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CHRONIC DIARRHEA

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SELF-ASSESSMENT QUESTIONS

Each question has one or more correct answers.

1. Viral gastroenteritis is most commonly caused by:
   a. Rotavirus.
   b. Adenovirus
   c. Coxsackie virus.
   d. Parovirus.
2. The disaccharidase most frequently affected in gastroenteritis is:
   a. Lactase.
   b. Sucrase.
   c. Maltase.
   d. Trehalose.
3. One or more of the following stimulate cyclic adenosine monophosphate to cause diarrhea:
   a. Toxigenic *Escherichia coli.*
   b. Lactose.
   c. Bile acids.
   d. Rotavirus.
   e. Prostaglandins.
4. Factors predisposing to milk allergy are:
   a. Lactose intolerance.
   b. IgA deficiency.
   c. Gastroenteritis.
   d. Bile acid malabsorption.
   e. Bacterial overgrowth.
5. Subtotal villous atrophy may be seen in:
   a. Celiac disease.
   b. Cystic fibrosis.
   c. Gastroenteritis.
   d. Milk allergy.
   e. Giardiasis.
6. Diarrhea caused by *E. coli* is due to:
   a. Those typed as pathogenic.
   b. Heat-labile toxin.
   c. Invasive *E. coli.*
   d. Non-typeable *E. coli.*
7. *Yersinia* enterocolitica disease may present as:
   a. Sepsis.
   b. Diarrhea.
   c. Upper gastrointestinal bleeding.
   d. Right lower quadrant pain.
   e. Pancreatitis.

8. The antibiotic treatment of *Salmonella* diarrhea may be:
   a. Never necessary.
   b. Trimethoprim.
   c. Penicillin.
   d. Always necessary.
   e. Ampicillin.
9. Lactose intolerance occurs with increased incidence in:
   a. Caucasians.
   b. Blacks.
   c. Orientals.
   d. Semites.
   e. American Indians.
10. The patient most susceptible to *Giardia* infestation has:
   a. Type O blood type.
   b. IgA deficiency.
   c. Cystic fibrosis.
   d. Crohn's disease.
11. Antibiotic-related diarrhea is due to:
   a. Lactose intolerance.
   b. Superinfection with *Clostridia*.
   c. Superinfection with *Lactobacillus*.
   d. Bile acid malabsorption.
12. Sucrose intolerance is characterized by:
   a. Positive reducing substances in the stool.
   b. Wheat intolerance.
   c. Acid stool pH.
   d. Milk intolerance.
13. Explosive diarrhea may be caused by:
   a. Squash.
   b. Amine precursor uptake, decarboxylase cell tumor.
   c. Dietetic candies.
   d. Ascaris.
   e. Milk.
14. The diagnosis of celiac disease depends upon:
   a. Small bowel biopsy.
   b. Clinical response to gluten elimination.
   c. Low serum IgG.
   d. A negative sweat test.
   e. Documented steatorrhea.
15. The treatment of inflammatory bowel disease involves:
   a. Corticosteroids.
   b. Salicylate derivatives.
   c. Exchange transfusion.
   d. Parenteral hyperalimentation.
   e. Desensitization to allergens.

Answers are listed at the end of the article

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CHRONIC DIARRHEA can be one of the most perplexing problems to the physician as well as to the affected infant and his parents. In our experience it has been also a common disturbance, in view of the fact that children under 3 years of age comprise approximately 40% of the patient population of the Yale Pediatric Gastroenterology Clinic. Chronic, or intractable, diarrhea is defined as that which persists for more than 3 weeks.[1] An exact definition of diarrhea is a bit more difficult. All are agreed that diarrhea refers to the loose consistency rather than to the frequency of stools. Sunshine et al. describe diarrhea as fecal evacuation causing water losses that exceed 5 – 10 ml/kg/day.[2] Diarrheal stools may be mushy, gelatinous or mucoid, watery or containing formed bits of stool that leave a large water ring in the diaper. Our patients have often been symptomatic for months to several years before their referral; in some instances mothers state that their children have never passed a formed stool since their birth. The rapidity of referral varies directly with the physical condition of the patient: those who fail to grow or who show significant weight loss are referred for diagnostic evaluation rather quickly, whereas those who maintain a relatively normal growth pattern are referred later, when parents become concerned about toilet training.

The response of diarrhea to a clear liquid diet or to bowel rest and intravenous therapy is not only therapeutic but in some ways diagnostic. Diarrhea that clears rapidly is usually caused by dietary factors, whereas the persisting type is more often associated with an immunoglobulin disorder, congenital malformation or hormone-secreting tumor. Among the vast number of causes of chronic diarrhea (Table 1), the 3 most common ones identified in our patients[3] have been postinfectious gastroenteritis syndromes, gastrointestinal food protein allergy and, ever more frequently, transient immunodeficiencies.

TABLE 1.—CAUSES OF CHRONIC DIARRHEA

- Dietary
  - Overfeeding
  - Well water
  - Allergy (milk, soy or other)
  - Dietetic candies and gum
- Parenteral
  - Otitis media
  - Urinary tract infection
  - ? Teething
- Infection
  - Bacterial
  - Viral
  - Fungal
  - Parasitic
- Postinfectious
  - Carbohydrate malabsorption
  - Allergy
- Irritable Bowel
  - Paradoxical diarrhea with chronic constipation
- Immune Deficiency
  - Hypogammaglobulinemia
  - IgA deficiency
  - Combined immune deficiency
  - Defective cellular immunity
- Malnutrition
  - Starvation
  - Maternal nutritional deprivation
- Carbohydrate Malabsorption
  - Lactose
  - Sucrose
  - Isomaltose
  - Glucose
  - Galactose
- Antibiotic-Related Diarrhea
- Toxic Diarrhea
  - Chemotherapy-induced
  - Radiation-induced
- Metabolic
  - Endocrine tumors
  - Neuroblastoma
  - Ganglioneuroma
  - Pancreatic tumors
  - Carcinoma
  - Familial chloride diarrhea
  - Folic Acid malabsorption
  - Abeta- and hypobetalipoproteinemia
  - Galactosemia
  - Tyrosinosis
  - Selective malabsorption of vitamin B_{12}
  - Wolman's disease
- Endocrine
  - Hyperthyroidism
  - Adrenal insufficiency
- Pancreatic Diarrhea
  - Cystic fibrosis
  - Enterokinase deficiency
  - Shwachman's syndrome
  - Chronic pancreatic insufficiency
- Small Bowel Abnormalities
  - Celiac disease
  - Intestinal lymphangiectasia
- Hepatic
  - Absence of bile salts
  - Chronic hepatitis
  - Biliary atresia
- Vascular Lesions
  - Mesenteric artery insufficiency
  - Intestinal ischemia
  - Necrotizing enterocolitis
  - Early portal hypertension
- Anatomical Lesions
  - Hirschsprung's disease
  - Malrotation
  - Partial small bowel obstruction, stenosis
  - Blind loop syndrome
  - Enteric fistulae
  - Short gut syndrome
  - Small bowel tumors: lymphosarcoma, polyp
  - Intestinal pseudoobstruction
- Autoimmune
  - Regional enteritis
  - Ulcerative colitis

Several disturbances are operant in chronic diarrhea and it is not unusual, regardless of the primary cause, for one or more of these factors to be actively involved in precipitating or promoting diarrhea.

Water and electrolyte overexcretion. Toxigenic organisms such as *Escherichia coli, Vibrio cholerae,* some *Shigella* and probably *Klebsiella* secrete toxins that affect intestinal transport systems to cause active secretion of water and electrolytes into the small intestinal lumen.[4] Catecholamine-producing tumors, such as

ganglioneuromas and pancreatic tumors releasing vasoactive intestinal peptide (VIP), stimulate intestinal secretion. Conditions that impair disaccharide or monosaccharide absorption cause osmotic diarrhea through secretion induced by intraluminal hyperosmolarity. Disturbances associated with rapid intestinal transit simply do not allow enough time for adequate water reabsorption and thus cause diarrhea. Anatomical lesions causing partial intestinal obstruction are characterized by increased water and electrolyte secretion in the dilated proximal intestinal segment.

Cyclic adenosine monophosphate (AMP) is now known to be actively involved in electrolyte secretion and to function by inhibiting the coupled absorptive process for sodium chloride, thereby stimulating sodium secretion. Cyclic AMP production is stimulated by *V. cholerae* and *E. coli* toxins, dihydroxy- bile acids, VIP and prostaglandins. Conversely, adenosinetriphosphatase (ATPase) is inhibited by these agents. The fecal sodium losses in secretory diarrhea are well in excess of 50 mEq/L/day.

Carbohydrate malabsorption. Malabsorption of carbohydrates causes an osmotic as well as fermentative type of small bowel diarrhea by the action of colonic bacteria on the unabsorbed carbohydrate. The sugars are broken down into lactic acid, acetic acid and gas that produce explosive, watery (soufflé-like), vinegar-smelling stools. Lactose intolerance most commonly follows small bowel injury, as in gastroenteritis or celiac disease, but in some cases this is also accompanied by sucrose or even monosaccharide malabsorption.

