of hydrolysis and absorption occurring at the brush border membrane of the intestinal epithelial cell.

The zone of hydrolysis has been depicted by Crane as external to the lipid diffusion barrier across which the monosaccharides are transported but others have suggested that the disaccharidases and the carbohydrate 'carrier' form one supramolecular complex (Semenza, Tosi, Vallotton-Delachaux, and Mulhaupt, 1964), or that transport mechanisms as well as disaccharidases are randomly scattered over the whole surface of the microvilli (Hamilton and McMichael, 1968).

DISACCHARIDASES OF THE INTESTINAL MUCOSA

A number of disaccharidases, some with overlapping specificities, have been characterized by heat inactivation or gel separation in homogenates of intestinal mucosa (Dahlqvist, 1962; Semenza, Auricchio, and Rubino, 1965). These include four or five maltases, all of which hydrolyse maltose; two of them also split starch and are therefore amylases, two also hydrolyse sucrose and are therefore sucrases, and one, isomaltase, also splits isomaltose and palatinose.¹ There are also two

¹This enzyme is sometimes called palatinase. ED.

TABLE I

CLASSIFICATION OF INTESTINAL DISACCHARIDASES

Heat Denaturation Method (Dahlqvist, 1962)

Separation by Gel Filtration and Heat Denaturation (Semenza et al, 1965)

Enzyme	Substrate Hydrolysed	Proportion of Total Maltase Activity (%)	Enzyme	Substrate Hydrolysed	Proportion of Total Maltase Activity (%)
Maltase 1a = isomaltase ¹	Isomaltose Maltose	} 50	Maltase 5 = isomaltase ¹	Isomaltose Maltose	} 75
Maltase 1b = sucrase	Sucrose Maltose		} 25	Maltase 4 = sucrase 2	
Maltase II	Maltose	} 25		Maltase 3 = sucrase 1	Sucrose Maltose
Maltase III	Maltose		Maltase 2	} = γ -amylase	Starch Maltose
Trehalase	Trehalose	Nil	Maltase 1		Starch Maltose
Lactase = cellobiase	Lactose Cellobiose	} Nil	Trehalase	Trehalose	Nil
			Lactase 1 = lactase	Lactose	Nil
		Lactase 2 = lactase, hetero-galactosidase	Lactose β -Galactosides	} Nil	

¹ Isomaltase also hydrolyses palatinose. ED.

lactases, one specific for lactose, the other also splitting heterogalactosides (Table I).

The levels of enzyme activities of both duodenum and jejunum in 'control' adults, infants, and children (Burgess and Levin, unpublished observations) are shown in Table IIa, while Table IIb shows those of some other investigators for comparison. Our own results are from patients in whom a malabsorption syndrome was suspected but later excluded because the mucosa was normal histologically; they cannot therefore strictly be considered normal. There are wide differences between the mean levels of enzyme activities, both in children and adults, in the different series. The levels for duodenum are lower than those for jejunum. The range is wide for each enzyme, especially lactase, and therefore interpretation of an individual low result must be cautious except when it approaches zero.

DISORDERS OF DIGESTION AND ABSORPTION OF CARBOHYDRATES

Only those conditions affecting hydrolysis of disaccharides or transport of monosaccharides will be considered. They may be congenital or acquired. In the congenital variety, as in other inherited metabolic disorders, the abnormal disaccharidase arises from a gene mutation and results in a specific carbohydrate malabsorption. On the other hand acquired malabsorption of carbohydrate occurs when a reduction

of the total absorbing surface area of the intestine causes a non-specific reduction of disaccharidase activity as seen in enteritis, coeliac disease, sprue, or injury to the small bowel.

