Specific Etiologies of Chronic Diarrhea in Infancy

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Diarrhea is one of the most common symptoms of illness in pediatric practice. It usually appears in the form of acute diarrhea, but it may also progress to a chronic state.

The differential diagnosis of chronic diarrhea is very extensive (Table 1). Regardless of specific etiology, the major pathogenetic mechanisms are osmotic diarrhea, increased intestinal secretion, inhibition of active ion absorption, and abnormalities of motility (1). In Israel, most cases of chronic diarrhea can be attributed to a limited group of etiologies, namely, postinfectious gastroenteritis, parasitic infestation, disaccharidase deficiencies, celiac disease, and chronic non-specific diarrhea.

The work-up of patients with chronic diarrhea can be very tedious, and at times, even after sophisticated studies, the exact diagnosis cannot be reached. In such cases the patients should be treated symptomatically, bypassing the pathophysiologic disturbances. This enables the infants to grow and develop and in some cases to overcome the ill effects of malabsorption secondary to the chronic diarrhea.

In this chapter, I try to summarize some of the specific etiologies of chronic diarrhea in infancy and childhood, with emphasis on pathophysiology and approaches to therapy.

INFECTION AND INFESTATION

Bacterial

Escherichia coli

Escherichia coli can cause diarrhea by a variety of mechanisms. These include release of either heat-labile or heat-stable enterotoxins and invasion of the bowel mucosa (2). Recently, a third mechanism has been proposed: the ability of the bacteria to colonize and adhere to the small intestinal mucosa (3).

The heat-labile enterotoxin of E. coli can produce a cholera-like secretory diarrhea through activation of adenylate cyclase and stimulation of the intra-
### TABLE 1. Etiology of chronic diarrhea

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The cellular production of cyclic AMP. The latter interferes with coupled sodium and chloride absorption by the villous cells while stimulating secretion of anions from the crypt cells. In contrast, the heat-stable enterotoxin stimulates guanylate cyclase activity, which enhances the production of cyclic GMP (4). In addition, the toxin inhibits ATPase. The net result is secretion of electrolytes followed
by net water movement into the intestinal lumen. Since the coupled sodium–glucose absorption is not interrupted, the treatment should consist of an oral solution containing electrolytes as well as glucose. The invasive strain of \textit{E. coli} produces the characteristic features of bacterial dysentery: local inflammation, hyperemia, ulceration, and exudate. The invasive strains are usually limited to several serotypes. The treatment consists of absorbable antibiotics based on the sensitivity assay of the stool culture.

Enteropathogenic \textit{E. coli} serotypes that are nontoxigenic and noninvasive have also been recognized as causes of diarrhea. The pathophysiologic mechanism by which these strains produce disease remains obscure. In 1980 Ulshen and Rollo (3) described an infant suffering from chronic diarrhea with \textit{E. coli 0125} overgrowth in the small intestine. Since the initial description, several other reports have described enterocyte-adherent \textit{E. coli 0119} and \textit{0111} causing protracted diarrhea in infants (5,6). Disaccharidase activities were diminished in Ulshen's patient. On light microscopy the villi were observed to be blunted, and crypt hypertrophy and infiltration of the lamina propria with inflammatory cells, mainly histiocytes, have been described. Electron microscopy in the areas of bacterial adherence has revealed that the enterocytes have blunted microvilli, diminished glycocalyx, and "cupping" of the plasma membrane around bacteria. The actin filaments of microvilli and a portion of the terminal web were also absent. The damaged enterocytes had large lysosomes, disorganized endoplasmic reticulum, and swollen mitochondria (5). Successful treatment has included either intravenous gentamicin or oral neomycin for 5 days and nutritional support.

\textit{Yersinia enterocolitica}

\textit{Yersinia} can cause chronic diarrhea and colicky abdominal pain, at times accompanied by erythema nodosum and arthritis (7). Fever is sometimes present (8), and the pain is often localized to the right lower quadrant, mimicking acute appendicitis (9). Diarrhea is present in 80% of the patients, and gross blood is often present (10). Pathologic studies have revealed terminal ileal and colonic mucosal ulceration with acute and chronic inflammation. In addition to invasion, enterotoxin production has also been postulated (8). The recommended treatment is trimethoprim, tetracycline, or chloramphenicol for 2 weeks.

\textit{Campylobacter jejuni}

\textit{Campylobacter} has recently been incriminated as a common bacterial cause of enteritis (11). In a typical case, the patient exhibits diarrhea, abdominal pain, and fever. Bloody stools occur in 30% of the patients. Usually the patients recover quickly, but in some patients, the disease may be relapsing or persistent (12). The pathogenesis of \textit{Campylobacter} infection is probably by direct mucosal invasion of the gut. Evidence from autopsy findings suggests that the organisms
have infected the small intestine as well. However, colitis resembling inflammatory bowel disease has also been reported in an adult (13). It is claimed that erythromycin is the drug of choice, but we have observed that an in vitro sensitivity test demonstrates resistance to erythromycin in only one of 20 patients (14).

As has been described in the literature, *Campylobacter* is sensitive to aminoglycosides and to chloramphenicol (15). This is consistent with our findings.

Salmonella

*Salmonella* infection can cause either dysentery or watery diarrhea. The organisms invade the distal small intestine and the large bowel (16). *Salmonella* can penetrate the mucosa, resembling *Shigella* infection, or provoke secretion with increased colonic cyclic AMP levels (17). Prostaglandin-enhanced secretion in *Salmonella*-induced secretory diarrhea has recently been demonstrated (18). Since prostaglandins are potent activators of adenylate cyclase, elevated cyclic AMP levels may therefore cause secretion of electrolytes and fluid. The disease is usually self-limited, and antibiotic treatment does not modify the natural history of the illness; moreover, it prolongs the carrier state. It is our practice, however, to treat young infants or debilitated patients with ampicillin, trimethoprim, or chloramphenicol.

Shigella

*Shigella* organisms usually produce diarrhea characterized by the presence of blood, pus, and mucus. The organisms produce enterotoxins that affect mainly the distal large bowel; the organisms penetrate the mucosa and cause ulceration, hemorrhage, and exudate (17). On rectal biopsy, crypt abscesses indistinguishable from ulcerative colitis can be found. The organisms can also produce a neurotoxin that at times can cause convulsions even prior to the onset of the diarrhea. The disease is usually self-limited, but chronic diarrhea can occur in rare cases. An increased percentage of immature neutrophils regardless of the total leukocyte count suggests the diagnosis of shigellosis. Treatment with ampicillin or trimethoprim is recommended, especially in infants.

Viral

The etiologic role of viral agents in producing gastroenteritis has been suspected for many years. In 1945, Reimann et al. (28) produced viral disease in healthy volunteers with oral administration of a stool filtrate. Hodes (19) enumerated several viruses that have been proven or are suspected to induce a symptomatic enteritis. Rotavirus is the most common agent in children under the age of 5 years. The incidence of diarrhea caused by rotavirus is highest during the winter months. Transmission is presumably from person to person by the fecal–oral
route. The incubation period is between 2 and 3 days. Vomiting may precede the diarrhea, and fever is found in about half of the patients. The diarrhea usually lasts for 4 to 8 days. Tympanic membrane and pharyngeal erythema accompany the diarrhea in almost half of the patients (30). There is evidence that breast feeding provides some protection against rotavirus infection (31).

The pathophysiology of viral enteritis in the human and in various experimental animals has been studied extensively. Bishop et al. (32) demonstrated diminished disaccharidase activities in the proximal small intestine in children suffering from acute viral enteritis. In the newborn piglet model, infection with either human rotavirus or transmissible gastroenteritis virus resulted in a reduction of sodium transport as a result of the immaturity of the undifferentiated crypt-like enterocytes on the villi and diminished Na\(^+\)-K\(^+\) ATPase activity (33,34). Holmes et al. (35) suggested that lactase acts as a receptor and as an uncoating enzyme for rotavirus. This hypothesis may also explain, at least in animal models, the susceptibility of neonatal but not adult animals to rotavirus, as adults normally have low activity of lactase. We have shown that in suckling mice infected with reovirus type 3, enterokinase activity was significantly diminished, as were lipase and amylase activities (36). These finding are possible contributing factors to the pathogenesis of viral enteritis (37). During a 12-week study period, Yolken et al. (38) recently demonstrated gastroenteritis caused by enteric-type adenovirus in 14 of 27 cases of diarrhea. Adenovirus was found in the stool of only one of 72 children without diarrhea.