Bile acid malabsorption. Damage to the terminal ileum – the major site of bile acid absorption in older infants and adults – results in bile acid malabsorption. Bile acids, particularly those which are deconjugated, stimulate cyclic AMP to cause sodium excretion in the colon and a watery "cholerrheic diarrhea." If this malabsorption continues over a prolonged period, the total bile acid pool becomes depleted and intraluminal bile acids secreted into the proximal small bowel fall below the critical level for micelle formation – a phase essential to fat emulsification and digestion. The end result is steatorrhea.[5]

Protein sensitization. After the first few days of life the normal intestinal mucosa is relatively impermeable to macromolecular penetration.[6] Nevertheless, if the intestinal mucosa is injured and its integrity is disrupted, absorption of protein molecules may occur.[7] This has been noted to occur in celiac disease and during recovery from acute gastroenteritis. In certain children (and probably more often in those with IgA immunoglobulin deficiency), gastrointestinal allergy to milk, soy or gluten develops and perpetuates the original insult.

Bacterial overgrowth. It is difficult to conceive that delayed intestinal transit may at times be associated with diarrhea, but

bacterial overgrowth due to low motility in the small bowel has been reported as a consequence of acute gastroenteritis. Bacterial culture from the small intestine in such cases yields coliforms, anaerobes and occasionally *Candida albicans*. The significance of bacterial overgrowth in the small bowel lies in the ability of these organisms to deconjugate bile acids. Some studies suggest that bacterial overgrowth (cultures yielding more than 10^6 colonies) not only competes for dietary vitamin B_{12}, but also impairs carbohydrate absorption.[8]

Abnormalities of small bowel mucosa. A subtotal villous atrophy has been reported to occur during acute gastroenteritis caused by various infectious agents; this indeed seems to represent a nonspecific response of the small intestinal mucosa to injury. Although the mucosal epithelial cells are not usually flattened to the degree typical of celiac disease, there is a decreased absorptive surface and a reduced level of mucosal enzymes. In some viral infections there is increased mucous secretion as cell turnover is increased and immature crypt cells take the place of mature surface epithelium.[9]

Malnutrition. If diarrhea is severe and prolonged, leading to malnutrition, further complications ensue, such as atrophy of the intestinal mucosa, continuing protein depletion due to malabsorption and impaired sugar and amino acid absorption. A secondary pancreatic insufficiency may develop in severely protein-depleted children.

Infectious diarrheas are usually self-limited in older children but in those under 3 years of age it may persist for months because of one or more of the aforementioned physiologic abnormalities. The causes listed in Table 1, which are those most commonly encountered, are the subject of this monograph.

INFECTION

Viral Gastroenteritis

Although the isolation and culture of enteric viruses has not been very successful, the use of electron microscopy to identify virus particles and their reaction to specific antisera has been helpful in defining 2 groups of agents: parovirus-like, largely responsible for viral disease in older children, and reovirus-like agents, which affect infants. Enteric viral infections are often associated with bacterial ones and it is not always certain which is producing the clinical disease. Less common viral agents are astro- or coronavirus, adenovirus and echovirus type 18.[10]

Parovirus-like agents have been identified and named after specific locations of epidemics, i.e., Norwalk, Hawaii and Montgomery County. They have not yet been successfully propagated in vitro. Studies in which Norwalk virus was administered to

healthy volunteers have shown an incubation period of 18–48 hours and a symptomatic disease state lasting for 24–48 hours. Mild-to-marked vomiting and/or mild-to-severe diarrhea were associated with cramping, headaches, myalgias and transient leukocytosis. Histologic examination of the proximal small intestinal mucosa revealed shortening of the villi and crypt hyperplasia with change of normal columnar epithelial cells to vacuolated cuboidal ones. Biopsy samples from gastric and colonic mucosa were found normal. Mild steatorrhea, abnormal xylose absorption and diminished brush border enzyme activity occurred during the acute illness and persisted for at least 1 week after infection.

There is yet no routine serologic test for the diagnosis of parovirus-like agents. Evidence suggests that although a transient immunity develops, it is not long-lasting and reinfection may occur at a later date.

Reovirus-like agents, otherwise termed rotavirus, orbivirus, or infantile-gastroenteritis virus, have major infection rates during the winter months and primarily affect infants 6–24 months of age. Experimentally, incubation periods vary between 48 and 64 hours. Diarrhea is often associated with vomiting and persists for 5–8 days, accompanied by fever and leukocytosis. The pharynx and tympanic membranes are also affected. These agents account for 40–50% of all cases of winter diarrhea in children that require hospitalization.

Histologic changes in the small intestine vary from normal to flattened mucosa and involve primarily the proximal 5 in. of bowel, although some lesions are found in mid- to lower small intestine. There is infiltration of the lamina propria with chronic inflammatory cells and a change of surface epithelial cells to cuboid cells. Evidence suggests that there is rapid cellular proliferation; secretory crypt-type cells move out to populate the jejunal villi, which are characterized by absence of mature villus epithelial cells. The virus is identified early and is absent after 40 hours. The histologic characteristics, however, do not revert to normal until 3–8 weeks later. As in parovirus infection, the gastric and colonic mucosa remain unaffected. Disaccharidases are depressed in degrees correlating with the severity of the histologic lesion. There is impaired sodium transport, failure of sodium flux to respond to glucose and normal levels of cyclic AMP, which differentiates this type of diarrhea from that due to enterotoxins.

This virus has been grown in human fetal intestinal culture but serial passage is difficult. Serologic tests based on complement fixation techniques have been developed for diagnosis. Antibody, presumably maternal, decreases with age: it has been detected in 75–80% of neonates but in only 10–15% of 6-month-old infants.

Escherichia coli

The classification of *E. coli* organisms which cause diarrhea has undergone considerable revision during the last decade.[4] For years we were dependent upon serotyping for identification of "enteropathogenic" *E. coli* with certain serotypes associated with community and neonatal epidemics of diarrhea. We were secure in treating disease after a specific pathogenic organism had been isolated. Now it is well recognized that *E. coli* organisms can cause diarrhea by either direct mucosal invasion or by the production of toxins. Many and perhaps most of the early enteropathogenic strains have now been shown neither to be invasive nor to produce toxin. Pathogenicity of other strains, which are untypable, is demonstrated by laboratory evidence. Sensitive laboratory techniques are now used to determine pathogenicity but are yet too expensive and time-consuming to assume a place in routine screening procedures. Invasiveness is determined by the ability of the organism to induce keratoconjunctivitis in guinea pigs or to invade cultured cells; toxigenicity, by the organism's ability to stimulate secretion in isolated rabbit ileal loops.

The *enteroinvasive E. coli* organisms have an incubation period of 8–24 hours and cause a syndrome consisting of chills, high fever, myalgia, abdominal cramps and profuse diarrhea. The disease affects particularly the ileum and cecum but may involve the entire colon and cause local ulcerations, inflammation and a polymorphonuclear exudate. Sigmoidoscopic examination may reveal an acute colitis. Interestingly, not only does this illness resemble that caused by *Shigella,* but a number of the *E. coli*-O groups causing it possess somatic antigens related to one or another of the *Shigella* serotypes.

Enterotoxigenic E. coli organisms exert their effects either through a heat-stable, nonantigenic toxin whose action is not well defined or through a heat-labile, antigenic toxin which activates cellular adenyl cyclase and promotes secretion of water and sodium through increased intracellular adenosine monophosphate. The organisms preferentially multiply in the jejunum and ileum and, through their toxins, produce a cholera-like secretory diarrhea. They neither invade the intestinal tissue nor alter small bowel histology. The incubation period varies from hours to weeks and may cause mild to violent diarrhea. Traveler's diarrhea has recently been associated with enterotoxigenic *E. coli* and Pepto-Bismol has been effective in decreasing the diarrhea by presumed binding of toxin. Toxigenic diarrhea is probably prolonged by the conventional use of antidiarrheal agents which slow intestinal transit.

In a few children, chronic diarrhea with a malabsorptive picture may be caused by these organisms.

An increased incidence of necrotizing enterocolitis and neonatal sepsis due to a *nonendotoxic, noninvasive* (by standard laboratory criteria) *mucoid strain of E. coli* has recently been reported from one newborn center. Obviously, much remains to be learned about the vagaries of *E. coli,* which can produce such severe symptoms with apparent lack of invasiveness or toxin production. Perhaps a more intensive search for concomitant viral infection in such patients will provide a better understanding of their disease.

Diagnosis of *E. coli* disease rests upon a high degree of suspicion on the physician's part. Treatment with appropriate antibiotics must be determined by individual sensitivities. Neomycin, 100 mg/kg/day orally every 6 hours for 5 days or colistin, 10–15 mg/kg/day orally every 6 hours for 5 days, are recommended drugs for treatment of toxigenic *E. coli.* Invasive forms of disease must be treated by an absorbable antibiotic.