CONGENITAL DISACCHARIDE MALABSORPTION The presenting sign in congenital disaccharide malabsorption is profuse watery diarrhoea which is sour smelling and acid, and occurs very soon after ingestion of the sugar involved. In lactose intolerance this occurs when milk feeds, breast or artificial, commence, and is severe enough to require intravenous therapy. With sucrose malabsorption it begins as soon as this sugar is introduced into the diet, but dehydration requiring resuscitation with intravenous fluids only occurs if sugar is given in the first few weeks of life. The symptoms are less severe the later cane sugar is introduced, the main manifestation then being failure to thrive and a diarrhoea which is mild or moderate, but persistent. An associated starch malabsorption may also be present, but it is usually mild and may not be obvious.

Examination of faeces The stool is acid with a pH less than 5. The disaccharide can be detected and identified by paper chromatography. In some instances the disaccharide may also be present in the urine.

Oral tolerance test After an overnight fast the blood glucose response to a dose of disaccharide,

TABLE IIa

LEVELS OF DISACCHARIDASE ACTIVITY IN DUODENAL AND JEJUNAL MUCOSA OF CHILDREN AND ADULTS¹

		Lactase	Maltase	Palatinase	Sucrase
Children	<i>Duodenum</i>				
	Mean	2.3 ± 0.5 (7)	15.1 ± 2.4 (7)	1.3 ± 0.2 (7)	5.7 ± 0.9 (7)
	Range	0.2 - 3.5	7.5 - 25.4	0.4 - 2.2	2.2 - 8.7
	<i>Jejunum</i>				
Adults	Mean	4.9 ± 0.4 (25)	26.3 ± 1.8 (25)	2.5 ± 0.2 (23)	8.9 ± 0.7 (25)
	Range	1.9 - 9.3	11.8 - 48.4	1.3 - 5.1	4.8 - 19.8
	<i>Jejunum</i>				
	Mean	5.6 ± 0.7 (7)	27.9 ± 2.9 (7)	2.2 ± 0.1 (4)	9.4 ± 1.1 (7)
	Range	4.2 - 8.3	17.8 - 44.3	1.1 - 2.8	5.1 - 14.4

¹Results are expressed as μ moles substrate split/g mucosa/min. and are given as mean and range or as mean $\pm$ the standard error of the mean.

TABLE IIb

OTHER REPORTED LEVELS OF DISACCHARIDASE ACTIVITY IN DUODENAL AND JEJUNAL MUCOSA OF CHILDREN AND ADULTS¹

		Lactase	Maltase	Isomaltase	Palatinase	Sucrase	Reference
Children	<i>Duodenum</i>						
	Mean	2.7 (8)	18.8 (8)	5.7 (8)		5.2 (8)	² Auricchio <i>et al</i> (1965)
	Range	0.9 - 5.2	9.8 - 26.7	3.0 - 7.8		2.4 - 7.6	
	Mean $\pm$ SE	2.5 $\pm$ 0.1 (90)	18.0 $\pm$ 0.7 (90)		1.5 $\pm$ 0.1 (64)	4.9 $\pm$ 0.2 (90)	Antonowicz <i>et al</i> (1968)
	<i>Jejunum</i>						
	Mean $\pm$ SE	5.2 $\pm$ 0.5 (35)	32.5 $\pm$ 1.9 (35)	7.9 $\pm$ 0.6 (35)		10.0 $\pm$ 0.7 (35)	Eggermont (1968)
	Mean	3.0 (17)	15.1 (21)	5.4 (14)		5.8 (18)	³ Burke <i>et al</i> (1965)
	Range	0.9 - 8.1	5.1 - 37.6	1.9 - 10.8		2.0 - 14.0	
	Mean	8.5 (6)	20.8 (6)		2.5 (6)	7.5 (6)	Arthur (1966)
	Range	4.4 - 11.6	17.9 - 24.5		2.0 - 3.0	5.5 - 9.2	
Adults	<i>Jejunum</i>						
	Mean	11.2 (10)	61.8 (10)	16.6 (10)		17.9 (10)	² Auricchio <i>et al</i> (1965)
	Range	4.1 - 26.9	32.3 - 116.2	6.8 - 28.0		7.3 - 33.9	
	Mean $\pm$ SE	6.8 $\pm$ 1.3 (9)	43.6 $\pm$ 5.8 (9)	13.4 $\pm$ 1.9 (9)		13.5 $\pm$ 1.8 (9)	Eggermont (1968)
	Mean $\pm$ SE	3.1 $\pm$ 0.4 (17)	21.5 $\pm$ 1.5 (26)		1.8 $\pm$ 0.2 (25)	5.7 $\pm$ 0.4 (26)	Knudsen <i>et al</i> (1968)
	Mean $\pm$ SE	3.5 $\pm$ 0.2 (100)	22.3 $\pm$ 0.7 (100)	7.2 $\pm$ 0.7 (14)		5.9 $\pm$ 0.2 (100)	Newcomer and McGill (1967)