There is as yet no specific treatment for viral enteritis. Thus, the approach toward viral enteritis is preventive, by improved hygiene and symptomatic treatment. We can hope that an effective vaccine for the most common viral pathogens will result in a reduction of the high incidence of viral diarrhea.

Parasitic Infestation

Giardia lamblia

The protozoan *Giardia lamblia* is a frequent gastrointestinal pathogen and is a very common pathogen in Israel. Most individuals infected with *Giardia lamblia* are asymptomatic. In symptomatic cases, diarrhea is the most common complaint and is most often acute and self-limited. At times, a chronic relapsing water diarrhea, steatorrhea, and malabsorption are found (19). Anorexia, nausea, malaise, abdominal distention, weight loss, and abdominal pain are reported frequently (20). The pathogenesis of diarrhea in giardiasis remains obscure. Nevertheless, several mechanisms have been proposed: mechanical occlusion of the mucosa, competition for nutrients, release of toxic products, epithelial damage with invasion of mucosa, altered motility, excessive secretion, bacterial overgrowth, deconjugated bile acids, decreased tryptic activity, vitamin B\(_{12}\) and folate malabsorption, protein-losing enteropathy, and disaccharidase deficiencies (21,22). A study of epithelial cell kinetics in a mouse model (23) demonstrated
an increased turnover of cells in the crypts and migration of immature cells to
the villi. These immature cells are less capable of normal absorption (23), and
thus the clinical presentation can resemble celiac disease. In patients with si-
multaneous celiac disease and giardiasis, the final diagnosis can be made only
after successful eradication of the protozoan and close surveillance of the patients,
Levinson and Nastro (24) reported an adult suffering from giardiasis with total
villous atrophy.

The association between giardiasis and immunodeficiency is well known (25).
Nonetheless, in our experience and that of others (20), IgA deficiency is no
more common in patients with giardiasis than in patients suffering from other
diarrheal illnesses.

All patients with giardiasis should be treated with metronidazole or quinacrine
for 7 days. However, in a recent report (26), only the combination of these two
drugs cured a patient suffering from chronic giardiasis. In another report, furazo-
lidine was found more effective and better tolerated than quinacrine for the
Treatment of giardiasis (27).

**Amebiasis**

*Entameba histolytica* causes colitis and ileitis, and in addition, it can invade
the liver and several other organs. The trophozoite invades the bowel, producing
typical ulcers with undermined edges. The clinical presentation can be dysentery-
like diarrhea, celiac-type syndrome, or chronic diarrhea. The presence of ingested
erthrocytes inside the parasite is claimed to be indicative of virulence. The
drug of choice for asymptomatic intestinal infection is metronidazole. For symp-
tomatic patients, metronidazole or paromomycin have both been recommended.

**Parenteral Diarrhea**

Diarrhea is frequently associated with upper respiratory infection, otitis media,
and urinary tract infection and may at times be accompanied by abdominal
pain. The mechanism of the diarrhea is unknown, but it can be attributed to
the etiological factors causing the infection, to the antibiotic treatment, or to
other medications prescribed in some of the patients. Tallett et al. (39) studied
27 children with rotavirus diarrhea; one-third of their patients had manifested
respiratory symptoms. They suggested that the virus may concurrently infect
the respiratory tract. Yolken et al. (38) described an enteric type of adenovirus
as a causative agent of infantile diarrhea. Thirteen of the 14 children with this
type of adenovirus had diarrhea and respiratory symptoms.

Among our 21 patients suffering from *Campylobacter* enteritis, nine had
additional foci of infection: two had otitis media, one had a respiratory infection,
and six had both. All of these patients belonged to the younger age group (14).
De Sousa et al. (40) reported that in nine out 16 infants with intractable diarrhea,
latent mastoiditis was found. They proposed that the occult ear infection could
be primary, secondary, or concurrent with the diarrhea. Thus, either the same organism causes the enteric disease and systemic symptoms or the patient with enteritis, especially with chronic diarrhea, is more susceptible to other infections.

**Postinfectious Diarrhea**

Postinfectious diarrhea is defined as the persistence of diarrhea and failure to gain weight more than 7 days after admission to the hospital for gastroenteritis (41). In a recent report, Halliday et al. (41) described a 19% incidence of persistent diarrhea. In more than half of their patients with postinfectious diarrhea, etiological factors could be identified. These factors include di- or monosaccharide intolerance, persisting or unsuspected pathogens, and cow's milk protein allergy. The authors also defined a high-risk group of patients in whom there was a significant potential for developing postinfectious diarrhea. The parameters included young age, noncaucasian origin, previous history of diarrhea, longer duration of diarrhea prior to hospitalization, use of antibiotics or antidiarrheal agents prior to admission, severe diarrhea during the initial enteritis, weight below the 10th percentile for age, lower blood urea nitrogen concentration, and bacterial etiology of the initial enteritis. Tripp et al. (42) demonstrated that in patients with postinfectious diarrhea, the mucosal Na\(^+\)-K\(^+\) ATPase activity of the small intestine was significantly reduced compared with the controls, but the activity of adenylate cyclase did not change.

Clinically, early diagnosis and management with a disaccharide-free formula is indicated. It is important to avoid prolonged periods of starvation, which might cause malnutrition and exocrine pancreatic dysfunction and thus a malabsorptive state, each of which may contribute to the vicious cycle of diarrhea (43). In severe cases, elemental diets or total parenteral nutrition can be life saving.

**DIETARY**

**Cow's Milk Protein Allergy**

Cow's milk protein-sensitive enteropathy is the most common allergy in infancy. There are more than 20 proteins in cow's milk, the most antigenic of which are \(\beta\)-lactoglobulin, casein, \(\alpha\)-lactalbumin, bovine serum globulin, and bovine albumin. \(\beta\)-Lactoglobulin is by far the most allergenic (44). Milk protein allergy can cause a spectrum of clinical manifestations, the most common being gastrointestinal symptoms such as vomiting, diarrhea, abdominal pain, gastrointestinal bleeding, colitis-like syndrome, protracted diarrhea of infancy, and protein-losing enteropathy. Recurrent respiratory infections, chronic rhinitis, wheezing, hemoptysis, otitis media, eczema, anaphylaxis, irritability, failure to gain weight, and sudden infant death syndrome have all been described in relation to cow's milk protein allergy (45). The incidence of cow's milk protein
allergy varies between 0.3 to 7% and is even higher in allergic individuals. Undoubtedly, many infants who are diagnosed as having cow’s milk protein allergy are actually suffering from secondary lactase deficiency. On the other hand, Iyngkaran et al. (46) demonstrated that in infants recovering from gastroenteritis, secondary cow’s milk protein allergy commonly occurs. The latter is an important cause of acquired carbohydrate intolerance as well as malabsorption of monosaccharides.

The immune reaction towards cow’s milk protein includes several stages. Initially, there is an increase in the population of plasma cells producing IgE as well as mast cell degranulation and release of histamine, serotonin, and slow-reacting substance of anaphylaxis. These substances, in turn, probably stimulate smooth muscle contraction and increase vascular permeability. Concomitantly, the lamina propria is infiltrated with eosinophils and polymorphonuclear leukocytes. Twenty-four hours after milk challenge, the small intestinal mucosa demonstrates an increase in IgA plasma cells (47). Other than these findings, the histology varies from normal to focal villous atrophy or even subtotal villous atrophy.

The treatment is a milk-protein-free formula. It is advisable to avoid formula containing soy protein, as 30 to 40% of infants with milk protein allergy also potentially suffer from soy protein allergy. Usually the majority of the patients achieve tolerance of milk protein during their second year of life.

**Soy Protein Allergy**

The clinical spectrum of soy protein allergy is very similar to that of cow’s milk protein sensitive enteropathy. Since the majority of these patients are also sensitive to cow’s milk protein, treatment with formula containing casein hydrolysate is recommended. When there is no sucrose intolerance, Nutramigen® (Mead Johnson) is satisfactory, but in cases with associated sucrose intolerance, Pregestimil® (Mead Johnson) is the formula of choice.