Yersinia Enterocolitica

As culture techniques have been perfected during the past few years, this gram-negative rod resembling non-lactose fermenting *E. coli* has been recognized as a human pathogen causing active enteritis, mesenteric adenitis or enterocolitis, fever and diarrhea.[11] Usually mild, the disease may also affect other family members and has been responsible for hospital and community outbreaks of diarrheal disease. Special techniques are required for its isolation and identification from stool cultures, therefore, unless a laboratory is specifically prepared, the correct diagnosis might be overlooked.

Colicky abdominal pain and liquid, bilious diarrhea of weeks to several months' duration are the major symptoms and anorexia, weight loss, vomiting, erythema nodosum and arthritis are the less common complications. Temperatures vary from subnormal to 39 or 40 C. Pain is often localized to the right lower quadrant and mimics that of acute appendicitis.

The laboratory findings are nonspecific; the white blood cell count is normal or shows mild-to-moderate leukocytosis and the erythrocyte sedimentation rate is elevated.

Pathologic studies reveal small mucosal ulcerations throughout the terminal ileum and colon, with acute and chronic cellular inflammation of the mucosa. Radiologic appearance is normal in some and abnormal in others, where it resembles Crohn's disease of the terminal ileum.

The diagnosis is confirmed by isolation of the organism, but may be suspected from a rise in *Yersinia* antibody titers 3–4 weeks after the clinical onset of disease, with the lowest significant titers of 1:100. There is a serologic cross-reaction with some *Brucella* strains; rising brucella titers may be occasionally found by routine studies of febrile agglutinins. Since *Brucella* infections

are so rare in this day, increased titers in a patient with chronic febrile diarrhea should immediately alert the physician to search for *Yersinia enterocolitica.*

Tetracycline or chloramphenicol for a 2-week period constitutes the treatment. Although this is curative in most cases, the occasional radiologic abnormalities may persist for months.

Salmonella

Infections due to *Salmonella* are not unusual; they are transmitted through poultry, milk, eggs, shellfish and household pets such as cats, dogs and turtles. The source of nursery epidemics is often an asymptomatic mother.

The incubation period for *Salmonella* ranges between 12 and 72 hours and infection, like that of other enteritides, is characterized by fever and a watery diarrhea.[4] Over the past few years we have become increasingly aware that *Salmonella* can cause a mucoid bloody diarrhea both in children and adults. Some organisms invade the mucosa without stimulating secretion, whereas others provoke secretion both in the large and small bowel. In such instances, colonic cyclic AMP is increased, but as yet an enterotoxin has not been identified. Organisms which penetrate the mucosa are phagocytized by the macrophages of the lamina propria. The major pathologic effect is ulceration of the right colon and terminal ileum. Bacteremia has been reported in association with *S. typhimurium* and enteritides strains. In chronic or recurrent infections in children the organisms are harbored in the Peyer's patches and not in the biliary tract. Cultures from bile and proximal small bowel are sterile, whereas stool cultures are positive. One child with persistent diarrhea and recurrent *Salmonella agona* infection had transient abnormalities in the serum glutamic-oxaloacetic transaminase (SGOT) and alkaline phosphatase while cultures of bile remained negative.

In the newborn, *Salmonella* infection is particularly serious; infants may develop sepsis or meningitis before the clinical onset of diarrhea. Children with sepsis also have splenomegaly and a fine maculopapular rash. Causative organisms are *S. choleraesuis* or *S. paratyphi.* Severe chronic *Salmonella* diarrhea can result in protein-losing enteropathy.

The diagnosis is confirmed by culture of the organism in appropriate media. Blood cultures should be obtained routinely and any infant with central nervous system signs should have immediate examination and culture of the cerebrospinal fluid. A rise in agglutination titers occurs 4 days after onset and is sometimes helpful in cases in which the organism has not been cultured. Spurious titer rises may occasionally occur in patients with inflammatory bowel disease or systemic diseases without evidence of infection.

Young infants, debilitated patients or those with sickle cell

anemia should receive antibiotic therapy. Ampicillin or trimethoprim is usually effective, but with resistant organisms or in cases of recurrent infection, chloramphenicol is recommended. Older children do not require treatment and usually recover within a week. There is evidence that treatment with antibiotics does not hasten recovery and, in fact, it prolongs the carrier state. One of the children with recurrent infection was found to have granulomatous disease of childhood and, consequently, we routinely study granulocyte and immunologic function in children with repeated severe infections.

Shigella

Infection by *Shigella* organisms involves the colon and produces "bacillary dysentery" with diarrhea characterized by blood, mucus and pus. The organisms produce enterotoxins and/or exotoxins which cause injury to both the intestine and the central nervous system. Transmission is indirect, through contact with infected food or linens. The majority of cases are caused by *Shigella sonnei; S. flexneri* is prevalent in developing countries and *S. dysenteriae* in Central America. Those working in emergency rooms of large cities can identify districts from which most cases of *Shigella* arise.

Unlike *Salmonella*, the *Shigella* organisms exert their major effects on the sigmoid and rectum, where they penetrate the mucosa and cause edema, petechial hemorrhage and exudate. The lymphatic tissue hypertrophies, the mucosa ulcerates and histologic examination shows crypt abscesses resembling those of ulcerative colitis. Tenesmus is marked and it is not unusual for rectal prolapse to occur in young children. Sepsis is rare except in the newborn; the reported cases have been caused by *S. sonnei, dysenteriae, flexneri* and *alkalescens*. An endotoxin has been identified from *S. dysenteriae* which causes enteritis and increased secretion in animal loops.

The disease most often affects children under 10 and has an incubation period ranging between 24 and 48 hours. Diarrhea is severe and there is fever and a certain degree of toxicity. In some cases, convulsions precede the onset of diarrhea. The illness is self-limited and usually ends after 5–7 days but a few children have chronic diarrhea persisting for several months.

Stool cultures must be plated rapidly; a delay of 2 hours may decrease recovery of the organism by half. Eosin methylene blue (EMB) medium is the recommended carrier vehicle because, unlike other carriers, it does not inhibit *Shigella*. The white blood count shows either leukopenia or leukocytosis but regardless of cell count there are usually more nonsegmented than segmented polymorphonuclear cells. Radiologically the colon appears normal, except for severe cases, in which collar button ulcerations can be seen.

A good deal of controversy exists as to whether *Shigella* infections should be treated, since 30–70% of patients are clinically improved and free of the organism in about 7 days. Nonabsorbable antibiotics seem ineffective in changing the course of the illness, but ampicillin in a dosage of 100 mg/kg/day intramuscularly or orally elicits a good clinical and bacteriologic response. Ampicillin-resistant strains, whose incidence is increasing, are promptly controlled with trimethoprim (.06 μg/ml) plus sulfamethoxazole (1.25 μg/ml). Infants under 1 year tend to carry the organism for many weeks. The adult carrier state is rare except in those with biliary tract disease. I personally would treat infants under 1 year and older children who have toxic conditions.

Tropical Sprue

The most common malabsorptive disease of the tropics and subtropics, tropical sprue, affects individuals of lighter complexion of all ages.[12] Although the cause is yet unknown and no specific viral or bacterial agents have been isolated from throat, stool or blood, there is evidence to implicate bacterial overgrowth in the small bowel. Jejunal cultures have shown increased counts of such organisms as *Klebsiella pneumoniae, E. cloacae* and *E. coli,* some of which are enterotoxigenic.

Resembling celiac disease, tropical sprue has, nevertheless, certain individual morphologic features. The disease involves the terminal ileum as well as the proximal small bowel, whereas in celiac disease the terminal ileum is spared. Although there is blunting of the villi and cellular infiltrate, the mucosal epithelial cells are not entirely flat. Fat, xylose, and fat-soluble vitamins are malabsorbed. Hypocalcemia and hypomagnesemia may be significant. Gastritis and histamine-fast achlorhydria are present in 5–30% of patients. Typical hematologic changes are megaloblastic anemia and bone marrow depression related to vitamin B_{12} and folate malabsorption. Similarly, serum carotene is depressed.

The diarrhea may begin several weeks to months after a visit to the tropics and occurs intermittently, but finally becomes continuous and results in malabsorptive-type stools. Abdominal pain and distention are marked. As the disease progresses, the patients develop a bronze-type pigmentation, hypoproteinemia and edema.

The diagnosis must rely on small intestinal biopsy and culture of jejunal aspirate, along with the typical hematologic findings. Treatment consists of simultaneous administration of folic acid, 5 mg 3 times daily, vitamin B_{12}, 30 μg per day and tetracycline (in appropriate dosage for age) for 1–2 weeks. These are continued in lesser dosage for several months.

Whipple's Disease

This systemic disorder causes malabsorption and affects the skin, joints, pleura, heart and central nervous system. Although

most often seen in middle-aged adults, it has been reported in 1 infant and in several children. The etiologic agent has not been identified, but it is presumed to be of infectious origin because a gram-positive organism has been identified in the intestinal mucosa of some patients and the disease responds to treatment with antibiotics.

