# Delaying Absorption as a Therapeutic Principle in Metabolic Diseases

**Edited by**
**W. Creutzfeldt and U. R. Fölsch**

# Delaying Absorption as a Therapeutic Principle in Metabolic Diseases

Ludwig-Heilmeyer-Symposium of the „Gesellschaft für Fortschritte auf dem Gebiet der Inneren Medizin"
Düsseldorf 1982

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# 1. Introduction

W. Creutzfeldt, Dept. of Medicine, University of Göttingen

I would like to set the stage for this meeting by making a few general remarks. The basic treatment of the three most important metabolic diseases, i.e. diabetes mellitus, hyperlipoproteinaemia and obesity is the control of the nutrient entry. This may be realized firstly by decreased food intake, secondly by *decreased* food assimilation and thirdly by *delayed* food assimilation.

Decreased food intake in the conventional sense may be achieved by strict diet. But this is often extremely difficult for the patient. Psychotherapy is not everyone's choice and of doubtful value, and anorectic drugs are certainly also a great problem because of serious side effects. Surgical mutilation, the most primitive approach to this problem, starts with the gastrointestinal or ileal bypass and ends with jaw wiring.

The first example of decreased food assimilation was the use of the biguanides. It may be realized by inhibition of digestion as with the use of acarbose or fiber. Decreased food assimilation is also partially realized by bypass operations. But the main effect of such an operation is that the subjects have such unpleasant diarrhea that they are forced to eat less, which means that two mechanisms come into action. Now the third possibility, *delayed* food assimilation, has the aim of avoiding glucose and anabolic hormone peaks. This can be achieved by dietary regimen, classically by consuming multiple small meals. Today, however, other possible ways of achieving this are under investigation such as by delay of gastric emptying or of absorption or digestion. I am convinced that the use of enzyme inhibitors and/or fibres is an important approach to the treatment of metabolic diseases.

Now let me thank all the invited speakers who took the trouble to come here a long way and to prepare their manuscripts. Especially, I would like to thank two colleagues who came at very short notice. Unfortunately, Dr. *Kritchevsky* from Philadelphia, had to cancel his attendance. Prof. *Stiehl* from Heidelberg was so kind to replace him by giving the lecture on "Inhibition of bile acid and cholesterol absorption". Secondly, Prof. *Schöffling* could not come because he had to have an urgent operation this week. Prof. *Laube* from Gießen kindly took on the lecture on "Clinical significance of delaying absorption". The rest of the programme will be as printed and I hope we all will have an interesting time. Thank you.

# 2. Rationale for Delaying or Inhibiting Intestinal Absorption

P. Lefebvre, Hôpital universitaire de Bavière, Institut de Médecine, Liège

## Introduction

The proper functioning of the digestive tract includes a number of events comprising motility, exocrine and endocrine secretory processes, digestion itself as well as intestinal absorption of nutrients and other components of the diet. In this finely balanced intrication of processes, food is in principle most effectively transfered from outside the body to its inside in order to meet plastic and energetic requirements. Ideally, the whole system works quite effectively with minimal fecal excretion of undigested or unabsorbed components of the diet. Any perturbation in these mechanisms leads to pathologic states which include subtile to extreme changes in body weight, various degrees of specific or generalized deficiences or excesses or appearance of peculiar syndromes such as those which occur when undigested or unabsorbed food components reach the large intestine.

In human therapeutics, the digestive tract is certainly the most anciently known and, still in the present time, the most widely used way for drug administration. In most instances, the digestive tract is simply considered as a route for drug administration *i.e.* that the target is outside the digestive tract itself. In that respect, major progress has been made in order to accelerate, reduce or, at least, control the rate of drug absorption by the gut by modifying the chemical structure of the drug itself or changing its galenic presentation. More recently a great deal of attention has been paid to drugs or factors which may act by regulating events taking place within the digestive tract itself. The present Symposium is precisely devoted to this new therapeutic principle that might reside in slowing, delaying or inhibiting digestion and/or intestinal absorption. A relatively ancient use of such principle is the treatment or prevention of hyperkalemia by resins exchanging cations such as sodium or calcium for potassium in the lumen of the digestive tract. Such resins have greatly helped in correcting or preventing the life-threatening rise in plasma potassium which often occurs in several forms of kidney failure.