**Chronic Nonspecific Diarrhea**

Chronic nonspecific diarrhea, also known as irritable bowel syndrome of children, appears in children aged between 6 months and 2 years. It is a self-limiting disease, usually ceasing spontaneously before the age of 4 years. The typical patient has 4 to 10 loose mucoid bowel movements per day. However, the patient’s growth and development are normal, and there is no associated malabsorption (48).

The etiology of the diarrhea is unknown (49). It usually follows an acute infection or gastroenteritis. Cohen et al. (50) observed that among their patients with chronic nonspecific diarrhea, dietary manipulation, namely, a low-fat diet, was the common denominator. When they prescribed a daily intake of at least 50 g of fat, the parents of most of their patients reported resolution of the
diarrhea. As the increase in fat intake was the only change in the management of their patients, it is conceivable that a low-fat diet might be incriminated in the pathogenesis of chronic nonspecific diarrhea. Cohen et al. (50) suggested that the explanation for the diarrhea while on a low-fat diet is that fat normally delays gastric emptying time and reduces intestinal transit time. Lloyd-Still (51) studied 108 children with chronic diarrhea. The majority of the children had chronic nonspecific diarrhea. He concluded that unnecessary elimination diets for prolonged periods perpetuated the problem.

Dodge et al. (52) demonstrated elevated plasma prostaglandin $F_{2\alpha}$ levels in many of their patients with chronic nonspecific diarrhea. The origin of the increased plasma prostaglandin in these patients has not been defined. A good clinical response was observed in some of the patients following treatment with aspirin, a known prostaglandin synthetase inhibitor. They also found marked improvement in 12 patients who were treated with the antidiarrheal agent loperamide regardless of the patients' prostaglandin levels. This drug was found to bind to opiate receptors and has been shown to prevent diarrhea induced by administration of prostaglandins. Although small intestinal mucosal morphology is normal in these children, Tripp et al. (42) demonstrated significantly elevated $Na^+\text{--}K^+$ ATPase and adenylate cyclase activities in jejunal biopsies obtained from the patients. It is possible that enhanced synthesis of prostaglandins may account for the increased adenylate cyclase activity.

CARBOHYDRATE MALABSORPTION

Secondary disaccharidase deficiencies are a common occurrence in pediatric practice. Many factors can lead to damage to the brush border membrane and secondary disaccharidase deficiency. These include infectious, allergic, inflammatory, toxic, and mechanical insults. As a result, disaccharidase deficiencies ensue. Primary specific enzyme deficiencies also occur without mucosal injury; these are discussed separately. Monosaccharide malabsorption can also be either secondary to mucosal destruction or, rarely, a primary phenomenon.

The degree of secondary disaccharidase deficiency is directly related to the extent and severity of the mucosal damage. Among the disaccharidases, lactase is the most vulnerable, the first to be affected, and the last to recover. Sucrase-isomaltase deficiency follows in frequency, and maltase deficiency occurs very rarely.

When disaccharidases are deficient, the absorption of the corresponding sugars is impaired. Unabsorbed carbohydrate is subsequently fermented by enteric bacteria into smaller molecules and organic acids, which are osmotically active and induce secretion of fluid and electrolytes into the bowel lumen. It is assumed that the increased intraluminal volume and acidity stimulate intestinal motility, decrease the transit time of the bowel content, and thus aggravate the diarrhea. The acidic fluid and the elevated concentration of the organic acids may also have a direct toxic effect on the transport mechanisms in the colon (53,54).
Since the colon plays a role in carbohydrate absorption by salvaging carbohydrate that is unabsorbed by the small bowel (55), colonic conservation of malabsorbed sugar is rendered less effective. The symptoms of carbohydrate malabsorption in infants vary and include explosive watery diarrhea, vomiting, dehydration, abdominal distention, crampy abdominal pain, and failure to thrive.

Treatment initially includes rehydration and, later, a diet that contains a replacement carbohydrate source for the disaccharide(s) that is not digested and absorbed.

**Primary Congenital Lactase Deficiency**

Congenital lactase deficiency was described by Holzel (56) in 1959. His diagnosis was based only on lactose tolerance tests. The diagnosis of primary lactase deficiency should consist of the demonstration of normal histology of the jejunal mucosa as well as normal levels of all brush border enzymes except for lactase. This disorder is quite rare. Lebenthal (57) reported that in more than 1,600 small intestinal biopsies, the diagnosis of probable congenital lactase deficiency was made in only one case. An infant with lactase deficiency would present watery diarrhea, vomiting, dehydration, irritability, abdominal distention, and failure to thrive shortly after the institution of a lactose-containing diet. Steatorrhea can also be a feature of lactase deficiency (58). It has been suggested that the osmotic diarrhea causes dilution of the intraluminal bile salts, thus decreasing the effective micellar concentration, which in turn diminishes fat digestion and absorption, eventually causing steatorrhea (58). A lactose-free diet is curative.

Primary late-onset lactase deficiency is very common, especially in some ethnic groups, where it affects older children and adults, but will not be further discussed herein.

**Congenital Sucrase-Isomaltase Deficiency**

Congenital sucrase–isomaltase deficiency is a rather common disorder, inherited as an autosomal recessive trait (59). Conflicting results have been reported concerning the molecular nature of sucrase–isomaltase deficiency. Preiser et al. (60) reported the absence of the protein band in the expected position of sucrase–isomaltase on polyacrylamide gel electrophoresis of mucosal homogenates. In contrast, Dubs et al. (61) demonstrated the presence of immunoreactive, functionally inactive sucrase–isomaltase by immunohistochemical methods. The sucrase–isomaltase molecule contains two distinct α-glucosidase subunits: sucrase and isomaltase. However, recently, Skovbjerg and Krasilnikoff (62) demonstrated the presence of the isomaltase moiety of the sucrase–isomaltase in one of their patients. They speculated that patients with sucrose intolerance constitute a heterogeneous group, some of the patients lacking both sucrase and isomaltase activities and others having residual active isomaltase.
Symptoms begin following introduction of sucrose to the diet. Starch appears to play a less important role in the pathogenesis of the disorder. The symptoms consist of watery diarrhea, abdominal distention, and stools that contain large amounts of lactic acid. In older children, irritability can be a feature, and growth may be normal or retarded.

The treatment consists of the elimination of sucrose and reduction of starches in the diet.

**Glucose-Galactose Malabsorption**

The syndrome of glucose-galactose malabsorption is of autosomal recessive inheritance (63). The defect is in the small intestinal active transport system that is shared by both glucose and galactose. The patients exhibit glucosuria, probably stemming from a similar defect in the renal tubules. The clinical findings are early onset of explosive watery diarrhea, dehydration, and metabolic acidosis. There is clinical improvement towards the second half of the first year.

Initially, treatment with carbohydrate-free formula with the addition of fructose is mandatory. When the infant is about 7 months old, foods with low starch content can be added (64).

**IMMUNE DEFICIENCIES**

Chronic diarrhea may be an important symptom of immune deficiency states. It can occur in association with congenital or acquired agammaglobulinemia, dysgammaglobulinemia, isolated IgA deficiency, thymic dysplasia, severe combined immunodeficiency, chronic granulomatous disease, and graft-versus-host disease. Gryboski (47) found that one-third of her patients suffering from chronic diarrhea had immune deficiencies. It is important to note that several specific entities with chronic diarrhea are accompanied by secondary immune deficiency. In intestinal lymphangiectasia, there is a cell-mediated immune defect as a result of loss of thymic-derived lymphocytes via the intestinal lumen. Similarly, in protein–calorie malnutrition, there is cell-mediated immune deficiency.

I shall focus the discussion on the entity of lymphoid nodular hyperplasia (LNH), which is commonly associated with immunoglobulin deficiency. This ill-defined disorder is subdivided pathologically by the presence of lesions in the small and large bowel. Its peak incidence is from 1 to 3 years of age. The etiology of the disorder is unknown, but it is considered to represent the normal response of lymphoid tissue to a variety of stimuli, mainly infections and allergens.

Histologically, it is characterized by the presence of lymphoid follicles with enlarged germinal centers within the lamina propria. When the LNH is confined to the small intestine, it may be associated with immunoglobulin deficiencies, mainly acquired agammaglobulinemia, isolated IgA or IgM deficiencies, dysgammaglobulinemia, thrombocytopenia, and leukopenia (65). Nonetheless, Knutsen et al. (66) described a child with colonic LNH in whom near-normal
serum immunoglobulin levels were found. However, studies of humoral immune function revealed a markedly reduced ability to synthesize antibodies in response to several antigens.