The small bowel wall is edematous and the villi are thickened and blunted. There is extensive infiltration of the lamina propria with macrophages, which stain a deep fuchsin color with periodic acid-Schiff (PAS) reagent. Fat droplets are present in the lamina propria and within lymphatics. Fat transport through the lamina propria is impaired at this step and further by the enlarged mesenteric nodes. Diarrhea is watery and foul-smelling. Systemic symptoms are fever, arthritis of large and small joints and edema secondary to hypoproteinemia. Radiologic examination cannot distinguish this disease from celiac disease; therefore, small bowel biopsy studies are indicated. Successful treatment has been obtained after long-term courses of penicillin or tetracycline.

Related Vibrio Infection

Relatively rare, enteric infection from related vibrios can produce severe diarrhea which, if untreated, is prolonged and associated with frequent relapses. Special culture techniques and a sodium thioglycollate medium are required for organism isolation. Treatment with either neomycin or tetracycline for ten days is curative.[13]

Other Infectious Diarrheas

Vibrio, Klebsiella, Pneumococcus and *Pseudomonas* diarrheas have been reported in acute forms and have not been associated with chronic types of diarrhea so that they will not be dealt with in this monograph.

Parasitic Infestations

Roundworm Infestation

Strongyloides stercoralis is a roundworm measuring about 2.5 mm in length; disease symptoms are caused through parasite inhabitation of the proximal small bowel.[14] Infestation is particularly serious in debilitated patients and in those on steroids. It is common in the tropics and Far East and also endemic in the South (United States). The cycle begins with a rhabditiform larva discharged from the bowel into the soil, where it changes into a free-living adult, infective for man. It penetrates the skin, passes through the bloodstream into the lungs, where the adolescent female is fertilized, and then deposits eggs into the bronchial epithelium. Some larvae pass up the trachea into the pharynx and are swallowed. Females then are fertilized in the gastrointestinal tract and lay their eggs in the intestinal mucosa. Some tissue

hemorrhage occurs during migration and pseudotubercles and granulomas form locally. Pneumonitis develops and persists for 2–3 weeks as the larvae migrate through the lungs. As the parasites invade the bowel, they cause abdominal pain, nausea and vomiting. Later they cause a malabsorption syndrome and a protein-losing enteropathy. Marked mucosal edema may cause intestinal obstruction.

The diagnosis is made extremely difficult by the small numbers of larvae that are excreted. Radiographic findings vary from normal to nonspecific inflammation of the proximal bowel. In more advanced cases there are nodular intramural defects from granulomas or effacement of the mucosal pattern due to fibrosis. Changes in the colon, which occur rarely, may simulate ulcerative or granulomatous colitis. There is peripheral eosinophilia.

Treatment with thiabendazole, 25 mg/kg twice a day for 2 days, has a cure rate of almost 100%. Pyrvinium, 5 ml 3 times daily for 8 days, is effective in older children.

Ascariasis

Ascaris is the largest intestinal roundworm found in man; adult worms measure 20–40 cm in length. Although found throughout the United States, it is most common in the South. The eggs, quite resistant to drying, are transmitted by contamination of food or fingers and, after ingestion, they hatch in the duodenum. Larvae invade the intestinal wall, travel to the lungs through the portal system and migrate up the pharynx, where they are swallowed and reenter the small intestine to mature into adult worms.

Infants with heavy infestation suffer from a severe pneumonitis, whereas those with lighter infestations have no pulmonary symptoms. Bowel infestation is characterized by chronic diarrhea, weight loss and colicky abdominal pain. Worms which are passed are described as pencil-sized and flesh-like.

Diagnosis is established by the finding of eggs in the stool. There is often an accompanying eosinophilia. Heavy infestations can cause pancreatitis or hepatitis after the worms migrate up the pancreatic or biliary ducts; children who appear toxic should have liver and pancreatic enzyme tests.

The preferred treatment is pyrantel, 10 mg/kg in a single dose that does not exceed 1 gram. Piperazine, 50–75 mg/kg not to exceed 4 gm and given in a single daily dose for 2 days, is the second choice. Thiabendazole, 25 mg/kg twice a day for 2 days, is also effective.

Hookworm Disease

The adult *Ancylostoma duodenale* and *Necator americanus* also cause human disease. Measuring only 1 cm in length, they lodge in the small intestine and produce a blood loss of .02–2 ml/day for each worm. Tropical and semitropical climates favor this parasite

because the ova are very susceptible to drying. After excretion into the soil the ova change into the rhabditiform and then the filariform larvae, which penetrate the skin and cycle through the lung as does *Strongyloides*.

The clinical picture includes coughing and pulmonary infiltrate during migration and epigastric pain, vomiting and diarrhea during intestinal invasion. In approximately 6 weeks, as maturation of the adult worms progresses, anemia becomes apparent. In heavy infestations, anemia may be so severe as to provoke cardiac failure, malnutrition and edema.

The eggs are easily detectable in fecal smears. The stools contain gross or occult blood. There is peripheral leukocytosis with eosinophilia of 15–30%.

Treatment with bephenium hydroxynapthoate in 1 dose containing 2.5 gm cures 70–90% of *Ancylostoma* infestations and if given for 3 days, cures 55% of *Necator* infestations. Thiabendazole, 25 mg/kg twice a day for 2 or 3 days has a cure rate of 55–85% and is useful in treating mixed infestations.

Trichuriasis

The whipworm, *Trichuris trichiuria*, is a common parasite in the South but is also seen in the North. The ova are ingested in water, dirt or contaminated food and hatch directly in the duodenum. They migrate to the cecum but in heavy infestations may inhabit the entire colon. Hemorrhage and inflammation develop at points of attachment. Whipworms, as the hookworms, ingest significant quantities of blood causing anemia.

Clinical manifestations are diarrhea, weight loss, abdominal distention and tenesmus. Small children may have rectal prolapse which will persist until the infestation is treated.

Diagnosis can be made after finding ova or worms in the stool. Sigmoidoscopic examination may reveal a carpet of whipworms undulating along the rectal wall.

Asymptomatic infestations are not treated. Thiabendazole, 25 mg/kg twice a day for 2 days, is curative in only 20% of patients. After administration of a 2% saline enema the night before and another one 2 hours before treatment, a hexylresorcinol enema (0.1% solution in 100 ml of water) with the anus protected by petrolatum remains the standard treatment. The procedure is repeated weekly for 2–5 weeks. Dithiazanine, although recommended for treatment of this parasite, should not be used because its absorption is increased when the bowel is inflamed and in several patients it has been reported to cause peripheral collapse and death.

Protozoal Infection

GIARDIA LAMBLIA.—Although this parasite may inhabit the small intestine of healthy adults, it acts as a pathogen in

others.[15, 16] A pear-shaped flagellate, *Giardia* attaches to the proximal small bowel mucosa by means of a ventral suction disk. It is found in warm areas, among socioeconomic strata which are high in poverty and poor in hygiene, and it has also been associated with diarrhea epidemics through water contamination in ski resorts. An estimated world-wide incidence approximates 10%.

Giardia cysts live in moist soils and retain their viability for weeks in warm temperatures. After ingestion, the incubation period varies from 48 hours to 4–6 days and the clinical illness lasts for 10–12 weeks. It is believed that in asymptomatic carriers the organism does not attach to the intestinal mucosa.

A spectrum of disease states is attributed to *Giardia*: peptic ulcer symptoms related to duodenitis, fever and diarrhea, malabsorption and even bloody diarrhea resembling that of ulcerative colitis. A number of patients describe a "rotten egg" odor to their stools and, after personal examination of several specimens, I endorse this clinical observation.

The diagnosis is not always easy. If the infestation is heavy, trophozoites or cysts are found in the stools, but this happens in only about 40% of infected patients. Peripheral eosinophilia is usually less than 20%. Radiologic examination of the upper gastrointestinal tract is suggestive when thickening of the duodenal and proximal jejunal mucosal folds is evident. The most definitive diagnostic techniques are duodenal aspiration and biopsy and examination of a slide imprint from the mucosa. Small bowel histologic findings vary from normal to subtotal villous atrophy and some tissue sections may contain the parasite. Lesions tend to be spotty and one normal biopsy sample cannot be considered conclusive.

Treatment with quinacrine, 5–8 mg/kg/day given every 8 hours for 5–10 days, is usually adequate, with cure rates of 80–95%; a second course of therapy may be required if symptoms recur. Furazolidone, 5–8 mg/kg/day every 8 hours for 10 days, is now considered the alternate drug. Metronidazole, active against flagellates, has now been shown to be a bacterial mutagen and has been disapproved for the treatment of *Giardia*. Lactose intolerance often accompanies *Giardia* infestation and resolves within 1–2 months after treatment. During the course of illness, however, it is advisable to recommend a lactose-free diet.

Since *Giardia lamblia* is frequently associated with immunoglobulin deficiencies, we obtain immunoglobulin values in all patients with documented infection.