More recent are the manipulations of intestinal digestion or absorption in order to modify lipid or carbohydrate metabolism. In this introductory lecture, I will attempt to justify the reasons for such an approach in the two main fields which will be covered in detail in the next two days namely the control of hypercholesterolemia and the one of excessive changes in blood glucose.

## Attempts to Reduce Hypercholesterolemia

Type II hyperlipoproteinemia in its genetic forms represents a major risk factor of atherosclerosis and, as such, justify appropriate dietary and pharmacological approaches. Among the drugs available, *colestyramine* and *colestipol* represent precisely drugs acting in the digestive lumen and exerting beneficial metabolic effects. These two drugs are resins which are not absorbed from the gut and exert their action by exchanging chloride ions for bile acids in the digestive tract. By interrupting the enterohepatic circle of bile acids these two compounds increase the fecal excretion of these acids and effectively reduce circulating levels of cholesterol.

*Sucrose polyester* (SPE) is composed of hexa-, hepta- and octa-esters of sucrose, it has the consistency of fat and can be incorporated into the diet as a substitute for fat (*Mattson* and *Volpenheim* 1972). It is not hydrolyzed by pancreatic lipase and hence is not absorbed to any measurable extent. In experimental animals and in man, it acts as a cholesterol lowering agent (*Crouse* and *Grundy* 1979). This effect is due

to decreased cholesterol absorption probably as a consequence of a partition, in the intestinal lumen, of cholesterol out of the micellar phase into an oily, SPE phase which would render it non-absorbable.

While the bile acid sequestring resins and SPE mainly act by diverting bile acids or cholesterol from intestinal absorption through chemical or physicochemical binding, manipulating *small bowel transit time* has also been shown to be an effective means of modifying cholesterol absorption. Recent data of *Ponz de Leon* et al. (1982) have shown that metoclopramide *acceleration* of small-bowel transit was consistently associated with decreased cholesterol absorption, whereas atropine-induced *slowing* of transit had virtually no effect on intestinal cholesterol absorption. The extent to which pharmacological manipulations of small bowel transit time might be useful in limiting dietary cholesterol absorption and, in turn, overaccumulation of cholesterol in body tissues remains to be established. In any case, these observations suggest that other dietary components, such as *unabsorbable plant fibers*, may also reduce cholesterol absorption, and as a consequence cholesterol plasma levels, by reducing intestinal transit time, a well accepted effect of some of these dietary fibers.

## Attempts to Control the Magnitude of Blood Glucose Changes after Meals

The end-products of carbohydrate digestion in man are essentially glucose and, to a lesser degree, fructose and galactose, these last two oligosaccharides being rapidly converted by the liver into glucose. On the other hand, circulating glucose is not only a substrate for catabolism but also precursor in the anabolism of the two main energy storage molecules in the body: glycogen in the liver and in muscles and triglycerides in adipose tissue. For these reasons, circulating glucose is considered as the cornerstone of all metabolic pathways when energy fluxes are considered. A caricatural picture of the metabolic events occuring after carbohydrate ingestion is precisely the one obtained when a load of 50 to 100 g glucose is given orally. Because free glucose is usually not found in the human diet, we should emphasize that this is a highly artificial and non-physiological situation (*Lefebvre* and *Luyckx* 1976). Nevertheless, it is a useful model and has been used as such for many years in the most classical oral glucose tolerance test (OGTT). Others in this Symposium will review in detail the endocrinology of nutrient entry. For the sake of our discussion, let us emphasize that, in normal man, the ingestion of a glucose load is followed by a rapid but transient insulin response due to both an effect of glucose itself on the insulin producing cells of the islets of Langerhans and the participation of one or more intestinal mediators of insulin secretion, among which GIP seems to be most important. The insulin response to glucose is crucial: it will prevent an excessive rise in blood glucose by facilitating its utilization and by orientating it to the previously mentioned storage sites. Two extreme abnormal responses are: (1) an excessive blood glucose rise in all forms of intolerance to glucose or diabetes, due to insulin lack or insulin resistance and, (2) an excessive post-hyperglycemic hypoglycemia which may occur when the insulin response is excessive or delayed, a situation encountered in some forms of "alimentary" and so-called "reactive" hypoglycemia.