Lymphoid nodular hyperplasia of the small intestine is often accompanied by chronic diarrhea, infestation with *Giardia lamblia*, bacterial overgrowth, protein-losing enteropathy, and malabsorption. Several patients eventually developed adenocarcinoma of the gastrointestinal tract in midadult life.

Treatment of LNH associated with immunodeficiency has been essentially unsatisfactory. Prolonged administration of metronidazole may be indicated in order to eradicate *Giardia lamblia* infestation. Diarrhea and malabsorption are ameliorated by tetracycline and replacement therapy (67).

In the colon, LNH may be localized or affect the entire colon. The barium enema typically demonstrates small polypoid mucosal elevations 1 to 3 mm in diameter with central umbilication. Symptoms include rectal bleeding, abdominal pain, and diarrhea. Despite these findings, Riddlesberger and Lebenthal (68) concluded that in children LNH involving only the colon is a benign lesion and that treatment is not indicated.

**Congenital Chloride Diarrhea**

Congenital chloride diarrhea (CCD) is a rare familial disease with autosomal recessive inheritance. Holmberg et al. (69) reviewed 21 Finnish patients with CCD. Hydramnios was present in every case, suggesting that the diarrhea may be of intrauterine onset. Many of their patients had voluminous watery diarrhea from birth, accompanied by abdominal distention. The neonates had marked weight loss associated with hypochloremia and hyponatremia. Those who presented beyond the neonatal period suffered from diarrhea, failure to thrive, hypochloremia, hypokalemia, and metabolic alkalosis.

The defect in CCD is attributed to impaired active Cl⁻ absorption resulting from disturbance of the Cl⁻/HCO₃⁻ exchange mechanisms (70). The unabsorbed Cl⁻ is lost into the bowel lumen and causes osmotic diarrhea. The decreased HCO₃⁻ in the lumen causes the intestinal content to be more acidic, which in turn restricts the absorption of Na⁺. Secretion of K⁺ is also increased. The site of the defect in Cl⁻ absorption is the distal ileum and colon (69). The diarrhea results in hypovolemia and hypoelectrolytemia. As a result, the renin–angiotensin II–aldosterone system is stimulated. Hyperaldosteronism results in hypokalemic alkalosis and subsequently in nephrocalcinosis (71).

As the upper small intestine is still permeable to Cl⁻, the distal loss can be successfully compensated for by administration of an oral supplement that contains the necessary electrolytes and water. Adequate replacement of water, NaCl, and KCl prevents the secondary renal lesions and the growth retardation, but the diarrhea persists and even increases with age. Treatment with a prostaglandin synthetase inhibitor corrects the electrolyte imbalance and the elevated renin and aldosterone levels (72), but it cannot replace the continuous intake
of water, NaCl, and KCl. It may be of value only in patients who are on inadequate replacement therapy or in the initial management of patients who are diagnosed later in life if they have marked hyperreninemia.

**Abetalipoproteinemia**

Abetalipoproteinemia is a rare genetic disease inherited as an autosomal recessive trait (73). It is characterized by fat malabsorption, failure to thrive, and acanthocytosis, with subsequent development of ataxia and retinitis pigmentosa. Death in early adult life has been reported, usually as a result of cardiac involvement (74).

The basic biochemical defect is the absence of β-lipoproteins secondary to a defect in the corresponding apoproteins. Following a fatty meal, chylomicrons are absent from the serum, and there are decreased plasma levels of cholesterol, triglycerides, and phospholipids. Small intestinal biopsy reveals relatively normal villous architecture except for the existence of fat droplets in the enterocytes (Fig. 1). The absence of the apoprotein, which is a part of the fat carrier moiety, leads to a defect of lipid transport from the absorptive cells to the lymphatics. Treatment consists of a low-fat diet with supplementary medium-chain triglycerides and vitamins A, E, and K (74,75).

![FIG. 1. Abetalipoproteinemia. Small intestinal biopsy; normal villous architecture. Note fat droplets in the epithelial cells. (Courtesy Dr. Y. Bujanover, Rokah Hospital, Tel Aviv, Israel.)](image-url)
Wolman's Disease

Abramov et al. (76) in 1956 described a patient suffering from generalized xanthomatosis with calcified adrenals. Since then, few other patients with this extremely rare entity have been described. Wolman's disease is a cholesterol storage disease of unknown etiology, but an absence of acid lipase in the liver and spleen has been postulated. Lipids are stored within the reticuloendothelial system as well as in the epithelial cells of the intestinal mucosa. Histology of the small intestine reveals general loss of villous structure with mucosal atrophy and foamy histiocytes in the lamina propria. Onset of diarrhea occurs in early life and tends to be chronic, accompanied by vomiting, poor weight gain, abdominal distention, and marked hepatosplenomegaly. Vacuolated lymphocytes and calcification within enlarged adrenals are characteristic. There is no known therapy for this disease, and the outcome has been fatal in all of the reported patients (77).

Acrodermatitis Enteropathica

Acrodermatitis enteropathica (AE) is a rare familial disorder with autosomal recessive inheritance. The disease may be precipitated on weaning from breast feeding to cow's milk. It is typically characterized by dermatitis involving the perioral and perianal regions and distal extremities, chronic diarrhea, failure to thrive, and alopecia (Fig. 2) (78). There is also a defect of cell-mediated immunity (79). Patients with AE have been shown to have low plasma zinc levels, but

FIG. 2. Acrodermatitis enteropathica. Child with alopecia, dermatitis on perioral, perianal, and lower extremities. (Courtesy Dr. S. Freier, Shaare Zedek General Hospital, Jerusalem, Israel.)
several reports (80,81) have demonstrated the occurrence of the disease without hypozincemia. Nonetheless, these patients had a good clinical response to therapy with zinc, and cessation of zinc treatment resulted in relapse.

The small intestinal biopsies obtained from patients with AE may show normal mucosal architecture or focal lesions with partial villous atrophy and inflammatory cell infiltration in the lamina propria (82). Bohane et al. (83) described the electron microscopic findings of Paneth cells containing inclusion bodies that disappeared after zinc therapy. They concluded that the inclusion bodies may represent a derangement of Paneth cells in AE related to zinc deficiency.

A few cases of optic atrophy have been reported in surviving patients with AE. This finding was initially attributed to iodochlorhydroxyquin, which was formerly the treatment for AE. Sturtevant (84) hypothesized that the optic atrophy may be secondary to zinc deficiency per se.

Recently, Zimmerman et al. (85) and Parker et al. (86) described premature infants who were fed human milk exclusively and developed transient AE. Since the major accumulation of zinc occurs during the last trimester, it is conceivable that in the premature infant, the total body zinc stores are diminished. In addition, Zimmerman et al. (85) demonstrated low zinc content in the mothers’ milk of these premature infants. They speculated that a deficiency or abnormality of a zinc-binding ligand is responsible for the low zinc content of the milk.

Treatment with zinc sulfate, 150 mg/day orally, produces a dramatic clinical recovery.

HORMONE-SECRETING TUMORS

APUDoma

Neural crest tumors account for 8% of pediatric malignancies (87). Ectopic hormonal secretion by the tumor can cause protracted diarrhea, but its incidence is less than 10% of pediatric patients suffering from neural crest tumors (88). These tumors are included in a group referred to as APUDoma (amine precursor uptake and decarboxylation) (89). Verner and Morrison (90) reviewed the pancreatic cholera syndrome, which is characterized by watery diarrhea, hypokalemia, and achlorhydria, associated with non-β-islet-cell tumor of the pancreas. The proposed mediator of effects of these tumors is vasoactive intestinal polypeptide (VIP) (91). In children, only ganglioneuromas and ganglioneuroblastomas have been associated with production of VIP (87,92). It was initially believed that the catecholamines were the cause of the diarrhea in neural crest tumors. However, it was found later that the diarrhea ensued regardless of the catecholamine levels and only when VIP levels were elevated in the plasma or tumor tissue (87). Thus, the diarrhea is presumably related to elevated VIP. When the tumor is removed, and VIP levels decrease, the diarrhea abates (93).