AMEBIASIS.—*Entamoeba histolytica* causes primary amebiasis in the colon but may also invade the ileum, liver, lungs, brain and pericardium.[17, 18] Although the disease is most common in the tropics, estimates of its frequency in the United States approach 10% and it is being seen more frequently as young people increase their sphere of travel. Transmitted through fecal contami-

nation of food, hands or water, the cysts pass through the gastrointestinal tract to reach the distal small bowel, where they excyst to yield 8 trophozoites each. These continue to multiply by binary fission and invade the distal small bowel and proximal colon where they form typical flask-shaped ulcers in the mucosa and submucosa. The ulcers are discrete and irregular in shape with undermined edges. Grossly they may be confused with those of ulcerative colitis.

Infants and debilitated older patients are particularly prone to intestinal perforation. The acute form is associated with colicky diarrhea and fever. Some children have a celiac-type syndrome and pass foul-smelling, bulky stools. Chronic amebic infection may simply be characterized by a mild-to-moderate chronic diarrhea associated or not with the passage of blood and mucus.

In order to avoid confusion with ulcerative colitis, examination of the fresh stool and of a rectal biopsy sample for the parasite is imperative. Ideally stools should be examined while still warm. Serologic tests are not always positive during active disease but are positive in 90% of patients with hepatic involvement. Processing unfortunately requires several weeks before the results are returned.

If the asymptomatic carrier is treated at all, diodohydroxyquin is the recommended treatment, in doses of 40 mg/kg/day (maximum 2 gm) orally every 8 hours for 20 days. For those with mild-to-moderate colitis, paromomycin, 25 mg/kg/day (maximum 1.5 gm) orally every 8 hours is administered for 20 days. Severe dysentery is treated with metronidazole, 50 mg/kg/day orally every 6 hours (not to exceed 2.25 gm/day) plus tetracycline, 40 mg/kg/day orally or intravenously (not to exceed 2 gm/day) plus dehydroemetine, 1–1.5 mg/kg/day intramuscularly for 5–10 days. This combined therapy is then followed by diiodohydroxyquin, 40 mg/kg/day orally every 6 hours for 20 days.

Other parasites causing chronic diarrhea are *Balantidium coli* and *Capillaria philippinensis*. Although extremely rare in the United States, infestation with these parasites has been encountered in people who have visited the Carribean or the Philippine islands. It is imperative that a travel history be taken in all cases of chronic diarrhea, no matter how young the patient.

Fungal Infections

Candida albicans

In 15–50% of the population, *Candida* is a harmless saprophyte. In babies, in older patients with lowered resistance from immune deficiency or debilitation and in patients who have had antimetabolite or antimicrobial therapy, *Candida* may act as a pathogen.[3, 19]

It is the mycelia form which has the capacity to invade tissue.

Mycelia were found to have invaded the small bowel in all of the fatal cases of *Candida* enteritis. Most patients with enteritis also have typical oral or cutaneous lesions of monilial infection. Diarrhea is rather nonspecific and may be associated with vomiting. Typically, the perianal region is red, excoriated and surrounded by monilial satellite lesions.

The presence of yeast forms in the stool is not significant, whereas mycelia signify pathogenicity. Serologic testing is being developed but as yet does not always differentiate between local and systemic infection. The *Candida* skin test is positive in the majority of older infants and children; a negative skin test is suggestive of impaired immunity. Nevertheless, we have encountered patients with positive skin tests and impaired lymphocyte transformation in the presence of *Candida* in whom transfer factor was required for successful treatment of their disease. In most cases, oral treatment with nystatin results in marked improvement within 3 days and should be continued for 7 – 10 days. Resistant, severe infection must be treated with amphotericin B given intravenously in dosages of 0.25 – 1 mg/kg/day for the same length of time.

Histoplasmosis

Although it has a world-wide distribution, *Histoplasma capsulatum* is usually found in the central regions of the United States. The organism exists as a small yeast at body temperature, but in nature it occurs as a mold. Entry is through the lung, causing a self-limited pneumonitis and, rarely, a chronic calcifying disease. In endemic areas 80% of the population have evidence of infection, as demonstrated by positive skin tests.[20]

The organism reaches the gastrointestinal tract where it causes lesions simulating those of granulomatous enterocolitis, with thickening of the submucosa and scattered mucosal ulcerations. Noncaseating granulomas with giant and mononuclear cells appear in the bowel wall and the mesenteric nodes.

The symptoms are nonspecific, including diarrhea, abdominal pain, fever, adenopathy, hepatosplenomegaly, anemia and leukopenia. A chest film will show pneumonitis or hilar adenopathy.

It is essential to obtain serologic titers before skin testing to avoid distortion of titer interpretation. A rise in titer followed by a fall during convalescence is suggestive of the diagnosis. Radiologic examination of the intestine may show ulceration, pseudopolyps or stricture. Identification and culture of the organism from affected tissue is the definitive diagnostic procedure.

Daily treatment with amphotericin B intravenously must be continued for at least 12 weeks, starting with 5 – 10 mg/kg/day initially and increasing the dose to 35 mg/kg/day.

ANTIBIOTIC-RELATED DIARRHEAS

It is not at all unusual for young children to develop diarrhea during a course of oral antibiotic therapy. In most instances this is related to ingestion of penicillin, ampicillin, tetracycline or neomycin. Diarrhea is usually self-limited and clears within several days after antibiotics are discontinued. A change in enteric flora is usually considered causative and mild chronic cases may be improved by the addition of *Lactobacillus* in the form of commercial preparations, such as Bacid, or natural ones, such as yogurt. In more severe chronic cases, stools should be cultured for fungus or for resistant enteric pathogens.

Other than the change effected in the intestinal flora, the mechanism by which most of these antibiotics cause diarrhea is unknown. Neomycin, not commonly used in general practice, does induce alterations of small bowel structure, with malabsorption of xylose, glucose and disaccharides. The vehicles in which antibiotics are packaged are sugars: lactose for capsules and tablets, sucrose in syrups. It is important to exclude presence of a disaccharide intolerance which is being aggravated by the antibiotic vehicle.

Pseudomembranous enterocolitis has been reported in association with ampicillin and particularly with clindamycin administration and was orginally thought to develop in patients with delayed intestinal transit (whether inherent or induced by medication). Last year it has been shown in animals that this disease could be transmitted to healthy animals through cecal contents and could be prevented by either vancomycin or gas gangrene polyvalent antitoxin. Clindamycin-resistant *Clostridium difficile* and *C. sardelli* have been the predominant anaerobes recovered from such stools.[21] *Clostridium welchii* is present in up to one third of normal stools and has not yet been implicated in this form of colitis. Cytogenicity assays for toxin using tissue culture techniques or animal model transfer experiments are still only research tools and are not routinely available in diagnostic laboratories. These are certainly significant data that may open a new area of anaerobic studies in less serious chronic postantibiotic diarrheas.

CARBOHYDRATE INTOLERANCES

Most sugar intolerances that occur in the infant and young child are secondary to mucosal damage from gastroenteritis and only rarely can a primary sugar malabsorption be detected.[22] Carbohydrates are ingested as polysaccharides and disaccharides (lactose and sucrose). Briefly, polysaccharide starches are hydrolyzed by salivary and pancreatic amylases into maltose and isomaltose. These and other disaccharides are presented to the in-

testinal epithelial cells where they are hydrolyzed within the brush border: lactose into glucose and galactose: sucrose into fructose and glucose: and maltose into 2 glucose molecules. Although disaccharides are absorbed slowly in a jejunoileal gradient, the component monosaccharides glucose and galactose are rapidly transported through the cell by a sodium-activated transport system. Fructose is transported separately, probably by a nonactivated sodium system. All disaccharides can be found in the 3-month embryo except maltose 1; they reach their maximal development during fetal life.[23] Lactases develop later than the others and, therefore, the very small premature infant may enter life with a physiologic lactose intolerance.

When, for some reason, a disaccharide is not absorbed and hydrolyzed within the small bowel, it remains intact within the lumen and causes an osmotic diarrhea with influx of water and electrolytes and increased intestinal transit.[24] Sugar entering the colon is fermented, as noted earlier. The low molecular weight organic acids change the stool pH from a normal of 7 or 8 in the older infant to a value of 5 or 6. A simple screening test for the presence of reducing substances uses the Clinitest tablet. One part of stool mixed with 2 parts of water is centrifuged. The tablet is added to 15 drops of supernatant and the color reaction is graded as for glucose. Values over 1+ in infants older than several weeks of age suggest sugar malabsorption.[25, 26] Sucrose, however, is not a reducing sugar, therefore, the stool must be hydrolyzed with acid before testing for sucrose. Specific disaccharide tolerance tests are administered in doses of 2 gm/kg (maximum 100 gm) to the fasting child and blood samples are drawn at 0, 15, 30, 45, 60, 90 and 120 minutes. A normal response is a rise in blood sugar of 20 mg/100 ml or more over baseline levels. An abnormal test must be followed by separate monosaccharide tests (usually glucose) to rule out glucose-galactose malabsorption. A breath test, measuring hydrogen excretion after an oral disaccharide load, is positive if hydrogen excretion increases to greater than 10 parts per million above baseline. These tests are usually adequate to diagnose disaccharidase deficiencies but in some centers disaccharidase activities are routinely assayed in small bowel biopsy specimens. Although enzyme concentrations vary within the intestine, there are rather constant ratios between the enzymes. Maltase is the predominant enzyme, with activities 3 or 4 times higher than those of sucrase and isomaltase. Lactase, the most variable enzyme, is in least concentration, measuring 1–4 times less than sucrase and isomaltase. In cases of mucosal injury, lactase is the first enzyme affected.