In the simple model that is the OGTT, factors that might modify the magnitude of the blood glucose rise and/or plasma insulin response include the size of the load, the rate of gastric emptying and the rate of glucose absorption by the gut.

If we move one step further and if we replace glucose by sucrose in the oral tolerance test, one additional factor comes into play namely the rate of digestion of sucrose into glucose and fructose a process under the control of the sucrase activity present in the brush border of the cells of the mucosa of the small intestine. A new possible step for modulation will therefore be to interfere with the activity of this enzyme. Finally, when more complex carbohydrates are ingested, such as starch, other digestive steps, also susceptible to therapeutic modulation, are involved such as the salivary and pancreatic amylases acting in the lumen of the digestive tract and several other glucosidases located in the mucosa of the small intestine.

The therapeutic means permitting to interfere with carbohydrate digestion or absorption are either relatively newly recognized or have been recently developed. I will simply enumerate them since the whole meeting is precisely devoted to the analysis of their mode of action.

Some dietary fibers will slow gastric emptying, reduce the rate of glucose absorption, improve glucose tolerance and reduce the insulin response to sugars. Alpha amylase inhibitors, like the BAY g 7791, prepared from wheat, inhibits the rise in glucose and insulin after starch loading tests. Alpha glucoside hydrolase inhibitors such as Acarbose, a tetrasaccharide of bacterial origin, reduces the rise in blood glucose which occurs after meals containing starch and/or sucrose (review in *Creutzfeldt* 1982). Other compounds may directly interfere with glucose absorption at the enterocyte level. Sodium chloride, for instance, increases the blood glucose and plasma insulin response to an oral glucose challenge; the interpretation was that sodium and glucose are coupled in their active transport through the gut barrier (*Ferrannini et al.* 1982). In contrast, other compounds such as the biguanides, used until recently as oral antidiabetic agents, have some inhibitory effects on intestinal glucose transport.

What might be the interest of delaying or inhibiting carbohydrate digestion or absorption? In *diabetes mellitus* of either type 1 (insulin dependent) or type 2 (non insulin dependent), maintaining blood glucose within narrow limits, close to those observed in non diabetic subjects, is now almost universally considered to be the major goal of therapeutics. There is little doubt that the occurrence of the microangiopathic complications of diabetes is linked to the duration and magnitude of hyperglycemia. A current theory proposes that non enzymatic glycosylation of structural proteins might be the mechanism, or one of the mechanisms, by which microangiopathy occurs. For these reasons, *control of blood glucose* is, in these years, considered to be the first goal in diabetes management. In this respect, controlling the magnitude of the post-prandial blood glucose rises is often difficult to achieve. Until recently, available techniques included reduction of the carbohydrate content of food and splitting meals. Additional and effective means include now the use of dietary fibers and of α-glucosidase inhibitors. Several studies performed in both type 1 and type 2 diabetics have unequivocally shown that a better control can be achieved using these new approaches, they will be reviewed later in this Symposium.