Carcinoid syndrome occurs rarely in childhood. Presenting symptoms include diarrhea, abdominal cramps, flushing of the face and upper extremities, and
bronchial wheezing. These symptoms usually denote metastatic seeding of the liver. Urinary excretion of 5-HIAA is usually increased. The diarrhea and other symptoms are believed to be related to tumor-mediated elevation of serotonin, bradykinin, and prostaglandins (94). It is interesting to note that the latter two mediators were claimed to be responsible for the watery diarrhea seen in patients with medullary carcinoma of the thyroid.

Zollinger–Ellison Syndrome

Zollinger–Ellison syndrome is seldom encountered in the pediatric population. It is caused by a gastrin-secreting tumor, usually arising in the pancreas or its vicinity (95). It is characterized by peptic ulcer disease, usually refractory to medical treatment. More than one-third of the patients suffer from diarrhea, and approximately 7% of the patients present with secretory diarrhea. The pathophysiologic mechanisms producing the diarrhea are complex and probably operate simultaneously. Gastric acid hypersecretion undoubtedly plays a major role in the pathogenesis of both the secretory diarrhea and the steatorrhea. The acid in the upper small intestine exerts a deleterious effect on the mucosa, which can lead to subtotal villous atrophy. The pH in the duodenal lumen is decreased; hence, pancreatic enzymes, especially lipase, are inactivated. At the acidic pH, bile salts tend to precipitate, and their emulsifying capacity is thereby decreased, further contributing to the steatorrhea. Hypergastrinemia alone increases intestinal secretion of potassium and inhibits the absorption of sodium and water by the small intestine, thereby intestifying the diarrhea (96).

There are essentially two approaches to therapy: total gastrectomy and H₂ receptor antagonists. Buchta and Kaplan (97) in 1971 reviewed the literature relating to children with Zollinger–Ellison syndrome and concluded that all the long-term survivors had undergone total gastrectomy. It has been suggested that total gastrectomy may result in the regression of the primary tumor and its metastases. However, Zollinger et al. (98) found no evidence of tumor regression following total gastrectomy among their patients. As total gastrectomy has obvious disadvantages, nonsurgical approaches have been attempted. The medical treatment with cimetidine provides an alternative to total gastrectomy (99) in most patients. Drake et al. (95) reported successful treatment with cimetidine in a 12-year-old boy. Richardson et al. (100) recommended vagotomy and administration of cimetidine for the management of these patients. This combined approach produced excellent results. Moreover, it has the potential of discovery and removal of isolated tumors in some patients.

ENDOCRINE DISORDERS

Hyperthyroidism

Diarrhea is a common symptom in hyperthyroidism. Usually the other symptoms of thyrotoxicosis lead to the diagnosis. The diarrhea abates on specific treatment with antithyroid drugs and/or surgery.
Adrenal Insufficiency

In patients suffering from chronic adrenal insufficiency, diarrhea and steatorrhea may be the prominent gastrointestinal complaints, the mechanism of which is unknown.

Hypoparathyroidism

Several patients with hypoparathyroidism have been reported with steatorrhea and diarrhea (101). Diarrhea may be the presenting symptom. The pathogenesis of the diarrhea is obscure, but it is related to neuromuscular irritability of the intestine because of hypocalcemia. The severity of these symptoms is related to the degree of the hypocalcemia. Hypomagnesemia may also contribute to the diarrhea and steatorrhea. The diarrhea ceases on correction of the underlying defect.

Diabetes Mellitus

Chronic watery diarrhea and steatorrhea may complicate the course or even precede the appearance of diabetes mellitus (DM); the patients with these symptoms are often poorly controlled diabetics (102). Several theories have been suggested for the pathogenesis of the diarrhea associated with DM. The mechanism may be osmotic, following "spillage" of large amounts of glucose into the intestinal lumen. Several patients with DM were found to have bacterial overgrowth in the proximal small intestine, presumably because of neuropathy of the bowel, which in turn caused disordered intestinal motility. The diarrhea subsided after antibiotic treatment (103). The association of celiac disease and DM occurs more frequently than can be explained by chance, and therefore one should look for celiac disease in diabetic patients with diarrhea.

Celiac Disease

Celiac disease is a common cause of chronic diarrhea, steatorrhea, malabsorption, and growth retardation in childhood. The disease is induced by the introduction of gluten to the diet of susceptible patients. There are specific, though not pathognomonic, lesions of the small intestinal mucosa, which improve following a complete withdrawal of gluten from the diet.

The pathogenetic mechanism by which gluten contributes to changes in the small intestinal mucosa and induces clinical manifestations is still obscure. Several theories have been proposed to explain the mechanism of gluten-sensitive enteropathy. One suggests a protease or peptidase deficiency in the small intestinal mucosa (104) that results in accumulation of gluten or of its partially digested products, which are toxic to the mucosa. The enzyme deficiency has not been demonstrated in celiac patients to date. Ward et al. (105) suggest that a reduced number of Paneth cells in the jejunal mucosa of celiac patients may be a marker
of, or even the cause of, the sensitivity of these subjects to gluten. In accord with this theory, reduced mucosal lysozyme and raised serum lysozyme activity in celiac patients have been observed. The diminished phagocytic activity and the reduced number of Paneth cells suggest a defect in mucosal defense mechanisms. Weiser and Douglas (106) suggest a defect of the cell surface membrane that allows gluten to act as a lectin, and this reaction initiates cell toxicity.

Another theory hypothesizes an immunologic abnormality as the pathogenesis of gluten sensitivity. According to Trier et al. (107), an initial contact with gluten sensitizes the immunocytes in the lamina propria in susceptible patients. The sensitized cells then produce lymphokines and gluten-specific antibodies. On reexposure to gluten, these products interact with the absorptive cells and accelerate their premature degradation. This results in a flattened mucosa and compensatory deep crypts (Fig. 3), and the patient may consequently develop chronic diarrhea and malabsorption.

The causes of diarrhea and steatorrhea are multifactorial, involving defects in mucosal absorption, lipolysis, and micelle formation. Defects in gallbladder function, failure of enterohepatic circulation of bile acids, and changes in the propulsive activity of the gut may all play a role. Damage to the proximal small intestinal mucosa affects the production of cholecystokinin and secretin. In fact, the serum concentrations of these hormones have been shown to be lower in celiac patients (108). This can contribute to partial exocrine pancreatic insuf-

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**FIG. 3.** Celiac disease. Small intestinal biopsy; subtotal villous atrophy, deep crypts, inflammatory cell infiltrates in the lamina propria.
ficiency and diminished bile secretion. The diagnosis can be established after three consecutive small intestinal biopsies obtained (a) at initial diagnosis, (b) after elimination diet, and (c) after rechallenge with gluten. The final and ultimate diagnosis of celiac disease is extremely important in view of the life-long treatment it requires. This practice would also exclude patients with transient gluten sensitivity from patients with celiac disease.

The treatment of celiac disease consists of complete withdrawal of any food containing gluten. In the very young patient, determination of disaccharidase activities enables evaluation of lactose and sucrose tolerance. Restriction of these disaccharides is important initially but need only be transient. In severely affected patients it may be necessary to initially use an elemental diet or even total parenteral alimentation (Figure 4). Corticosteroids should be reserved for the life-threatening situation of celiac crisis or when secondary adrenal insufficiency has developed.

**Tropical Sprue**

Tropical sprue is a syndrome of unknown etiology. As the name implies, one must have visited the tropical regions in order to be a potential candidate for the development of this syndrome. The hallmark of the disease is malabsorption of at least two unrelated substances. The clinical manifestations and

**FIG. 4.** Celiac disease. Patient with severe malabsorption and failure to thrive. Note protuberant abdomen and loss of subcutaneous fat.
small intestinal mucosal biopsy findings may resemble those of celiac disease. However, in tropical sprue, there is no response to gluten-free diet, the mucosal alterations are patchy in distribution and involve the terminal ileum as well as the proximal small intestine, and the surface cell abnormalities are much less pronounced than those in untreated celiac patients.

The cause of the mucosal damage in tropical sprue is not known. However, several possibilities have been suggested: nutritional deficit, dietary toxin, or an infectious agent. Usually there are hematologic changes consistent with megaloblastic anemia, which is caused by folate and/or vitamin B$_{12}$ malabsorption.

