defective intestinal mucosal immune function. The relatively high oral vaccine failure rates in regions where environmental enteropathy is endemic has been proposed to be due to defective mucosal immune function.

There are presently no accepted clinical, laboratory, or histopathologic criteria that allow diagnosis of environmental enteropathy. Intestinal biopsy specimens have been examined in a small number of cases, and reported histologic features are more similar to severe celiac disease than infectious enteritis.

The underlying causes of environmental enteropathy are unknown, but defective intestinal barrier function, chronic exposure to fecal pathogens and other microbial contaminants, and repeated bouts of diarrhea within the first 2 or 3 years of life are likely involved. Many pathogens are endemic in these communities, but no single infectious agent has been linked to environmental enteropathy. Neither oral antibiotics nor nutritional supplementation, with calorie-dense foods, vitamins, or minerals, are able to correct these deficits. Moreover, recent data suggest that irreversible losses in physical development may be accompanied by uncorrectable cognitive deficits. Thus, the global impact of environmental enteropathy, which is estimated to affect more than 150 million children worldwide and may contribute to a very large number of childhood deaths, is difficult to overstate.

Autoimmune Enteropathy

Autoimmune enteropathy is an X-linked disorder characterized by severe persistent diarrhea and autoimmune disease that occurs most often in young children. A particularly severe familial form, termed *IPEX*, an acronym denoting immune dysregulation, polyendocrinopathy, enteropathy, and X-linkage, is due to a germline mutation in the *FOXP3* gene, which is located on the X chromosome. FOXP3 is a transcription factor expressed in CD4+ regulatory T cells, and individuals with IPEX and *FOXP3* mutations have defective function of these cells. Other defects in regulatory T cell function have also been linked to less severe forms of autoimmune enteropathy. Autoantibodies to enterocytes and goblet cells are common, and some patients may have antibodies to parietal or islet cells. Within the small intestine, intraepithelial lymphocytes may be increased, but not to the extent seen in celiac disease, and neutrophils are often present. Therapy includes immunosuppressive drugs such as cyclosporine and, in rare cases, hematopoietic stem cell transplantation.

Lactase (Disaccharidase) Deficiency

The disaccharidases, including lactase, are located in the apical brush-border membrane of the villus absorptive epithelial cells. Because the defect is biochemical, biopsy histology is generally unremarkable. Lactase deficiency is of two types:

- *Congenital lactase deficiency*, caused by a mutation in the gene encoding lactase, is an autosomal recessive disorder. The disease is rare and presents as explosive diarrhea with watery, frothy stools and abdominal distention upon milk ingestion. Symptoms abate when exposure to milk and milk products is terminated, thus removing the osmotically active but unabsorbable lactose from the lumen. As a result, congenital lactase deficiency was often fatal prior to the availability of soy-based infant formula.
- *Acquired lactase deficiency* is caused by down-regulation of lactase gene expression and is particularly common among Native American, African American, and Chinese populations. Acquired lactase deficiency can develop following enteric viral or bacterial infections and may resolve over time. Symptoms of acquired lactase deficiency, including abdominal fullness, diarrhea, and flatulence, due to fermentation of the unabsorbed sugars by colonic bacteria, are triggered by ingestion of lactose-containing dairy products.

Abetalipoproteinemia

Abetalipoproteinemia is a rare autosomal recessive disease characterized by an inability to secrete triglyceride-rich lipoproteins. It is caused by a mutation in the microsomal triglyceride transfer protein (MTP) that catalyzes transfer of lipids to specialized domains of the nascent apolipoprotein B polypeptide within the rough endoplasmic reticulum. MTP also promotes production of triglyceride droplets within the smooth endoplasmic reticulum. Without MTP, enterocytes cannot assemble or export lipoproteins. This results in intracellular lipid accumulation. The malabsorption of abetalipoproteinemia is therefore a failure of intraepithelial processing and transport. Because of the triglyceride accumulation, vacuolization of small intestinal epithelial cells is evident and can be highlighted by special stains, such as oil red-O, particularly after a fatty meal.

Abetalipoproteinemia presents in infancy and the clinical picture is dominated by failure to thrive, diarrhea, and steatorrhea. Patients also have a complete absence of all plasma lipoproteins containing apolipoprotein B, although the gene that encodes apolipoprotein B itself is not affected. Failure to absorb essential fatty acids leads to deficiencies of fat-soluble vitamins as well as lipid membrane defects that can be recognized by the presence of *acanthocytic red cells (burr cells)* in peripheral blood smears.

KEY CONCEPTS

Congenital and acquired (non infectious) disorders of the intestines

- **Abdominal hernias** may occur through any weakness or defect in the wall of the peritoneal cavity, including inguinal and femoral canals, the umbilicus, and sites of surgical scars.
- **Intussusception** occurs when a segment of intestine telescopes into the immediately distal segment. It is the most common cause of intestinal obstruction in children younger than 2 years of age.
- **Ischemic bowel disease** of the colon is most common at the splenic flexure, sigmoid colon, and rectum; these