In *obesity*, one of the main features is hyperinsulinism leading, through the phenomenon usually called "down regulation" of the insulin

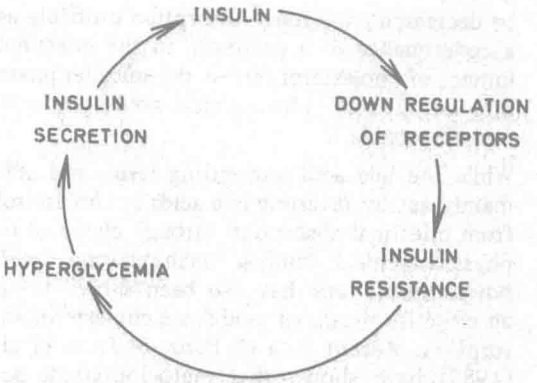


Fig. 1 The vicious circle operating in hyperinsulinemic states

receptors, to decreased insulin sensitivity. Such situation creates a vicious circle in which hyperinsulinism and diminished glucose tolerance are really intricated (Fig. 1). Here again, beneficial effects can be expected from factors such as dietary fibers, α-glucosidase inhibitors or biguanides which all decrease the insulin response to a given amount of carbohydrates presented to the digestive tract.

*In type IV (and IIb) hyperlipoproteinemia*, the increased synthesis of very low density lipoproteins depends upon glucose availability and is facilitated by insulin. Here also beneficial effects have been reported from the use of dietary fibers and studies in animal models suggest that α-glucosidase inhibition might represent an entirely new and effective therapeutic approach (*Zavaroni* and *Reaven* 1981, *Krause* et al. 1982).

In some patients the rise in blood glucose which occurs after a glucose or a sucrose load, or even a mixed meal, is followed by hypoglycemia refered to as "alimentary" when it is due to *rapid gastric emptying* or "reactive" when it is associated with *impaired glucose tolerance, renal glycosuria* or presents itself as an *isolated syndrome*. In some of these cases, the promptness and the magnitude of the hyperglycemia, associated with an excessive insulin response, seem to be responsible for the secondary hypoglycemia. Addition of fibers (*Mirouze* et al. 1979; *Monnier* et al. 1982), use of biguanides (*Giugliano* et al. 1979, *Lefebvre* et al. 1980), prescription of α-glucosidase inhibitors (*Gérard* et al. 1983) are logic and indeed effective means permitting to improve a syndrome which is too easy to simply call "neurotic".

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## Possible Untoward Effects of Manipulating Digestion and Intestinal Absorption

The "new therapeutic principle" of slowing intestinal absorption has to be evaluated not only in terms of potential benefits but also with regard to unexpected and unwanted effects. Only a positive balance between the desired and undesired effects will allow a wide use of this new approach.

Massive diversion of cholesterol and bile acids into the large intestine should be evaluated in the long run in terms of local carcinogenicity, a still unsettled question. Malabsorption of minerals and vitamins should always be searched when using drugs interfering with nutrient entry. The side-effects of Acarbose include in some patients abdominal discomfort and diarrhea and, in most, meteorism and flatulence; in many of these patients these untoward effects are transient and do not lead to interruption of treatment. Obviously, however, longer studies are needed to ascertain the total inocuity of these procedures which interfere with food digestion and nutrient entry.

*Acknowledgments*

We acknowledge the expert secretarial help of *E. Vaessen-Petit.*

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## Discussion

*Gray:* I was not aware of the work you quoted that sodium chloride augmented glucose absorption. The apparent lower absorption of the glucose might be due to the mannitol rather. If mannitol is in the intestinal lumen, it will have a marked osmotic effect. It will not be absorbed and it will not perhaps allow enough water to be available to accompany glucose in its absorption. And I wonder if anyone has addressed that? I'm very concerned that that may have been an interpretation on the part of the authors.

*Lefebvre:* This has been published I think a month ago (*Ferranini* et al., J. Clin. Endocrinol. Metab. 54 [1982] 455–458). The point of giving mannitol was to reach the same osmolarity as the one obtained by giving sodium chloride. But the mannitol by itself did not have the same effect.

*Gray:* The point is, this is an oral test, so everything in the intestinal lumen will be isotonic, so that using mannitol alone wouldn't have an effect on absorption. The correct control would have been to use glucose with water, not mannitol. Under those circumstances I would have expected glucose absorption to be exactly the same as it was with the additional sodium chloride.