Treatment consists of administration of folic acid orally and vitamin B$_{12}$ parenterally along with a broad-spectrum antibiotic such as tetracycline (109). The treatment should last for several months or until there is evidence that the intestinal function has returned to normal. The prognosis following the above recommendations is excellent, with complete recovery.

**Whipple’s Disease**

Whipple’s disease is an uncommon multisystemic disorder, which invariably involves the small intestine, that is extremely rare in pediatric practice (110). Clinically, there may be diarrhea, malabsorption, weight loss, fever, hyperpigmentation, anemia, arthritis, pleuritis, pericarditis, endocarditis, and central nervous system disturbances (111). The small intestinal wall appears thickened and edematous. The villi are blunted, and there is extensive infiltration of the lamina propria with macrophages. These are filled with a glycoproteinaceous material that stains with the periodic acid–Schiff (PAS) reagent. The demonstration of these PAS-positive macrophages is specific for Whipple’s disease. Ultrastructural studies of the lamina propria obtained from patients suffering from Whipple’s disease demonstrate many small bacilli (112). This finding is diagnostic of the disease and also provides evidence that the etiology of Whipple’s disease is primarily infectious. The advocated treatment for Whipple’s disease is long-term antibiotic therapy—penicillin, tetracycline, or trimethoprim. The prognosis is excellent.

**Intestinal Lymphangiectasia**

Intestinal lymphangiectasia (IL) has been characterized by dilated intestinal submucosal and subserosal lymphatics, diarrhea, steatorrhea, protein-losing enteropathy, hypoalbuminemia, edema, and lymphopenia. The disease may be primary, when congenitally abnormal lymphatic vessels are located in the intestinal tract, or secondary to such entities as congestive heart failure, Behcet’s disease, liver cirrhosis (113), retroperitoneal fibrosis, and lymphosarcoma (114). Intestinal lymphangiectasia may vary in its manifestations and severity. Diarrhea is the most common symptom. Vomiting and growth retardation frequently occur. Peripheral lymphedema and chylous effusion have been described (115).

The protein loss is presumably related to rupture of the dilated intestinal
lymphatics and consequent leakage of their contents into the intestinal lumen and peritoneal space. Small intestinal biopsies from affected areas will demonstrate the pathognomonic lesion (Fig. 5). Ultrastructural studies demonstrate gaps between basal epithelial cells, with direct communication between the edematous fluid in the lamina propria and the large vacuoles present between the enterocytes. The authors suggested that fluid may leak from lacteals through these gaps into the enterocytes (116).

Treatment with high-protein, low-fat diet with supplementation of medium-chain triglycerides is valuable. In severe diarrhea, total parenteral nutrition may be indicated. When the lymphangiectatic lesions are localized, surgical excision may be considered. Fleisher et al. (117) described three patients who had IL secondary to an inflammatory process. Corticosteroid therapy cured two of these patients and led to partial improvement in the third.

**Eosinophilic Gastroenteritis**

Eosinophilic gastroenteritis refers to a disorder of the stomach and the proximal small intestine characterized by infiltration of the mucosa or of the gut wall by eosinophils, with or without peripheral eosinophilia. The entity is further subdivided into two forms, the mucosal and circumscribed types. In the mucosal form, which tends to be diffuse, the features include vomiting, abdominal pain, diarrhea, protein-losing enteropathy, enteric blood loss, and failure to gain weight.
It is usually accompanied by peripheral eosinophilia, and many of the patients have an allergic background (118). The mucosal lesions are usually patchy in distribution; the degree of eosinophilic infiltration varies, and, similarly, villous architecture varies from normal to complete loss of villi (119). In the second form of eosinophilic gastroenteritis, there is a circumscribed lesion, usually located in the antral area, but which may also involve the small intestine. The lesions infiltrate more deeply and are located mainly in the submucosal layer, with occasional extension to the muscularis and serosa. The tumor-like lesions tend to be polypoid, may ulcerate, and usually produce symptoms of gastric outlet obstruction. They rarely involve the esophagus or terminal ileum and colon (thus mimicking Crohn’s disease) (120). In this form, there is rarely peripheral eosinophilia, and history of allergy is uncommon.

The etiology of this rare entity is poorly understood. Only about half of these patients have allergic manifestations. Caldwell et al. (121) suggest that both IgE-mediated and IgE-independent mechanisms may be operative in this entity. Food sensitivity, especially to cow’s milk protein, has been incriminated in some of the patients, but only a minority of the patients respond favorably to elimination diets. Intermittent corticosteroid therapy is indicated, and the response to it is usually prompt and sustained. In the circumscribed form, surgical treatment is advocated, with outcome usually favorable (118). However, even in this form, corticosteroids are considered to be effective.

Enterokinase Deficiency

Enterokinase is produced in the proximal small intestinal mucosa (12). It is the key enzyme for the activation of trypsinogen to trypsin. The trypsin in turn converts more trypsinogen to trypsin as well as chymotrypsinogen and procarboxypeptidases to their active forms. Several children suffering from enterokinase deficiency have been described (123,124). The disease is usually manifested by diarrhea, steatorrhea, failure to thrive, hypoproteinemia, and anemia, resembling the presentation of trypsinogen deficiency.

The steatorrhea is presumably related to deficiency of phospholipase, since its activation is also dependent on the presence of trypsin. Secondary enterokinase deficiency has been described in cases in which damage to the duodenal mucosa was found. It has been described in intractable diarrhea of infancy but not in celiac disease (125). Treatment with protein hydrolysate and pancreatic extract is very effective; the diarrhea abates, and growth is resumed.

EXOCRINE PANCREATIC INSUFFICIENCY

Cystic Fibrosis

Cystic fibrosis (CF) is the leading cause of exocrine pancreatic insufficiency (EPI) in infancy and childhood. The incidence of CF is between 1:1,000 and
SPECIFIC ETIOLOGIES

1:2,000 in the Caucasian population. The disease is inherited as an autosomal recessive trait and is characterized by altered function of exocrine glands. However, the nature of the underlying basic abnormality remains unknown. Increased sweat electrolyte excretion (Na\(^{+}\), Cl\(^{-}\), and K\(^{+}\)) is the one and only nearly pathognomonic laboratory feature of CF.

The clinical spectrum of CF is very broad. Most of the patients are diagnosed following chronic or recurrent respiratory disease, gastrointestinal disorders, or both. The digestive abnormalities associated with CF may be present at birth, with symptoms of intestinal obstruction secondary to meconium ileus, which occurs in 10 to 15% of patients suffering from CF. Infrequently, neonatal hepatitis may be the presenting symptom of CF. Other manifestations of CF include growth failure, intussusception, meconium ileus equivalent, rectal prolapse, increased incidence of peptic disease, cirrhosis, nasal polyps, sinusitis, infertility, and increased incidence of diabetes mellitus. The most common alimentary presentation of CF in infancy and childhood includes chronic diarrhea, steatorrhea, malabsorption, and failure to thrive because of EPI. Complete absence of pancreatic enzymes in duodenal fluid is present in about 85% of the patients. The function of the centroacinar ducts and the intercalated tubules is affected in nearly all CF patients. Thus, there is reduced secretion of bicarbonate and water, followed by diminished secretion of pancreatic zymogens.

This sequence of events can be demonstrated by the pancreozymin-secretin stimulation test (126). There is a small group of patients with CF who initially have normal pancreatic enzyme production but who later suffer from episodes of recurrent acute pancreatitis and eventually develop EPI, the exact mechanism of which is not known (127). It is, however, presumed that plugging of the pancreatic ductules by the hyperconcentrated viscid secretion causes ductular dilatation, cystic degeneration, dysfunction, and autodigestion of acinar tissue, followed by inflammation, fibrosis, fatty replacement of the parenchyma, and eventually EPI. The small intestinal mucosa is covered with thick, tenacious mucus. Inspissated material, which is periodic acid-Schiff positive, is found in the crypts of Lieberkühn. Antonowicz et al. (128) demonstrated that in patients with CF with normal morphology of the small intestinal mucosa, the activity of disaccharidase was significantly higher than in control subjects. A possible explanation for this finding may reside in the EPI, as proteolytic enzymes derived from the pancreas normally participate in the degradation of intestinal brush border enzymes, and in the absence of these enzymes disaccharidase degradation is impaired.

