

The Gastrointestinal Tract

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- Application of strict diagnostic criteria to celiac disease has led to the realization that there is a wide clinical spectrum within this disease.
- Normally there are immune reactions to dietary proteins, particularly secretory antibodies of IgA class, low titers of serum antibody and specific down-regulation of IgE and T cell reactivity (oral tolerance).
- From time to time, abnormal immunity to foods, either as inappropriately high titers of antibodies or qualitatively altered responses, produce disease.
- Lactase deficiency, with dose-related lactose and milk-intolerance, occurs in 50-90% of most populations. White, western Europeans are the exception.

Key words: Food-sensitive enteropathy, food-sensitive colitis, celiac disease, lactose intolerance, eosinophilic gastroenteritis

The Gastrointestinal Tract

Because of the similarities between food-induced reactions and the exacerbation, by eating, of symptoms of esophageal, gastric, intestinal and colonic diseases, it is particularly important that strict criteria be applied for diagnosis of food intolerance or allergy in patients with gastrointestinal symptoms.

General descriptive terms such as sensitivity or intolerance are preferable; the provoking agent may be a single food or ingredient, but sometimes, particularly in IgE-mediated food allergy, many different foods are involved.

Food allergy

Intestinal hypersensitivity reactions - relevant theoretical aspects.

Active immunization

Normally there should be oral tolerance (e.g. specific suppression) rather than induction of IgE antibody or sensitized T cells when antigen is ingested. Circumstances in which IgE is induced relate more to the fact that the patient is atopic, rather than to the nature, molecular form, dose of antigen, amount of gut permeability, or efficiency

of digestion. T cell sensitization may be genetically determined.

Localization of the IgE-sensitized mast cells

Mast cells in the wall of the gut may acquire IgE from plasma cells in the immediate vicinity, or they may have been sensitized as they migrate prior to lodging in the tissues.

Antigen challenge

The very small quantity needed for degranulation of IgE-sensitized mast cells probably reaches the tissues via the bloodstream, after entry into the body through the mucous membrane of the mouth, stomach or proximal intestine. Antigen which induces local immune-complex reactions or T cell mediated immunity probably reaches the gut lamina propria through the overlying surface epithelium.

"Cascade" of additional inflammatory and immunological responses to other antigens

As a result of secretion of cytokines and inflammatory mediators, the capillaries and epithelium of the affected tissue become more permeable to

the access of plasma, leucocytes and, in the gut, enteric antigens. Thus, soon after the antigen-specific hypersensitivity response starts, there may develop a variety of other hypersensitivity and inflammatory reactions.

Manifestations of food allergy and hypersensitivity in the gut

Many food antigens have been implicated, and there are no particular allergens which predispose to expression of IgE reactions in the gut. On the other hand celiac disease, thought to be predominantly mediated by T cells, is provoked by certain cereal proteins.

Acute, local reactions

These are IgE-mediated. Within seconds of oral contact with or swallowing of provoking substances there may be facial angioedema, diarrhea or vomiting.

Food-sensitive enteropathy

This is usually found in children with an atopic background, but there is good evidence for T cell mediated hypersensitivity as well as IgG and IgE, in the pathogenesis. Small intestinal mucosal damage with malabsorption is best documented for cow's milk protein intolerance, but can also occur with soy, chicken, rice, fish and egg intolerance.

Classically the infant has diarrhea and failure to thrive, with vomiting. There is malabsorption, and jejunal biopsy is abnormal, but not usually so severely affected as in celiac disease. Treatment with a cow's milk-free diet (or other elimination diet) induces rapid remission. Once clinical recovery is complete, it may be appropriate to confirm the diagnosis by an in-hospital provocation test. Most of these children will be clinically tolerant of cow's milk by the age of a year.

Food-sensitive colitis

This is characterized by bloody diarrhea but differs from ulcerative colitis in many clinical and pathological features. Typically, an infant presents before the age of a year with loose stools containing mucus and blood. An elimination diet and clinical monitoring with rectal biopsy, confirm the diagnosis. The pathology differs from classical ulcerative colitis. In food-sensitive colitis there are many eosinophils in the lamina propria. Severe clinical colitis may be induced by a food challenge

and so this should not be done routinely. As is the case in food-sensitive enteropathy, most children can tolerate the offending food by the age of two.