¹Results are expressed as μ moles substrate split/g mucosa/min. and are given as mean and range or as mean $\pm$ the standard error of the mean.²The authors' results have been converted to μ moles/g mucosa/min. using their figure for nitrogen content of mucosa.³The authors' results have been converted to μ moles/g mucosa/min. by using an average figure of 61.0 mg N/g mucosa.

Bracketed figures indicate the number of cases.

2g/kg in an infant or child, and 50 or 100 g in an adult, is subnormal, whereas the response to a similar dose of glucose is normal. These tests should be performed when diarrhoea has ceased, the suspected carbohydrate being given last. Urine is collected throughout the test and for several hours thereafter for sugar testing, and stools passed during or after the test are examined for sugars and pH.

Assay of enzyme activities Disaccharidase deficiency is confirmed by a determination of the enzyme activity of a biopsy sample of jejunal or duodenal mucosa obtained by a Crosby or similar capsule. After examination under a dissecting microscope, biopsies are weighed and homogenized as soon as possible to avoid drying and loss of activity; the rate of liberation of glucose when a homogenate of the mucosa is incubated with the appropriate disaccharide is then determined (Burgess, Levin, Mahalanabis, and Tonge, 1964). Activity may be expressed as μ moles substrate split/min/g wet weight of tissue, or per gram protein (Newcomer and McGill, 1967).

Radiological diagnosis Radiography of the abdomen one hour after ingestion of a mixture of barium and the disaccharide shows characteristic changes with dilution of the contrast medium, dilatation of the small bowel, and rapid transit of its contents (Laws, Spencer, and Neale, 1967).

CONGENITAL LACTOSE MALABSORPTION The recognition that malabsorption syndromes can arise from lack of a specific mucosal enzyme is only recent. An inherited lactase deficiency was first postulated by Durand (1958) to account for the chronic diarrhoea of a 13-month-old girl and by Holzel, Schwarz, and Sutcliffe (1959) for lactose malabsorption and failure to thrive in two sibs.

The condition is rare, and although 18 cases have been recorded (Holzel, 1967) few are conclusively proven. A number were investigated only at some period after infancy, so that secondary or acquired lactose malabsorption could not be excluded. In most cases the diagnosis was based only on the characteristic symptoms and the results of oral

TABLE III

DISACCHARIDASE LEVELS IN INTESTINAL MUCOSA

Condition	Biopsy	Lactase (Units) ¹	Maltase (Units)	Palatinase (Units)	Sucrase (Units)
Congenital lactose malabsorption	Duodenum	0.07	5.3	1.6	4.0
Glucose-galactose malabsorption	Jejunum	5.6	14.2	1.8	6.4
Controls Mean	Jejunum	4.9	26.3	2.5	8.9
Range		1.9 - 9.3	11.8 - 48.4	1.3 - 5.1	4.9 - 19.8
Mean	Duodenum	2.3	15.1	1.3	5.2
Range		0.2 - 3.5	7.5 - 25.4	0.4 - 2.2	2.2 - 8.7

tolerance tests. Enzyme assays were performed in only two infants with diarrhoea from shortly after birth. Another infant under our observation developed watery diarrhoea on the third day of life while on breast feeding. Diarrhoea ceased on a low-lactose milk but recurred on cows' milk. A lactose tolerance test at 3 weeks, and again at $2\frac{1}{2}$ years of age, showed no rise in blood glucose although glucose and sucrose absorption were normal (Fig. 2).