Lactose Intolerance

There are actually 3 lactase enzymes but only 2 are capable of hydrolyzing natural lactose. A *familial lactose intolerance*[27] described in the European literature, is inherited as an autosomal recessive trait and is often a fatal disease. Vomiting is the major symptom, occuring shortly after the onset of lactose feeds and leading to dehydration and acidosis. There are lactosuria and aminoaciduria, central nervous system disorders and convulsions. The lactose tolerance test is normal; it is believed that a defect within the stomach permits an abnormal transport of lactose into the system. Elimination of lactose from the diet is therapeutic in some but not all infants and, despite therapy, some continue to vomit and eventually die.

Congenital lactose intolerance is a totally different disease in that, although diarrhea is the major component, some children also vomit. It is inherited as an autosomal dominant trait, with males affected more often than females.[28] Characteristically these infants develop diarrhea shortly after initiation of lactose feeds and pass watery or frothy acid stools described as smelling sour. The abdomen is distended and tympanitic and the anus becomes excoriated. A mild malabsorption may accompany lactose intolerance although the small intestinal morphologic configuration remains normal.

A total cure is accomplished by removal of lactose from the diet. After 6 months or more many of these infants can tolerate small quantities of lactose but some remain totally intolerant of it. After milk-substitute formulas are abandoned it is imperative that calcium and vitamins be added to the diet.

Late-onset lactose intolerance may develop on a racial and ethnic basis in older children in most world populations other than those of Northern white origin.[29] Although symptoms are rare before 5 years of age, the incidence rises linearly with age to the extent that, in adult life, 95% of the populations are affected. The use of the lactose tolerance test has significantly corrected a large number of earlier misdiagnoses of irritable bowel syndrome and in those patients diarrhea and flatulence have been cured by lactose restriction. Not always associated with diarrhea, lactose intolerance may cause generalized abdominal pain or right lower quadrant pain suggesting appendicitis. Lactose restriction with calcium supplementation is therapeutic in relieving diarrhea and cramping. A new product, Lact-Aid, is now available that can be added to milk to digest most of the available lactose to its component monosaccharides. Merely advising the patient to refrain from milk and milk products is not adequate, for lactose is present in innumerable and unthinkable products and a dietician's advice is paramount to clinical cure. After 6 months or more some patients may tolerate a low-lactose diet.

Sucrose-Isomaltose Intolerance

Originally considered rare, this disorder is now being recognized with increasing frequency.[30] Inheritance is of the autosomal recessive type and it has been suggested that the homozygote is symptomatic from infancy, whereas the heterozygote manifests milder symptoms at a later date. Affected children are intolerant to starches as well as to sucrose. Sucrase, isomaltase, palatinase and dextrinase activities are low or absent. These infants are well until sugars and starches are added to the diet, when symptoms similar to those of lactose intolerance appear. Diarrhea responds to an electrolyte-glucose solution but not to conventional clear liquids such as soda or juices. This disorder is most often confused with celiac disease because elimination of wheat products results in some improvement.

Typically, the child with diarrhea and an acid stool pH is placed on a milk-free diet and does not improve. A continuing acid pH is suggestive of sucrose intolerance and warrants a tolerance test. Celiac disease must be differentiated by means of a small bowel biopsy study performed while the child is taking wheat products. The biopsy is usually normal in children with sucrose intolerance but partial villous atrophy has been reported in some patients.

Treatment consists of elimination of sucrose, dextrins and starches. With time, some children can gradually tolerate corn or rice starches, which contain fewer 1 – 6 bonds than other types.

Secondary Disaccharide Intolerances

Secondary intolerances are far more common than primary ones; they usually follow an acute gastroenteritis and persist for weeks to 18 months. In other instances they may be associated with parasitic infestation, immunologic disorders or diseases affecting the small bowel mucosa.

Original studies of lactose intolerance after gastroenteritis showed that, if untreated, this can lead to sucrose and even monosaccharide intolerance.[31-33] Hypoglycemia may occur and intravenous glucose is required to maintain the blood sugar.

Chronic malnutrition states and even fetal malnutrition have been associated with lactose and/or sucrose malabsorption, factors which must be taken into account when dietary programs are formulated.

Disaccharide and monosaccharide absorption have been impaired after abdominal surgery in the infant and, in diseases such as Crohn's disease, celiac disease and even cystic fibrosis. Lactosuria and sucrosuria have been reported in Moncrieff's syndrome of hiatus hernia and mental retardation. The lactose intolerance

of ulcerative colitis may well occur on an ethnic basis, although changes in small bowel morphology have been reported during exacerbations of the disease.

Glucose-Galactose Malabsorption

Primary monosaccharide malabsorption is extremely rare. It is inherited in an autosomal recessive fashion.[34] Direct transmission from parent to child has never been reported and, although glucose tolerance tests have been normal in parents, jejunal glucose transport has been moderately impaired.

The characteristic defect is impairment in the ability of intestinal mucosal cells to actively transport glucose and galactose so that only about 10% of the ingested sugar is absorbed. Since ATPase and sodium transport are normal, it has been proposed that the abnormality is in the glucose-binding site of the mobile sugar carrier. Small bowel histologic appearance, disaccharidase and amino acid transport are normal. Patients with this disease have an intermittent glucosuria in the presence of normal blood glucose. Glomerular filtration rates and maximum tubular reabsorption of glucose are normal, although there is a reduced minimal glucose threshold.

The symptoms are similar to those of disaccharide malabsorptions, with stools containing both disaccharide and glucose. Symptoms begin after the first glucose feed and, if the disease is not treated, the outcome is fatal. The stools have a pH of 4 or 5 and are strongly positive for reducing substances as well as for glucose when tested with Clinistix. A sugar-free formula using casein hydrolysate of Cho-Free will result in prompt cessation of diarrhea. Sugar must be added to avoid ketosis and fructose is an acceptable carbohydrate source. It is wise to wait until the infant is stable before performing a glucose tolerance test.

Dietetic Candy and Gum Diarrhea

Mention must be made of the osmotic diarrhea secondary to ingestion of sorbitol and mannitol, which are so prevalent in dietetic candies and gum.[35] Recommended as substitutes in order to lessen the incidence of dental caries in our candy-oriented society, these hexitols are acted upon slowly by oral bacteria and are only passively and slowly absorbed through the intestine. Because of these properties they were used in the past in large dosage as laxatives. The symptoms are dose dependent: if a sufficient quantity is ingested, a watery, explosive diarrhea follows within several hours, accompanied by cramping and abdominal distention.

GASTROINTESTINAL ALLERGIES

Cow's Milk Protein Allergy

Allergy to cow's milk protein is a fairly common cause of chronic diarrhea in the infant and toddler. The incidence in healthy children varies between 0.3 and 7% and in allergic ones it reaches to estimates of 30%.[3, 36-38] The frequency of diagnosis varies with the index of suspicion; often a child is hospitalized 3 or 4 times for gastroenteritis before the proper diagnosis is made.

Why one child develops cow's milk allergy and another does not is unclear. Certainly we know that there is a strong family history of allergy in such patients and that many infants may have transient deficiencies of IgA, the major secretory immunoglobulin and the defense barrier for the intestinal mucosa. The normal infant, however, does not produce secretory IgA until 6 weeks of age or so. The intestinal mucosa during the first few days of life is permeable to macromolecules, but antigen penetration occurs later, only after mucosal damage. Antibodies to ingested antigens are produced by plasma cells within the lamina propria and are excreted into the lumen, where they function to complex with antigen and to decrease the amount of free antigen coming into contact with the mucosa. The major immunoglobulin of the gastrointestinal tract, IgA, secreted in combination with transport piece, is termed "secretory IgA." IgG, IgM and IgE antibodies are present in lesser concentrations.

It is obvious, therefore, that in situations where IgA is absent or diminished, gastrointestinal defenses are weakened. In support of this concept is the well-known fact that breast-fed infants have a far lower incidence of infectious diarrhea, presumably because they are receiving maternal IgA in the milk.

Several types of immune reactions take place within the intestinal mucosa in milk protein allergy. In the first few hours after milk challenge there is an increase in the IgE plasma cells, with mast cell degranulation and infiltration of the mucosa by eosinophils and polymorphonuclear leukocytes, as occurs in Type I hypersensitivity reactions. Biopsy specimens examined 24 hours after milk ingestion show an increase in the IgA-containing plasma cells.[39] The release of histamine, slow reactive substance-A, serotonin and other substances from mast cells probably stimulates smooth muscle contractions and increases vascular permeability, resulting in rapid transit and even mild degrees of malabsorption.[40]

Many antigens are present in cow's milk, of which casein, β-lactoglobulin and α-lactalbumin are most important. Antigenically active peptides have been prepared from β-lactoglobulin after its incubation with trypsin and it is likely that peptides re-

sulting from pepsin and trypsin digestion are antigenic to the young child.