Nutritional therapy for patients suffering from CF includes the use of a low-fat diet with added medium-chain triglycerides and pancreatic enzyme preparations given with meals. The steatorrhea can continue to be a problem even though high doses of pancreatic extracts are consumed. Moreover, in these patients, hyperuricosuria has been reported secondary to the purine-rich pancreatic extracts (129). Addition of antacids, and especially cimetidine (an H\(_2\)-receptor antagonist), to the pancreatic extracts results in significant improvement.
in fat and nitrogen excretion (130) by preventing the acid inactivation of lipase and trypsin, respectively. This therapeutic approach may enable reduction of the doses of pancreatic extracts. Weber et al. (131) demonstrated that in untreated patients with CF, there is malabsorption of bile acids, which, in turn, may aggravate the steatorrhea. Addition of pancreatic extracts to the diet decreased bile acid excretion in four out of five patients. The outcome of the disease is dependent mainly on the extent and severity of the pulmonary disease, but vigorous physical therapy, appropriate antibiotics, and nutritional support will each positively affect the life expectancy and quality of life of these patients.

Shwachman–Diamond Syndrome

Shwachman–Diamond syndrome (SD) is second to cystic fibrosis as a cause of exocrine pancreatic insufficiency in the pediatric population. The syndrome is rare with an incidence of one for every 50 to 100 cases of cystic fibrosis. The syndrome is inherited as an autosomal recessive trait. It is characterized by congenital pancreatic insufficiency, continuous or cyclic neutropenia, anemia, and thrombocytopenia, metaphyseal dysostosis, and severe growth retardation (Fig. 6) (132). Associated abnormalities, including increased fetal hemoglobin, immunoglobulin deficiency, and disorders such as Hirschsprung's disease, diabetes mellitus, or cirrhosis have also been reported (133). Recurrent severe
infections commonly occur. The pathogenetic mechanism of this syndrome is unknown. Diarrhea and steatorrhea are attributed to pancreatic insufficiency. Following pancreozymin–secretin stimulation, in contrast to cystic fibrosis, the secretion of water and bicarbonate in SD is not affected, but pancreatic enzyme secretion is diminished. Treatment with pancreatic extracts and a low-fat diet with added medium-chain triglycerides is indicated. Following treatment, the diarrhea and steatorrhea improve. Despite the therapy, however, most of the patients remain growth retarded, and the hematologic abnormalities are not improved by the treatment.

**ISOLATED PancreATIC ENZYME DEFICIENCIES**

**Amylase Deficiency**

Amylase deficiency in the first 4 to 6 months of life is considered to be physiologic, but a child suffering from diarrhea and growth retardation attributed to amylase deficiency has been described (134). Improved weight gain and growth occurred when disaccharides were substituted for dietary starch. Another case of congenital amylase deficiency and diminished trypsin secretion has been reported (135).

**Isolated Lipase Deficiency**

Several cases of lipase deficiency, including four members within two families, have been reported (136). The patients presented with oily stools from early infancy. Growth and development were unaffected despite the steatorrhea. In one patient, depressed amylase activity was also documented (137). Low-fat diet with added medium-chain triglycerides and pancreatic replacement therapy are beneficial in this condition.

**Trypsinogen Deficiency**

Trypsin is necessary for the activation of proteolytic proenzymes. Its absence causes chymotrypsinogen and procarboxypeptidase to remain in an inactive form; therefore, trypsinogen deficiency results in complete loss of proteolytic activity of the pancreas. The addition of enterokinase to the duodenal juice of affected patients produces no increase in proteolytic activity. However, the addition of exogenous trypsin to duodenal fluid in vitro causes a rapid activation of chymotrypsinogen and procarboxypeptidase to chymotrypsin and carboxy- peptidase, respectively, but additional trypsin is not detected (138,139).

The patients present with early onset of diarrhea, failure to thrive, severe hypoproteinemia, edema, and anemia. As the initiation of trypsin activation is dependent on the presence of enterokinase, the deficiency of the latter presents in a fashion similar to trypsinogen deficiency. These patients are successfully
treated with formula contained protein hydrolysate or amino acids and pancreatic extract.

**Hepatic Disorders**

Patients with chronic liver disease of various etiologies have a reduced bile acid pool as a result of either decreased synthesis or increased excretion of bile acids. It has been shown that infants with chronic cholestatic liver disease have decreased intraluminal bile acid concentration (58). This results in inefficient micellar dispersion of dietary fat and consequent steatorrhea.

Bile acid malabsorption secondary to terminal ileal disease, ileal resection, or primary bile acid malabsorption (140) causes refractory diarrhea. The diarrhea occurs as a result of both the reduced bile acid pool and the elevated concentrations of unabsorbed bile acids in the colonic lumen, which, in turn, induce sodium and water secretion.

Treatment of patients with bile acid malabsorption includes a low-fat diet, with the possibility of adding medium-chain triglycerides. Successful trials using cholestyramine or aluminum hydroxide, which act as bile acid binders, have been reported in secondary bile acid malabsorption (141).

**VASCULAR LESIONS**

Interference with the vascular supply to the bowel is a rare problem in pediatric practice. It is considered to be a pathogenetic mechanism in congenital atresia or stenosis of the intestine if bowel obstruction results.

**Necrotizing Enterocolitis**

Neonatal necrotizing enterocolitis occurs primarily in premature infants but has been infrequently documented in full-term infants as well (142). The exact etiology is still obscure. Nevertheless, the postulated pathogenetic mechanism includes invasion of previously hypoxic mucosa by intestinal bacteria, mainly *Klebsiella* and *E. coli*. The bowel ischemia is attributed to the "diving reflex" that is present during the neonatal period. The incidence of necrotizing enterocolitis is reported to be from 0.2 to 7.3% among newborns. The syndrome is characterized by abdominal distention, vomiting, bloody diarrhea, and pneumatosis intestinalis. Treatment consists of withholding oral feeding, nasogastric suction, and oral and parenteral antibiotics. Any evidence of rapid clinical deterioration constitutes an indication for surgical intervention. Usually total parenteral nutrition is necessary before oral feeding can be resumed (143–145).

Recently, Moss et al. (146) reported the occurrence of necrotizing enterocolitis in 26 patients beyond the neonatal period. The patients' ages ranged from 6 months to 17 years. In 19 of their 26 patients, there was indirect evidence of immunologic compromise. Five of the remaining patients had cyanotic heart
disease. The authors suggested that an altered immune state and hypoxemia could have been the mechanisms involved in the initiation of necrotizing enterocolitis.

ANATOMICAL LESIONS

Hirschsprung's disease

Hirschsprung's disease is a congenital disorder of the bowel defined by the absence of parasympathetic ganglion cells from the submucosal and myenteric plexuses. The disorder usually manifests itself after delivery by a delay in the first passage of meconium or somewhat later in life by abdominal distention and bilious or fecal vomiting associated with constipation.

One of the serious complications of Hirschsprung's disease is enterocolitis. Several pathophysiological factors, alone or in combination, may lead to enterocolitis as a complication of Hirschsprung's disease. These include ischemia of the bowel wall as a result of increased intraluminal pressure (147), the Shwartzman phenomenon (147), ulceration and necrosis of the mucosa, and secondary incompetence of the ileocecal valve as a result of increased intraluminal pressure in the segment proximal to the aganglionic segment (148). Invasion of the bowel wall by intraluminal microorganisms can be complicated by peritonitis, septicemia, and vascular collapse. In addition, secondary small intestinal mucosal damage can ensue (Fig. 7), with the development of severe disaccharidase deficiencies (149,150).

Enterocolitis may develop either before or after surgery for the removal of the aganglionic segment. Because of its very high mortality rate, this complication should be recognized and treated promptly. It is advisable to prescribe a lactose-free diet immediately after the diagnosis of enterocolitis. In severe cases, parenteral alimentation should be instituted, followed by an elemental diet by mouth.