FIG. 2. Congenital lactose malabsorption. Blood glucose levels following oral ingestion of carbohydrates (2 g/kg). Note failure of blood glucose to rise after lactose ingestion.

A jejunal biopsy at 14 months was normal histologically and showed almost complete absence of lactase with normal sucrase and palatinase but slightly low maltase activities (Table III). This is characteristic of a specific lactase deficiency. If diminished or absent lactase is accompanied by a reduction of all the other disaccharidases, the deficiency is acquired and not congenital. However, an acquired disaccharidase deficiency involving lactase only is not uncommon (see below).

CONGENITAL SUCROSE MALABSORPTION Although also uncommon this is probably less rare than

congenital lactose malabsorption. Many reports have appeared since the first descriptions by Weijers, van de Kamer, Dickie, and Ijsseling (1961) and Prader, Auricchio, and Murset (1961) but the earlier ones were not supported by enzyme assay. In a congenital sucrase deficiency isomaltase and maltase are always also reduced. If other enzymes are reduced, then the deficiency is acquired. An acquired sucrase malabsorption confined to sucrose or to sucrose and starch seldom occurs.

Oral tolerance test There is no rise in blood glucose following ingestion of sucrose and palatinose whereas starch, maltose, and glucose provoke an increase of over 30 mg/100 ml, usually maximal in the first 30 minutes (Fig. 3). The diarrhoeal stools are

FIG. 3. Congenital sucrose malabsorption. Blood glucose levels following oral ingestion of carbohydrates (2 g/kg). Note failure of blood glucose to rise after sucrose or palatinose.

typical—acid, sour smelling, and containing large amounts of the disaccharide; the latter is sometimes present in the urine also.

Enzyme assay Assay of the intestinal mucosa showed an almost complete absence of sucrase in all nine cases we have studied (Fig. 4). This was found in the older as well as the younger patients, and indicates that the improved clinical tolerance to sucrose

with age is not due to recovery of enzyme activity but to the decreased daily intake of cane sugar in relation to body weight.

Palatinase deficiency was also present, and in some this was as severe as the sucrase reduction. Maltase activity also was considerably decreased, since both sucrase and isomaltase together account for 75 to 80% of the total maltase activity (Dahlqvist, 1962). On the other hand, lactase activity was within normal limits.

The association of sucrase with isomaltase deficiency implies that two enzymes are simultaneously deficient, and if the two sucraes are distinct entities (Semenza *et al*, 1965) three enzymes must be affected. Mutation of a structural gene which controls the synthesis of a polypeptide common to the three enzymes (Burgess *et al*, 1964), or of a regulator gene controlling the synthesis of these enzymes, could be an explanation. However, there may be only one enzyme possessing different active centres (Launiala, Perheentupa, Visakorpi, and Hallman, 1964). The widely varying ratios of the levels of palatinase to sucrase activities in patients with sucrose malabsorption suggest that this is a heterogeneous group.

Genetically the equal incidence in males and

FIG. 4. Congenital sucrose malabsorption: disaccharidase levels in jejunal mucosa. Note almost complete absence of sucrase activity with very low palatinase and low maltase activities. Hatched area denotes controls' range and mean, arrows denote means of patients.

females, the occurrence of affected sibs, and the absence of affected parents point to an autosomal recessive inheritance. Kerry and Townley (1965) found significantly lower values for sucrase, isomaltase, and maltase in eight parents of affected children compared with normal controls, suggesting that they were heterozygotes.