# 3. Carbohydrate Digestion and Absorption

G. M. Gray, Div. of Gastroenterology, Stanford University,
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Despite the common concept that all dietary carbohydrate is quickly reduced to glucose which is then efficiently absorbed by the intestine, the processes of intraluminal digestion catalyzed by pancreatic α-amylase and surface intestinal digestion under the influence of a group of oligosaccharidases are crucial to the orderly hydrolysis of dietary polysaccharides and oligosaccharides. Notably, only starch which comprises 60% of the carbohydrate taken in the Western diet is hydrolyzed within the intestinal lumen to oligosaccharides. The other major dietary carbohydrates, lactose, which makes up about 50 gms/liter of milk and 10% of carbohydrate in the diet, and sucrose (dietary table sugar) can be hydrolyzed only by enzymatic breakdown upon making contact with the intestinal surface membrane oligosaccharidases.

## Starch Hydrolysis in the Intestinal Lumen

Dietary starch is named according to its structural characteristics. Amylose, composed of a straight chain of glucose molecules attached by α1,4 linkages, makes up about 25 percent of starch accounts for about three fourths of diestarch accounts for about three forths of dietary starch and in addition to the same straight chain basic structure of amylose, also contains α1,6 branching links approximately every 25 glucose residues along the chain. Fig. 1 diagrams the structure of the two types of starch. The structural characteristics of starch are important because a-amylase has specificity only for the α1,4 links and yields the final products maltose and maltotriose from amylose digestion. Because the α1,6 branching points in amylopectin are not suitable substrates for pancreatic α-amylase, the final products of its action on amylopectin include branched oligosaccharides, the so-called a-limit dextrins as well as maltose and maltotriose (1). Thus, the final oligosaccharide products of starch digestion in the intestinal lumen are a disaccharide, trisaccharide and the branched α-dextrins of varying size (average molecular weight of 1800). Pancreatic a-amylase has very little specificity for these final saccharide products because of the α1,6 branching linkage and the small number of glucosyl residues available for binding to the enzyme. On the other hand, the intestinal oligosaccharidases do have the appropriate specificity to yield glucose as the final product, as will be discussed below. In general, starch hydrolysis is a very efficient process that yields the final glycosyl-oligosaccharide products by the time the meal reaches the duodenal-jejunal junction (2). However, starch is relatively insoluble when presented as a component in food and as high as 3 or 5% can actually never be hydrolyzed and enters the colon for bacterial metabolism (3). This is, of course, of little nutritional consequence.

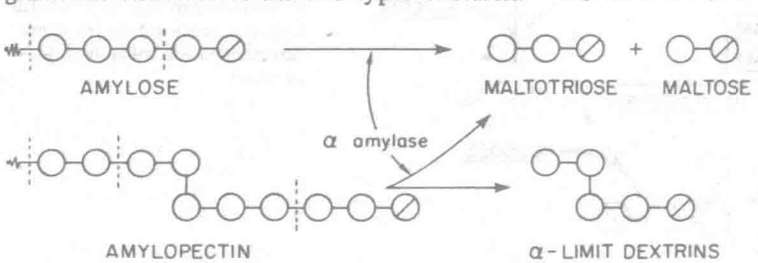


Fig. 1 Diagrammatic representation of the intraduodenal digestion of straight chain (amylose) and branched chain (amylopectin) starches to the final oligosaccharide products. The non reducing end of the representative polymer is shown on the left with each circle designating a glucose residue. Horizontal connections indicate α1,4 glucosyl links and the vertical links denote α1,6 links. The reducing glucose residue (at the right on each saccharide) is identified by the line within the circle.