Celiac disease

Celiac disease is a permanent condition of gluten intolerance, defined on the basis of the pathology of the small bowel mucosa, which recovers when the patient is treated with a gluten-free diet, and reintroduction of gluten into the diet will produce a histological relapse in the jejunal mucosa. Application of these strict diagnostic criteria has led to the realization that there is a wide clinical spectrum within celiac disease, and has reinforced the need for biopsy confirmation in every patient (Fig 1).

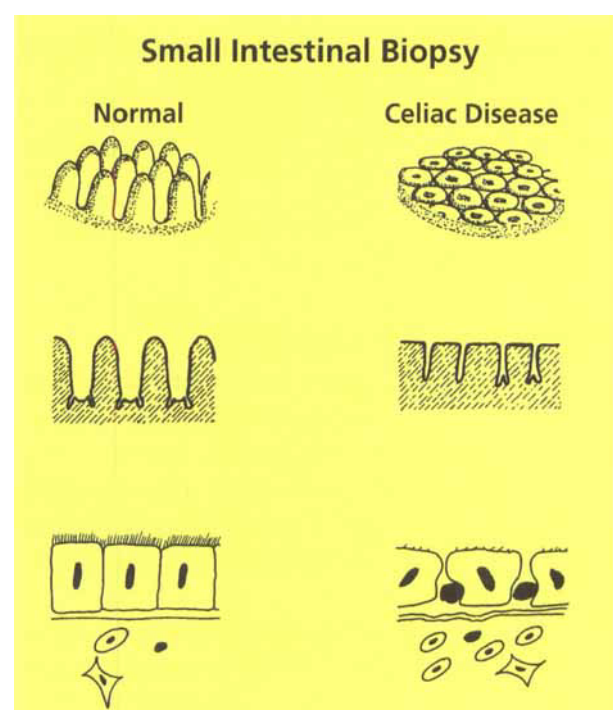


Fig 1

There is a considerable amount of data on celiac disease and on immunoregulation in experimental animals, to implicate induction of mucosal delayed-type hypersensitivity (DTH) as the underlying abnormality.

For reasons that are as yet unknown the clinical effects are remarkably heterogeneous. The textbook description of a celiac child is of a grumpy, rickety, anemic, growth retarded toddler with diarrhea, a pot belly and muscle wasting. It is now obvious that there are many children in whom the effects of malabsorption are much less severe so that only a single symptom or sign may be present,

for example growth retardation, iron deficiency anemia, or mild rickets. On the other hand, if gluten has been included in the diet from infancy, an accelerated form of the disease may occur, with abdominal distension, vomiting and constipation, suggestive of intestinal obstruction.

The condition may present in adult life as anemia, metabolic bone disease, diarrhea, or weight loss. Recent series have drawn attention to the numbers presenting with trivial, often unrelated, illness. Many cases of adult celiac disease will emerge as a result of investigation of weight loss alone, of minor abnormalities found on routine blood tests, or in the thorough work-up of patients with diseases known to be associated with celiac disease such as hyposplenism, recurrent aphthous ulceration, jejunal ulceration, abdominal lymphoma, old rickets.

A strict gluten-free diet for life is the cornerstone of management. This should exclude wheat, oats, rye and barley. However rice and maize are not toxic to celiacs, and can be useful as alternatives to protein-free wheat-derived flours. It must be accepted that patient compliance on such long-term treatment is not always ideal. Patients support groups, such as the Coeliac Society in the UK, play an important role, with practical advice on gluten-free products, recipes etc. Good food labelling is invaluable to celiacs, particularly for convenience foods. In some countries, suitable baby and some other foods are marked with a "gluten-free" symbol.

The effects of treatment should be monitored by simple clinical assessment (e.g. cessation of diarrhea) and, at 3-6 months, by repeat jejunal biopsy (Fig 2). The small bowel mucosa may not become completely normal in adults, and improvement may continue for 2 or more years.