Idiopathic Intestinal Pseudoobstruction

Idiopathic intestinal pseudoobstruction (IIP) syndrome is characterized by recurrent clinical symptoms of bowel obstruction in the absence of organic occlusion of the lumen (151). It can occur sporadically or in a familial form (152). This syndrome typically involves the small intestine but may also affect the colon. It is believed that the syndrome is attributed to ineffective intestinal propulsion, causing small intestinal stasis and, consequently, bacterial overgrowth (153). Although diarrhea is the hallmark of the disease, constipation may occur, simulating Hirschsprung's disease (154). The pathophysiologic mechanism is unknown. Puri et al. (155) suggested damage to the cholinergic innervation by a neurotoxic agent, most probably viral. A patient suffering from acute intestinal pseudoobstruction with elevated serum levels of prostaglandin E has been reported (156). A degenerative disease of smooth muscle was proposed by Schuffler et al. (151), and a functional abnormality of the smooth muscle was suggested (157).

There is no effective treatment for IIP, and hence the prognosis is poor. Therapeutic trials with steroids, several gut hormones, or special diets were of limited success. Antibiotic therapy may reduce bacterial overgrowth, leading to temporary improvement. Surgical approaches have been without benefit. Byrne et al. (158) advocated, for the time being, a program of total parenteral alimentation at home.

Inflammatory Bowel Disease

In the last decade, more young children suffering from inflammatory bowel disease have been reported; therefore, it is appropriate to include this entity in the spectrum of chronic diarrhea.

Ulcerative Colitis

Ulcerative colitis (UC) occurs very rarely in infancy. Most of the infants with characteristics resembling those of UC are essentially suffering from cow's milk or soy protein allergy, necrotizing enterocolitis, pseudomembranous enterocolitis, or have a family history of UC (159). The etiology is still obscure, but infectious and immunologic origins have been proposed. Psychological factors are considered to be involved in the disease process, especially during exacerbations. There is increased incidence of UC, and also of Crohn's disease, among the relatives of patients with UC.

The typical presentation of UC is crampy abdominal pain, bloody mucousy diarrhea with mucus and pus, poor weight gain or even weight loss, fever, and pallor. Not unusually, extraintestinal manifestations may occur and may even be the presenting symptoms. These include arthritis, liver involvement, conjunctivitis and uveitis, erythema nodosum, pyoderma gangrenosum, throm-
bophlebitis (160), and pulmonary vasculitis (161). In the acute stage, anemia, leukocytosis, thrombocytosis or thrombocytopenia (162), hypoalbuminemia and increased sedimentation rate are found. The disease process affects the colon and is mainly confined to the mucosa.

Infrequently, the inflammation can erode the bowel and produce a serious complication, toxic megacolon. The barium enema reveals typical findings that consist of loss of haustra, superficial erosions, and a shortened colon. In cases of prolonged disease, pseudopolyps can be identified. Colonoscopy demonstrates friable, ulcerated mucosa with exudate (Fig. 8), and biopsies obtained from the diseased areas show destruction of the surface epithelium, polymorphonuclear and mononuclear cell infiltration of the lamina propria, as well as crypt abscesses, with a decrease in the number of goblet cells (Fig. 9).

Recently, Ligumsky et al. (163) demonstrated enhanced production of prostaglandin E\(_2\), thromboxane A\(_2\), and prostacyclin in cultured rectal mucosa obtained from patients with active UC. They were able to inhibit the elevated prostaglandin levels by addition of steroids and salicylates (azulfidine) to the culture medium. The treatment consists of corticosteroids, azulfidine, and nutritional support. In severe cases, total parenteral nutrition should be instituted as well as intravenous steroids or ACTH.

The natural history of UC is of remissions and exacerbations. The only option for complete cure is total colectomy, which should be reserved for fulminant disease or when toxic megacolon does not respond within a short period of time to conventional therapy. As there is a significant risk of developing colonic malignancy, close long-term surveillance of the patients is mandatory (164).

**Crohn's Disease**

The incidence of Crohn's disease (CD) has increased in the last decade, both in the adult and the pediatric population. The etiology of CD is unknown. An infectious etiology is attractive, as an injection of homogenate from CD-affected tissue into the foot pads of experimental animals produces typical granulomata (165,166). Nevertheless, no specific pathogen, either viral or bacterial, has been consistently implicated as a transmissible agent.

**FIG. 8.** Ulcerative colitis. Colonoscopic features consist of friability, ulceration, and exudate.
The disease differs from ulcerative colitis (UC) in several aspects: CD can involve the alimentary tract from the mouth to the anus; in more than half of the patients, there is ileocolitis, and less frequently the disease is confined to the colon (167). Crohn's disease is a transmural disease and tends to be segmental in distribution. The classical presentation is abdominal pain, diarrhea, and growth retardation. When the disease affects the colon, the diarrhea can be bloody, indistinguishable from UC.

The laboratory findings and the extraintestinal manifestations are the same as in UC. Perianal disease, aphthous stomatitis, cholelithiasis, and nephrolithiasis are much more common in CD than UC, whereas toxic megacolon and increased incidence of cancer are less common. Although surgery is not curative in CD, surgical intervention is common because of complications such as intestinal obstruction, fistula formation, intestinal perforation, and severe growth and sexual retardation (168).

Barium meal and enema demonstrate the characteristic findings: thickened mucosa, elongated ulcerations, cobblestone appearance, and areas of dilatation proximal to stenotic regions (Fig. 10). The radiologic and colonoscopic findings of the colon can resemble those of UC. The demonstration of skip lesions is characteristic of CD, and the pathognomonic pathological finding is the presence of granulomata in the absence of tuberculosis (Fig. 11), but this is found in only 50% of the patients. Other, less specific findings include deep ulcerations, aphthoid ulcers, and dense mononuclear cell infiltration of the lamina propria.

FIG. 11. Crohn's disease. Colonic biopsy; granuloma within the lamina propria.
The medical treatment in CD is essentially the same as for UC. The prolonged use of azulfidine in order to maintain remission is less promising than in cases of UC. Recently, there have been several reports demonstrating the advantage of metronidazole, both in the healing of perianal disease (170) and in the maintenance of remission in CD (171). The quality of life is worse, and the long-term prognosis of CD is far less encouraging than in UC.

PSEUDOMEMBRANOUS ENTEROCOLITIS

Pseudomembranous enterocolitis (PMC), or antibiotic-associated colitis, is infrequently diagnosed in children. It is considered a severe and sometime fatal gastrointestinal disease. It is characterized by profuse diarrhea, dehydration, abdominal pain, fever, electrolyte imbalance, hypoproteinemia, and leukocytosis. Rectosigmoidoscopic findings consist of mucosal edema, friability, ulceration, and pseudomembrane formation (172). Rarely, it may affect the proximal colon alone, with sigmoid and rectum having normal appearance (173).

The pathophysiology of PMC is unknown, but several theories have been suggested. These include changes in intestinal microbial flora, direct effects of antibiotics or their metabolites (174), localized Shwartzman reaction (175), hypersensitivity reaction, intravascular coagulopathy, and elaboration of toxins by intestinal flora. Many studies have implicated the effect of antimicrobial treatment as the pathogenetic mechanism for the development of PMC. It has become apparent that the disease is caused by toxin-producing strains of Clostridium difficile (176). This organism and its toxin, however, may be isolated from the intestinal lumen of the healthy neonate or adult (177). Thus, the presence of the organism or its toxin is not sufficient in and of itself to diagnose the disease. Recently, Behan and Mills (175) reinforced the theory of the Shwartzman reaction in the pathogenesis of PMC. They suggested that antimicrobial treatment may alter the mechanism that limits the replication of Clostridium difficile. Consequently, in susceptible patients, the organism is able to proliferate, produce toxin, and cause the initial epithelial damage via its cytopathic effect. Subsequently, the toxin may provoke the second stage of reaction and thus produce the lesions associated with the local Shwartzman phenomenon. Behan and Mills (175) also demonstrated activation of the serum complement system as an evidence for this reaction.

The treatment of this life-threatening disease is not always satisfactory. Obviously, one should first withdraw the antibiotic that precipitated the process. Oral vancomycin has been considered to be the drug of choice for the disease (176), but the relapse rate is as high as 20% (178). For those patients who relapse following vancomycin, or as an alternative therapy, metronidazole has been used successfully (179). Others have suggested treatment with tetracycline (180) or cholestyramine (181), which bind the cytopathic toxin produced by Clostridium difficile. Supportive treatment with parenteral nutrition is advocated in severe cases (172). The beneficial effect of corticosteroids on the course of the disease is still unproven (172).
REFERENCES