Table 1 Characteristics of brush border oligosaccharidases

| *Enzyme* | *Principal substrates* | *Products* | *Km* mM | *MOL WT$_{app}$* |
|---|---|---|---|---|
| β-Galactosidase Lactase | Lactose | Glucose and galactose | 18 | 280,000 |
| α-Glucosidase Glucoamylase | Non-reducing α(1→4) link of glucosyl-oligosaccharides (including α-dextrins) $(G_2 \rightarrow G_9)^+$ | Glucose: residual oligosaccharide with α(1→6) link | 3.8 → 1.1 $(G_2)$ $(G_9)^+$ | 210,000 |
| Sucrase$^{++}$ | Sucrose; maltose; maltotriose; α(1→4) end links of α-dextrins | Glucose, fructose; residual oligosaccharide | 20 (sucrose) 3.6 ($G_3$) 2.6 ($G_2$) | 125,000 |
| α-Dextrinase$^{++}$ | Non-reducing α(1→4) end links of glucosyl oligosaccharides and α-dextrins; required for removal of non-reducing α(1→6) linked glucose in α-dextrins | Glucose | 5.0 (isomaltose) 1.0 (glucosyl α1→6 maltotriose) 11 ($G_3$) 3.1 ($G_2$) | 115,000 |

$^+$ G indicates glucose unit and subscript denotes the member of the α (1→4) linked glucose residues in the saccharide.

$^{++}$ Actually present in intestine as the non-covalently-linked hybrid enzyme sucrase-a-dextrinase but considered here separately since the hydrolytic sites act independently of each other for all substrates.

## Intestinal Surface Membrane Hydrolysis of Oligosaccharides

The oligosaccharide products of luminal starch digestion and the disaccharides lactose and sucrose can be assimilated only after hydrolysis at the intestinal-luminal membrane interface where they interact with their appropriate hydrolases (4). A list of the oligosaccharides and their appropriate substrates is given in Table 1. All are large glycoproteins strategically located at the outer intestinal membrane. Notably, there is a single β-galactosidase, lactase (5), and several α-glucosidases (6, 7) that in the aggregate are capable of efficiently hydrolyzing dietary oligosaccharides to their monosaccharide components which can in turn be transported across the intestine. The process of surface hydrolysis is very efficient so that more than enough monosaccharide is provided at the intestinal surface for the final transport process (8). Hydrolysis of larger oligosaccharides such as α-dextrins is a somewhat more complex process since more than one oligosaccharidase may actually act on this substrate and its products (9). Fig. 2 shows diagrammatically the series of cleavage steps of a typical α-dextrin and the brush border surface enzymes that catalyze

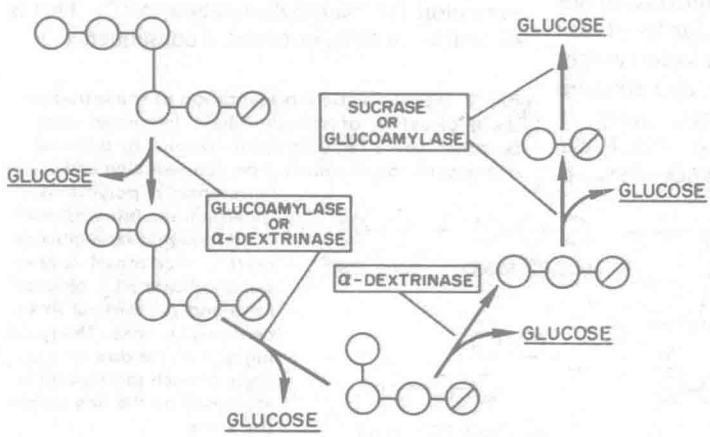


Fig. 2 Mechanism of cleavage of a model α-dextrin by intestinal oligosaccharidases. Symbols are the same as in Fig. 1. A single glucose residue is removed in sequence by one or more α-glucosidases. Note that only α-dextrinase can remove the α1,6 linked glucose starch from the tetrasaccharide intermediate product.

each hydrolytic step. Notably the α-dextrin can be cleaved only by sequential removal of a single glucose residue from the non-reducing end of the molecule. The final product is glucose which is then transported by a specific mechanism that is described in detail below.