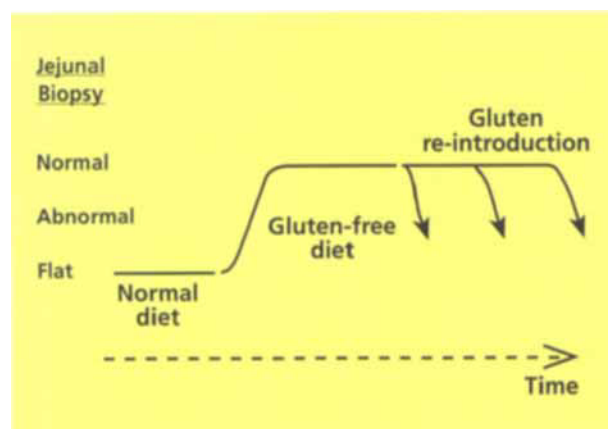


Fig 2. Results of gluten-free diet over time in celiac disease

Protein-losing enteropathy

When not accompanied by other signs of GI disease, this has in the past been attributed to food allergy. Certainly, in animal experiments, considerable increase in gut permeability to marker proteins occurs in association with anaphylaxis. However in clinical practice, a patch of lymphangiectasia or jejunal Crohn's disease should be considered.

Gastrointestinal bleeding

Blood loss associated with the use of formula diets instead of breast milk, has been proposed as an explanation of iron deficiency anemia in infants. There is no immunological evidence to support the theory that this phenomenon is important or that it has an immune basis.

Eosinophilic gastroenteritis

This term encompasses inflammatory lesions, discrete or diffuse, and the disease may affect any part of the gut. The relationship to foods probably varies from one case to another, and the presence or absence of atopy as an independent variable should be considered. Treatment with corticosteroids may be preferable to the empirical use of elimination diets. Proper studies of mucosal mast cells sometimes show that in fact these are abnormally abundant.

Intolerance

Mechanisms responsible include enzyme deficiency (e.g. lactase deficiency), pharmacological effects (e.g. due to caffeine), non-immunological histamine-releasing effects (e.g. by certain shellfish), and direct irritation (e.g. gastric acid in esophagitis, colonic wind in carbohydrate intolerance). Lactose intolerance is far and away the most important condition in this category.

Lactose absorption, lactase activity, lactose intolerance

Lactase is one of several disaccharidases contained within the brush border of the small intestine's epithelial cells (enterocytes). In the human, lactase activity is detectable in the fetal gut as early as eight weeks gestation. In most races, lactase activity drops sharply during childhood, but in some individuals, and in the majority of white European Caucasians, intestinal lactase persists into adult life. Family studies suggest that the ability to express lactase in adult life is inherited at a single

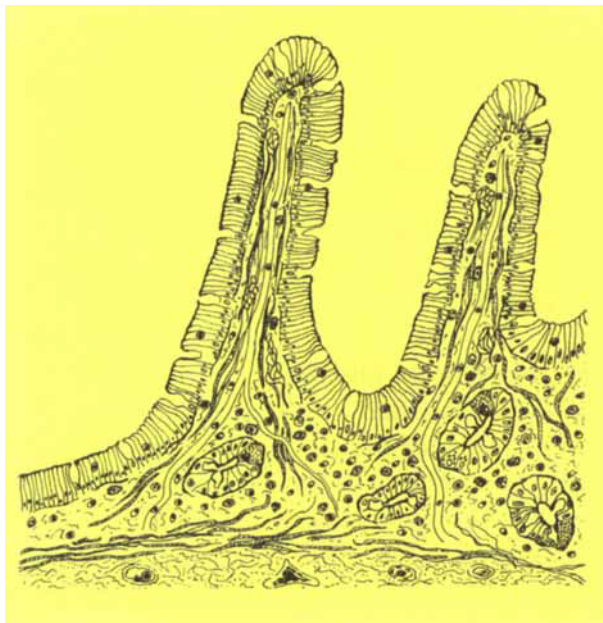


Fig 3. Small intestine and villi

gene locus.

Studies of the quantitative distribution of enterocyte enzymes along the villi and crypts of the intestine have shown quite different distribution patterns. In the case of lactase, there is virtually no enzyme activity in crypt enterocytes. Enzyme activity increases sharply in the mid-part of the villi and maximal enzyme activity per enterocyte is reached at the apex.