Symptoms. The usual gastrointestinal manifestations of cow's milk protein allergy are diarrhea and cramping. The stools vary in consistency from soft to watery and are often explosive. They may contain curdlike material, mucus and even blood. Most infants are symptomatic at 4–6 weeks of age but milk allergy may present at any time, even as early as 2 days of age. In a few babies, colic may be a more serious complaint than diarrhea. Eczema is not often associated but frequent colds, otitis media or chronic rhinitis are rather typical.

Rectal bleeding or even lower gastrointestinal hemorrhage may be the presenting symptom in the young infant, associated with what we term "milk-induced colitis"[41] which, in histologic and sigmoidoscopic appearance, resembles ulcerative colitis. Fortunately this condition clears completely after several days of milk restriction. Lactose intolerance, fat malabsorption and even monosaccharide malabsorption may occur. Small bowel histologic findings vary from normal to subtotal villous atrophy. Edema, hypoproteinemia and severe iron deficiency develop as a consequence of occult blood and protein loss.

Diagnosis is at times difficult. Skin testing is helpful but does not always correlate with symptomatology. Circulating antibodies to milk protein are prevalent in children with systemic symptoms but are not common in those with diarrhea. Similarly, serum IgE levels and milk-specific radioallergosorbent tests (RAST) are not always indicative of systemic allergy. Peripheral eosinophilia rarely rises above 5%, but an increase in stool leukocytes and eosinophils does occur after challenge. Coproantibodies to milk protein are present in the stools of many of these patients but have also been reported in stools from infants without diarrhea when the specimens were concentrated. In our experience, the presence of coproantibodies correlates well with a clinical diagnosis, although they are not present after short-term challenge. All children with diarrhea after milk ingestion should have a lactose tolerance test. If this is normal and 3 clinical challenges have been fulfilled by the criteria of Goldman et al.,[42] milk protein allergy is a reasonable diagnosis.

The treatment is a milk-protein free diet. Some children react to beef products as well and consequently, restriction of these is indicated. Later, well-cooked beef can be tolerated. Very few tolerate milk before 1 year of dietary restriction.

Soy Protein Allergy

As is the case with milk allergy, this disturbance may occur as a primary event or after mucosal damage from gastroenteri-

tis.[3, 43, 44] Soy has been known for years to be antigenic but only in the last decade have we become aware of the clinical problems associated with it, i.e., asthma, recurrent pneumonitis, anaphylaxis and diarrhea. The clinical symptoms resemble those due to cow's milk allergy. Often an infant is fed soy because other siblings were allergic to milk. Within days to weeks, a watery, mucoid diarrhea with occasional blood develops. The appetite remains good but weight gain decreases. In other cases, the infant allergic to milk is given a soy formula. Diarrhea either recurs after improvement of several days' duration or does not improve at all. A few young infants develop edema and hypoproteinemia. Significant rectal bleeding is associated with "soy-induced colitis."

In our experience, examination of the stool for coproantibodies to soy is helpful. The stool pH is occasionally acid because some patients have an associated sucrose intolerance. Small bowel biopsy remains normal in the majority of children, although a few have had subtotal villous atrophy.

Since many of these patients will also become allergic to milk, we prefer to treat them with a milk and soy-free diet using Nutramigen. If sucrose intolerance is present, the proper formula is Pregestimil, which contains glucose. Children can usually tolerate soy after 6 months of restriction.

Gluten Allergy

Allergy to gluten does not occur as a singlular event but follows in the wake of a milk or soy allergy in at least one third of affected children.[3, 45] The symptoms are less dramatic than those associated with milk or soy allergy and include usually an increased frequency of stools, which are mushy and mucoid. There may be a distinct malabsorption associated with the diarrhea.

Coproantibodies to wheat and to gluten fraction III are present in the stool. Small bowel biopsy is relatively normal with some plasma cell or eosinophilic infiltrate in the lamina propria; occasionally, it reveals subtotal villous atrophy. It is essential to perform biopsy and absorptive studies to differentiate this entity from celiac disease because in either case there is a prompt response to dietary restriction of gluten. Swedish researchers note that patients with true celiac disease usually have a later onset of symptoms than do those with allergy.[37] Since allergy is usually outgrown after 6–12 months, it is our policy to reintroduce gluten and to reevaluate the patient after 2–3 months.

CELIAC DISEASE

Lloyd-Still recently published an article titled "Where have all the celiacs gone?".[46] The diagnosis of celiac disease seems to be

made less frequently in the United States although it is still common in Europe. In view of the increased incidence of lymphoma in adult patients who have not maintained restricted diets, it is essential that the diagnosis not be overlooked and that proper life-time dietary therapy be initiated. Most estimates cite the incidence of celiac disease at about 1:3,000. Inheritance is likely effected through a dominant gene of low penetrance; parents, siblings and even twins have been affected. Eleven percent of "normal" relatives of patients have had abnormal small bowel biopsy specimens.

Celiac disease has been more often associated with blood types O and A and now is found to coexist in a number of patients with cystic fibrosis. It is clear that the offending agent is the gliadin fraction of gluten. Although no one enzyme deficiency has been isolated as causative, it is likely that one or more enzymes responsible for digestion of gluten are deficient and cause an accumulation of undigested toxic peptides. That the defect is genetically determined is further supported by the finding that 80–90% of adult celiac patients are positive for the histocompatibility antigen HL-A8. Local hypersensitivity is believed to be also involved in the etiology for 2 reasons: "gliadin shock" develops in some celiac infants when refed gluten and the disease is favorably affected by steroids. Immunologic features of these patients are a high incidence of gluten antibodies in the serum and an increase in IgA after gluten challenge. Many have splenic atrophy and impaired phytohemagluttination-induced lymphocyte transformation.

Intestinal change due to gluten has been well documented.[47, 48] Damage is most severe in the duodenum and proximal jejunum, with flattening of the villi, increase in crypt depth and flattening of the normal surface epithelium, with nuclear eccentricity. Goblet cells are decreased in number and the lamina propria is heavily infiltrated with lymphocytes, plasma cells and eosinophils. There is little relationship between the clinical severity of the disease and the degree of histologic change; symptoms are more related to the length of bowel involved. Symptomatic improvement occurs 1–2 weeks after treatment, although small bowel villi do not reappear for several months.

The bowel is hypomotile and water and electrolyte absorption are impaired. Malabsorption of fat, protein, calcium and magnesium as well as fat-soluble vitamins and folate occurs. A protein-losing enteropathy may further complicate protein nutrition. Because the brush border of the mucosal cells is disrupted, all of the brush border disaccharidases, peptidases and monamine oxidases are decreased.

The onset of celiac disease in children usually occurs between the ages of 8 months and 2 years, although it has been reported in infants of several months of age, manifested primarily by vomit-

ing. Diarrhea and poor growth are the most frequent complaints, but occasionally constipation with the passage of infrequent, large stools is the first suggestion of disease. Regardless of the type of presentation these children develop abdominal distention and loss of subcutaneous fat. Gluteal skin hangs in folds and only the buccal fat pads give some semblance of a once well-nourished child. Characteristically, these children are irritable and anorectic. Clubbing of the terminal phalanges is present in those with long-standing disease. Of older children, 86% have fingerprint changes consisting of ridge atrophy.

Criteria for diagnosis are presence of steatorrhea, a conclusive small bowel biopsy during gluten ingestion and clinical and laboratory response to a gluten-free diet. Since abnormal morphologic appearance can also be noted in milk and gluten allergy, purists demand that the disease be further documented by reversion to normal of the biopsy during dietary restriction and later rebiopsy after gluten challenge. The degree of steatorrhea is variable and, because of anorexia, it is essential that fat intake be measured during the quantitative fat studies. Fecal fat levels in children with celiac disease range between 4 and 26 gm/day, as compared to 3.5 gm/day or less in the child under 2 years of age and 5 gm/day in older children and adults. Serum carotene and folate levels are decreased and xylose absorption is impaired. Nearly one third of the patients are hypoproteinemic and many have low calcium, magnesium and iron levels.

Treatment consists of a strictly enforced gluten-free diet. This excludes rye, barley, oats and malt as well as wheat. Since lactose intolerance is secondary to mucosal change, it is advisable to include a lactose-free diet for the 1st month of therapy. Minor dietary lapses prevent an optimal response to treatment. Patients can take gluten at a later date without becoming symptomatic but it has been well documented that those who do, do not attain optimal growth. This is one of the most rewarding diseases to treat because not only do these children become completely well but they undergo a complete personality reversal and become happy and loveable.

PANCREATIC INSUFFICIENCY

Although cystic fibrosis is the most common form of pancreatic insufficiency, there are other diseases that may cause chronic diarrhea and must be considered in the differential diagnosis; i.e., Shwachman's syndrome, intrauterine viral infection and enterokinase and trypsinogen deficiencies.