## Rate Limiting Steps in Digestion and Absorption of Carbohydrate

The processes of intraluminal digestion of starch and brush border membrane surface hydrolysis of oligosaccharides are extremely efficient and in general yield more than enough final monosaccharide product for specific transport. However, there is one exception to this. Even in normal individuals who have optimal levels of lactase activity, the hydrolysis of lactose is a relatively slow process which does not provide sufficient glucose and galactose to saturate the final membrane transport process (8). Thus lactose hydrolysis is a rate limiting step for the overall assimilation of this disaccharide. For all other dietary disaccharide, the final monosaccharide transport step appears to be the slowest and therefore can be considered to be rate limiting. This has obvious implications for individuals who may have even transient reduction in intestinal function.

## Transport Mechanisms for the Released Monosaccharide

Entry of dietary sugar past the hydrophobic brush border lipoprotein barrier into the interior of the cell is restricted to monosaccharides of specific structure. Thus, glucose and galactose, having nearly identical structures, utilize a specific transport mechanism, often termed the glucose carrier (10–12). As depicted in Fig. 3, glucose, or galactose can readily bind to the surface membrane receptor which is presumably a hydrophobic protein having a hydrophilic channel through which the monosaccharide can move. Sodium binds to a separate site on the transporter and the efficiency of glucose transport into the intestinal cell is greatly facilitated by the co-transport of sodium (11, 12) and, in particular, by active uphill pumping of $Na^+$ by the sodium-potassium ATPase at the laterobasal membrane (Fig. 3). Two molecules of $Na^+$ appear to be transported for each molecule of glucose or galactose (11, 12). There is also evidence for a second carrier in the laterobasal membrane, the so-called serosal carrier which is responsible for exit of the bulk of the monosaccharide into the interstitial space (11–13). In addition, some glucose appears to diffuse through the relatively porous basolateral membrane. In addition to this special transport mechanism for glucose and galactose, there is a second mechanism that probably also requires a specific carrier protein that is responsible for the transport of dietary fructose, one of the monosaccharides released by hydrolysis of sucrose at the membrane surface. Little is known about the fructose transporter except that it supports a rate of assimilation of 50–75% to that of the glucose transporter and the fructose transport process does not appear to be sodium dependent.

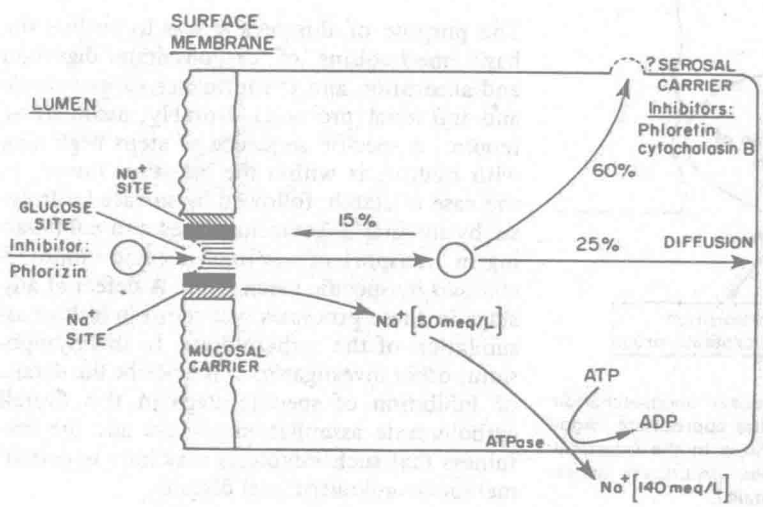


Fig. 3 Mechanism of glucose (or galactose) entry and transport through the intestinal cell. The circle denotes the free glucose molecule; percentages refer to the distribution after $Na^+$-coupled entry. Evidence for carriers at the brush border and laterobasal membrane is based on kinetic studies utilizing the inhibitors shown.