Sucrose malabsorption first presenting in adult life is even more rare than in infancy. In four of the five recorded cases symptoms dated at least from early childhood. In one there was no apparent sucrose intolerance before adult life (Neale, Clark, and Levin, 1965) but a long period of breast feeding and the limited amount of cane sugar available in war time could explain the lack of symptoms. It is possible that all are of congenital origin.

ACQUIRED DISACCHARIDE MALABSORPTION Lactose malabsorption may be due either to isolated intestinal lactase deficiency or may be associated with disorders of the intestinal mucosa.

Secondary isolated lactase deficiency There have been many reports of lactose malabsorption in adults due to isolated intestinal lactase deficiency since the first descriptions (Dahlqvist, Hammond, Crane, Dunphy, and Littman, 1963; Haemmerli, Kistler, Ammann, Auricchio, and Prader, 1963). Of 100 asymptomatic adults, Newcomer, McGill, and Butt (1966) found 7% with lactase deficiency, the other disaccharidases being normal. Neale (1968) found 6% of 50 hospital subjects of north European stock to have lactose malabsorption although they had no symptoms of the condition, and 10 of 12 subjects from other countries were similarly deficient. A high proportion of some African tribes also show severe lactase deficiency (Cook and Kajubi, 1966).

Since there is usually no history of milk intolerance in infancy and childhood, these are apparently not cases of congenital lactase deficiency. The mucosa is normal histologically and there is usually no associated disease. The condition may, however, have resulted from an attack of gastroenteritis with recovery of all the disaccharidases except lactase. Alternatively some adults may have a genetic predisposition to a decreasing lactase activity, inherited as an autosomal recessive (Ferguson and Maxwell, 1967). It is unlikely to be due to cessation of milk feeding, as infants or adults who have not had milk for long periods have normal lactase activity (Dunphy, Littman, Hammond, Forster, Dahlqvist, and Crane, 1965).

Secondary disaccharidase deficiency Lactose malabsorption is frequently associated with disorders in which the intestinal mucosa is damaged and the activity of all the disaccharidases is reduced.

TABLE IV

DISACCHARIDASE LEVELS IN INTESTINAL MUCOSA OF INDIVIDUAL PATIENTS WITH COELIAC DISEASE ON A GLUTEN-FREE DIET AND AFTER TRIAL REPLACEMENT ON A DIET CONTAINING GLUTEN

Patient	Tissue	Lactase (Units) ¹	Maltase (Units)	Palatinase (Units)	Sucrase (Units)
S.H.	Duodenum	1.0	12.0	—	3.5
	Jejunum	0	3.1	—	0.3
K.F.	Jejunum	7.2	28.8	—	7.9
	Jejunum	2.1	9.6	—	—
	Duodenum	0	2.3	0.2	0.6
P.S.	Duodenum	4.3	—	—	—
	Jejunum	0.2	4.5	—	0.9

¹Unit = μ moles substrate split/g mucosa/minute

In our series of children with coeliac disease confirmed by the clinical, biochemical, and histological findings, in whom an initial diagnostic jejunal biopsy was performed, all the enzymes were diminished, but lactase deficiency was the most marked (Fig. 5) (Levin, Burgess, Young, and Pringle, unpublished observations). A gluten-free diet resulted in return of activity; restoration of gluten for four weeks was sufficient to reduce it severely again (Table IV).

A temporary carbohydrate malabsorption in infants with infective diarrhoea may result from the mucosal damage due to the infection or from the resulting diarrhoea (Sunshine and Kretchmer, 1964; Burke, Kerry, and Anderson, 1965). In an attempt to assess each factor separately, we have examined the effect of helminth infection in the rat, which caused little or no diarrhoea, on disaccharidase levels of the jejunal mucosa (Lieberman and Levin, 1968, to be published). Marked decreases were observed in all enzymes but more especially in lactase (Fig. 6).