Thus enzyme activity may be reduced when there is disease of the small intestine with villus damage even in those with a homozygous inheritance for lactase persistence. Transient lactase deficiency and lactose intolerance are extremely important in diarrheal diseases and infections of infants. However because the adult intestine is relatively resistant to extensive epithelial damage, lactose intolerance secondary to infection, or in association with celiac disease, is very rarely seen in the adult (Fig 4).

Lactase status

The status can be tested by assay of the enzyme in a small bowel biopsy, or the capacity for lactose absorption can be evaluated by a non-invasive breath test.

On the other hand, lactose intolerance is a clinical phenomenon, usually associated with lactose malabsorption and delivery of unabsorbed carbohydrate into the colon. When an oral dose of lactose causes production of flatus, abdominal discomfort or diarrhea *and* the ingestion of a

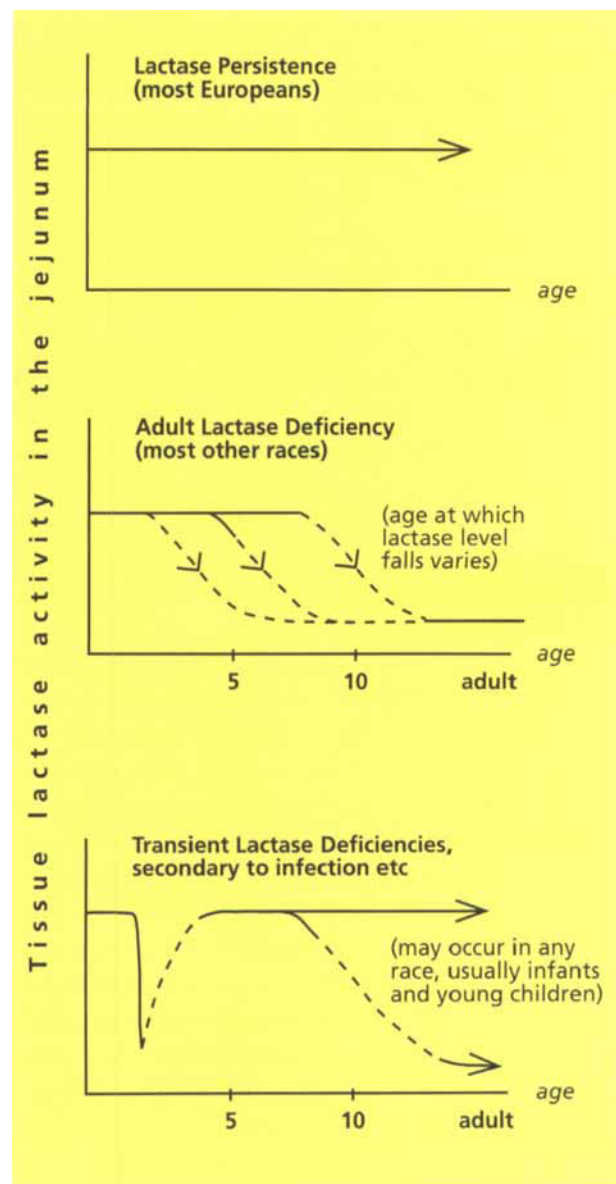


Fig 4. Lactase activity, age, race and deficiencies

similar dose of another carbohydrate does not produce these effects, it can be concluded that lactose malabsorption is likely to be present.

Clinical features of lactose intolerance

Adverse reactions which may develop after a lactase-deficient individual ingests lactose in food include nausea, bloating, abdominal pain and diarrhea. The clinical effects of lactose ingestion are closely related to dose and there is a wide variation among individuals.

Clinical syndromes of lactose intolerance

Modification of milk drinking habits

Milk avoidance is significantly commoner in lactose intolerant than tolerant patients.

Irritable bowel syndrome

Since the clinical effects of lactose intolerance are produced by altered gastrointestinal motility, the symptoms produced in some people will suggest a diagnosis of irritable bowel syndrome. Even when lactase deficiency is present in a patient with irritable bowel syndrome, the two diseases often co-exist and it is appropriate to treat the primary motility disorder by pharmacological or other dietary means (e.g. by an increase in dietary fiber).

The flatus production associated with lactose malabsorption may cause distress to patients and there are extremely colorful case reports in the literature.

Abdominal pain in children

Studies in the USA have shown lactose intolerance associated with abdominal pain is mainly relevant in children of the susceptible ethnic groups.