## Malabsorption of Carbohydrate

Carbohydrate assimilation depends on a discrete series of processes: 1. luminal hydrolysis (in the case of starch), 2. intestinal membrane surface hydrolysis, and 3. final transport of the released monosaccharides across the intestinal cell. A defect at any stage of overall hydrolysis or transport will prevent carbohydrate assimilation (14). Patients with severe pancreatic insufficiency may have mild maldigestion of starch because of a greatly reduced pancreatic amylase, but even 10 percent of the normal amylase is probably sufficient to catalyze starch breakdown to its final products (2). This appears to be related to the tremendous overabundance of pancreatic α-amylase present in the intestine under normal circumstances.

Deficiency of intestinal oligosaccharidases is very common. Indeed, the majority of the world's population groups have lactase deficiency as adults (14). A distinct symptom complex of abdominal fullness, bloating and distention, associated with nausea and even emesis, occurs 15–30 minutes after digestion of the offending carbohydrate. This is followed 30–180 minutes later by abdominal cramping pain and passage of watery bowel movements. The pathogenesis of oligosaccharide intolerance is outlined in Fig. 4. Because of the absence of oligosaccharidase (lactase in this case), the disaccharide remains in the intestinal lumen, there being no transport mechanism for its direct assimilation. As the unabsorbed saccharide moves down the intestine, it is metabolized by bacteria both to hydrogen and carbon dioxide gasses and to two- and three-carbon fragments which increase the intraluminal osmotic force. Because luminal fluids remain isotonic with plasma, there is a formidable influx of water into the intestinal lumen in response to these osmotic changes. The resultant increase in intraluminal volume distends the intestinal lumen and probably stimulates peristalsis. As a result, both liquid and flatus are passed. Secondary malabsorption of other nutrients may develop because of the acid condition and rapid transport time.

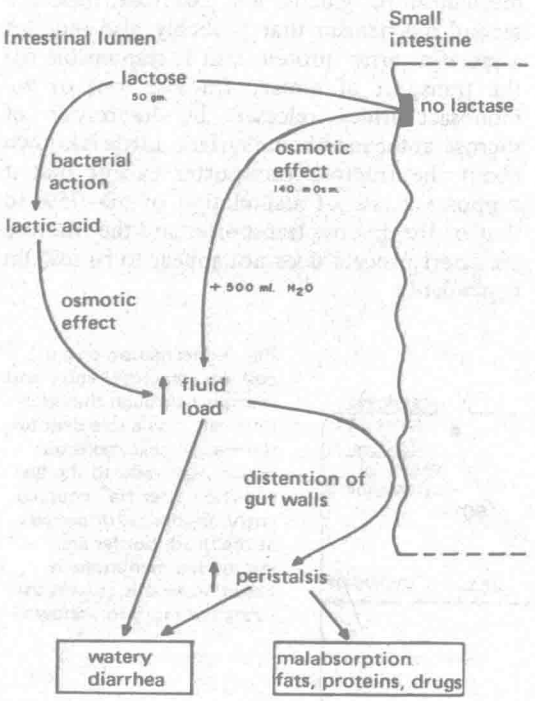


Fig. 4 Scheme for the pathogenesis of oligosaccharide intolerance. In the absence of the appropriate oligosaccharidase, the saccharide remains in the intestinal lumen and is cleaved to smaller osmotically active fragments (Cf text for further details).

Other speakers in this symposium will consider the blocking of oligosaccharidases by specific substrate analogues. Depending upon the extent of such inhibition, and the amount of oligosaccharide ingested daily, oligosaccharidase inhibitors can be expected to produce some or all of the symptomes seen in oligosaccharidase deficiency that are outlined above and in Fig. 4.

### Summary

The purpose of this review was to outline the basic mechanisms of carbohydrate digestion and absorption and the influence of pancreatic and intestinal processes. Notably, assimilation requires a specific sequence of steps beginning with hydrolysis within the intestinal lumen, in the case of starch, followed by surface hydrolysis by integral oligosaccharidases and culminating in transport of the final released monosaccharides by specific mechanism. A defect at any stage in these processes will result in lack of assimilation of the carbohydrate. In this Symposium, other investigators will describe the details of inhibition of specific steps in this overall carbohydrate assimilation process and the usefulness that such inhibitors may have in certain metabolic and nutritional diseases.

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