FIG. 5. Coeliac disease untreated: disaccharidase levels in jejunal mucosa. Note decreased activity of all enzymes, especially lactase. Symbols as in Figure 4. Coeliac mean as percentage of control mean; lactase 10.6, maltase 23.6, palatinase 24.0, sucrase 22.2.

FIG. 6. Effect of gastrointestinal infection upon jejunal enzymes of the rat. Note marked decrease of all enzymes, especially lactase. Note also recovery of enzyme activities with recovery from infection. Figures in columns = no. of rats.

Recovery of enzyme activities accompanied recovery from infection. In contrast an osmotic diarrhoea unaccompanied by infection resulted in a rise in the disaccharidase activities (Fig. 7). If applicable to man the results suggest that the carbohydrate malabsorption is due to the intestinal infection and not to the accompanying diarrhoea. This is consistent with the association of giardiasis in infants with carbohydrate malabsorption (Holzel, 1968). Furthermore kwashiorkor, which is caused by a

protein-deficient diet, is also associated with a reduction of intestinal disaccharidase activity (Stanfield, Hutt, and Tunncliffe, 1965). We have shown, however, that in rats fed on a protein-deficient diet disaccharidase activities rise (Solimano, Burgess, and Levin, 1967), so it is probably the gastrointestinal infection usually present in human protein malnutrition which causes carbohydrate malabsorption.

FIG. 7. Effect of acute non-infective (osmotic) diarrhoea upon the jejunal enzymes of the rat. Note marked increase of sucrase and especially of lactase activities. Figures in columns = number of rats.

CONGENITAL MONOSACCHARIDE MALABSORPTION
Only one variety of congenital monosaccharide malabsorption has been established, that which affects both glucose and galactose.

Glucose-galactose malabsorption The discovery of this rare syndrome (Lindquist, Meeuwisse, and Melin, 1962; Laplane, Polonovski, Etienne, DeBray, Lods, and Pissarro, 1962) supports the hypothesis of a specific glucose-galactose transport mechanism. So far 14 cases have been reported, but only one from Great Britain (Abraham, Levin, Oberholzer, and Russell, 1967). Profuse diarrhoea develops as soon as breast or artificial feeding begins and is not relieved when sucrose, lactose, or glucose is excluded.

Oral tolerance tests show that the blood glucose fails to rise after ingestion of glucose or galactose, and that the sugar is excreted in the faeces. Similar results are obtained with lactose, maltose, or palatinose. However, fructose is normally absorbed (Fig. 8). D-xylose is less readily absorbed, its transport possibly involving the same carrier as glucose-galactose (Alvarado, 1966; Salomon, Allums, and Smith, 1961). Glucosuria is usually found, indicating a defective transport mechanism in the renal tubular epithelium also.

FIG. 8a.

FIG. 8b.

FIG. 8. Glucose-galactose malabsorption. Monosaccharide (a) and disaccharide (b) tolerance tests.

FIG. 9. Transport of ^{14}C -glucose (Na^+ -dependent) and ^{14}C -leucine by intestinal cells in vitro. Note failure to concentrate glucose by patients' cells as compared with control cells. Concentration in cells expressed as ratio of radioactivity in tissue (Ct) to that in fluid medium (Cm).

Transport defect Glucose (or galactose) fails to concentrate in mucosal cells when incubated in a medium containing ^{14}C -glucose, whereas ^{14}C -leucine is concentrated normally (Meeuwisse and Dahlqvist, 1966; Eggermont and Loeb, 1966). The results in our case, as determined by Dr E. Eggermont, are shown in Figure 9. The histology of the mucosa was normal as were the disaccharidases (Abraham *et al*, 1967) (Table III).

Inheritance is probably by an autosomal recessive gene because sibs may be affected, but not parents (Lindquist *et al*, 1962; Meeuwisse and Dahlqvist, 1966).

Treatment is by a strict exclusion of all carbohydrates except fructose, at least for the first year of life, if not longer; later some starch, etc, may be taken.

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