Secondary, reversible lactose intolerance

Disaccharide intolerance may occur as a transient phenomenon associated with a wide variety of diseases of the small intestine in childhood including gastroenteritis, celiac disease, giardiasis, protein calorie malnutrition, cow's milk protein intolerance, immunodeficiency syndromes and intestinal resections. Currently, World Health Organization recommendations for management of children recovering from acute diarrhea are that nutrition, including breastfeeding, should, in general, be introduced within 24 hours.

Psychological intolerance and links to gastrointestinal motility disorders

Psychologically-based food reactions (food aversions)

These comprise both psychological avoidance - when the subject avoids food for psychological reasons - and psychological intolerance, which is an unpleasant bodily reaction caused by emotions associated with the food rather than the food itself and which does not occur when the food is given in an unrecognizable form.

There is plenty of evidence that local immunological reactions can influence gastrointestinal motility. Local reactions of immediate hypersensitivity can produce prepyloric or pyloric spasm, hypermotility of the small and large intestines and edema with increased secretion of mucus and rectal spasm. The clinical effects include nausea,

vomiting, abdominal pain and diarrhea.

However many apparently healthy people complain of food-provoked symptoms including nausea, bloating, abdominal pain, constipation and diarrhea, with no evidence of an immune reaction being involved. These features are those of the irritable bowel syndrome. The symptoms may arise either because of abnormal motility or because an individual is unduly aware of sensations accompanying normal contraction or distension of the gut. Not surprisingly, when these symptoms are closely related to foods, and when the person affected is introspective or anxious, the idea that there is some sort of food allergy underlying the symptoms is appealing.

Many people who avoid specific foods and have an unsubstantiated self-diagnosis of food allergy suffer from the irritable bowel syndrome. Their self-imposed alterations in diet will influence gut motility, the composition of the stools and the production of gas, and in an introspective individual such physiological changes greatly reinforce the patient's concern. Self-imposed elimination diets (or diets recommended by unorthodox practitioners on the basis of unproved laboratory test) may be nutritionally unsound and usually do not relieve the symptoms. Ideally, these patients should be treated psychologically as well as physically.

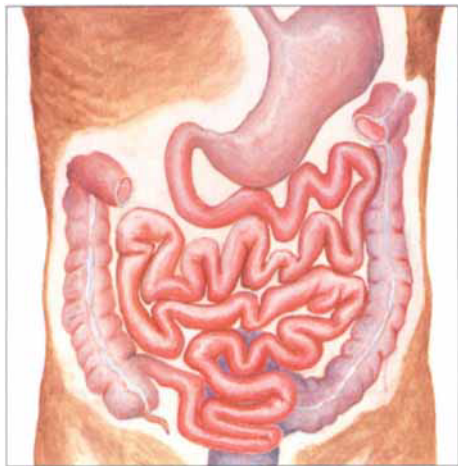
Spectrum of intolerance to a representative food - wheat

Changes in the amount of bread in the diet can have quite striking effects on gastrointestinal physiology. Typically an increase in the amount of dietary intake (e.g. change from white to brown bread) speeds up mouth to anus transit rate, increases stool weight, produces a softer stool, increases frequency of defecation and also increases the quantity of flatus. Awareness of these physiological changes may, particularly in introspective individuals, lead to anxiety or discomfort, and the clinical effects merge with those of the irritable bowel syndrome. Studies of the metabolism of bread starch have clearly shown that when flour with wheat gluten is ingested there is a degree of starch malabsorption and this is the substrate for bacterial metabolism and gas production in the cecum.

There are, normally, immune reactions to dietary proteins, particularly secretory antibodies of IgA

class, low titers of serum antibody and specific down-regulation of IgE and T cell reactivity (oral tolerance). From time to time abnormal immunity to foods, either in the form of inappropriately high titers, or qualitatively altered responses, produce disease. In the case of wheat, these diseases comprise celiac disease (a permanent gluten-sensitive enteropathy), the associated condition of dermatitis herpetiformis, transient gluten-sensitive enteropathy in infancy, wheat-sensitive diarrhea without enteropathy and baker's asthma. The latter two conditions are caused by reactions to non-gluten wheat proteins.

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