Shwachman's Syndrome

This entity, first described in 1964, combines pancreatic exocrine insufficiency with bone marrow hypoplasia, failure to thrive, neutropenia, elevation of fetal hemoglobin, inconstant galactosuria and metaphyseal dysostosis.[49, 50]

The inheritance suggests variable penetrance; although parents are not affected, several siblings in one family may have the disease. Spontaneous recovery occurs in a few patients but many develop a severe aplastic anemia which is eventually fatal. Pathologic studies reveal that the pancreatic tissue is replaced by fatty infiltration. Although the ducts remain patent, glands are shrunken and cells have pyknotic nuclei and contain no secretory granules. There is marked periductular fibrosis. Neutropenia, noted between the 1st day of life and the 5th year, is often cyclical, with neutrophils showing a maturation arrest.

Between 2 months and 1 year of age, infants begin to pass loose, oily, bulky and foul-smelling stools. Weight gain eventually ceases and growth is retarded. Eczematoid rashes have occurred in some patients. The appetite is ravenous and abdominal distention is prominent.

The diagnosis must be suspected in any infant with diarrhea associated with neutropenia and absence of trypsin in the stools. Neutrophil counts vary from 4–13% but rise to normal during infection. Thrombocytopenia, anemia and elevated fetal hemoglobin are characteristic hematologic findings. Metaphyseal dysostosis of the femur, tibia and ribs is supportive evidence. Steatorrhea is verified by an increased content of fecal fat. The sweat electrolytes are normal. Duodenal intubation and measurements of pancreatic secretion will determine pancreatic insufficiency.

Treatment is based on pancreatic enzyme replacement, using Cotazym or Viokase in dosages titrated against the degree of steatorrhea. Infants can be managed by Pregestimil formula, which contains glucose, medium-chain triglycerides and hydrolyzed proteins. In a few patients anemia may respond to folic acid, vitamin B_{12} or testosterone, but in most it is refractory and must be managed by transfusion.

Other variants of the disease have been reported in which there is associated liver disease or immunoglobulin deficiency.

Enterokinase Deficiency

Enterokinase is an enzyme secreted by the duodenal mucosa; its role is to activate the proteolytic enzymes as they are secreted into the duodenum.[51] The enzyme catalyzes the conversion of trypsinogen into trypsin, which in turn activates the formation of chymotrypsin and carboxypeptidase from their precursors. The

symptoms and laboratory findings associated with this enzyme deficiency are, therefore, those of abnormal protein absorption.

Symptoms include diarrhea, failure to thrive, anemia and steatorrhea, which become apparent during the first few months of life. The clinical picture cannot be distinguished from those of other malabsorptive syndromes.

Pancreatic enzyme studies show a deficiency of trypsin, chymotrypsin and carboxypeptidase. Volume, bicarbonate, amylase and lipase responses are normal. Histologic examination of the duodenal mucosa reveals no abnormality. A trypsin-inhibitor substance has been found in the duodenal aspirate of one patient. Incubation of pancreatic secretion with normal duodenal mucosa or with porcine enterokinase will convert the zymogens to active enzymes.

Treatment is the same as for any pancreatic insufficiency, with supplemental pancreatic enzymes.

Trypsinogen Deficiency

The physiologic description of this zymogen is noted above. Trypsinogen deficiency brings about impaired activation of the other proteolytic enzymes that require trypsin.[52] Symptoms appear to approximately 1 month of age; in addition to protein malabsorption, there is intermittent vomiting in some babies. Steatorrhea is present and stool protein losses reach as high as 60% of the dietary intake. Pancreatic stimulation tests show an absence of proteolytic enzymes; of these, all but trypsin begin to appear after addition of bovine trypsin, which constitutes the treatment.

Congenital Lipase Deficiency

Only a few cases of this defect have been reported and, in several families, siblings were affected.[53] The stools were offensive from the time of birth, with orange oil droplets staining stool and diapers. Fecal fat absorption measured 68–70%, although pancreatic lipase was reduced. Treatment consists of enzyme replacement and a low-fat diet.

Cystic Fibrosis

The most common disease associated with pancreatic insufficiency, cystic fibrosis affects the lungs, liver, intestines and exocrine glands as well. Inherited as an autosomal recessive trait, the disease is estimated to affect 1 in every 2,000 live births. Although most common in whites, it also occurs in blacks, Orientals and Puerto Ricans.[3, 54-56]

The sweat test after 1 month of age is essentially diagnostic if

performed properly; elevations of chloride above 60 mEq/L are considered abnormal. The stool trypsin in the infant is usually positive in dilutions of 1:100 but with increasing age and slowed intestinal transit, trypsin is not usually present in routine stools in older children. Screening of neonatal stools with the BM Test Meconium Strip detects increased albumin content of meconium and records an ink-blue coloration in the presence of albumin concentrations of 20 mg/gm dry weight of meconium. Identification of the heterozygote is more difficult and requires sophisticated research techniques.

The primary defect in cystic fibrosis remains unknown, although the alterations of normal physiology are well described. Pancreatic insufficiency is present in about 80% of infants at birth and in 90% by the end of the 1st year. The pancreas is originally edematous but with time it becomes fibrotic and atrophic. Parenchymal cells disappear, although the islets of Langerhans remain intact. Liver disease occurs in about 30% of patients and focal biliary cirrhosis is present as early as the 3rd day of life. The usual changes are mild periportal fibrosis, focal bile duct proliferation and moderate inflammation. A similar number of patients have abnormalities of the gallbladder varying from microgallbladder to cholelithiasis. The bile is white and viscous. The small intestinal structure is usually normal, but a few patients may have subtotal villous atrophy. There is a rather consistent change, however, from duodenum to rectum, namely, an increased number of goblet cells. Brunner's glands in the duodenum may be dilated and filled with inspissated acidophilic material.

The disease may present in any of its 3 forms: neonatal obstruction from meconium ileus, repeated respiratory infections or steatorrhea. Rarely may an infant be referred only for evaluation of hepatomegaly. The stools vary from frank diarrhea to a large and bulky mass; all, however, are malodorous. Most infants with cystic fibrosis fail to grow but, since this is not always the case, a height and weight in the 95th percentile do not preclude the diagnosis. Infants perspire heavily and taste salty when the mother kisses them. This loss of electrolytes makes them particularly susceptible to hyponatremia in warm weather. Typical findings of malabsorption as well as clubbing of fingertips and toes are common. Vitamin deficiencies may be clinically apparent, with evidence of bruising and xerophthalmia. Hemolytic anemia and jaundice reflect vitamin E deficiency, whereas edema may develop as a result of protein malabsorption (Table 2).

Older children may have a "meconium ileus equivalent," with recurrent abdominal pain and intermittent obstruction due to an accumulation of putty-like stool in the terminal ileum and cecum. Fecal masses are palpable in the right lower quadrant.

Diagnosis is made by the sweat test. Correlative evidence is obtained by radiologic examination of the chest, quantitative

TABLE 2.—SYMPTOMS AND CLINICAL FINDINGS IN CELIAC DISEASE, CYSTIC FIBROSIS AND GASTROINTESTINAL ALLERGY

	CELIAC DISEASE	CYSTIC FIBROSIS	GI ALLERGY
Family history	Occasionally +	Often +	Often +
Onset	8 mo. – 2 yr.	Less than 6 mo.; 95% by 1 yr	1 – 6 mo.
Respiratory symptoms	–	+	Asthma, bronchitis, 4 yr +
Eczema	Occasional	–	Occasional
Appetite	Poor	Excessive	Normal
Stools	Bulky, foul, occasionally liquid	Bulky, foul oil droplets	Soft, watery, mucoid; occasional blood
Growth	Normal 8 – 10 mo.	Retarded	Variable
Sweating	–	+	–
Vitamin deficiencies	Unusual	Occasional	Unusual
Calcium deficiency	+	Rare	Occasional
Carotene	Very low	Very low	Moderately low or normal
Folate	Very low	Normal	Moderately low or normal
Finger clubbing	+	+	–
Lactose intolerance	Frequent	Unusual	Occasional

GI = gastrointestinal. +, present. –, absent.

stool fat studies and appropriate blood studies of carotene, folate and fat-soluble vitamins. Vitamin B_{12} absorption is also impaired in cystic fibrosis, which is corrected by enzyme administration. Treatment consists of enzyme replacement by administration of Cotazym or Viokase just before or with meals and snacks. A dietary intake of 150–200 cal/kg/day is necessary for adequate nutrition. Water-soluble vitamins should be given in double dosage. Small infants are best fed Pregestimil for optimal fat and protein absorption; enzyme therapy is not required until solids are added to the diet.

As therapy has become more aggressive, the life span of children with cystic fibrosis has increased into adulthood. The most severe gastrointestinal complication is portal hypertension leading to variceal hemorrhage. Diabetes mellitus may appear after 10 years of age as an impaired endogenous glucose secretion develops in these patients. They have, however, enhanced tissue sensitivity to insulin.

Intrauterine Viral Infection

Congenital pancreatic insufficiency has been reported to be caused by intrauterine rubella infection[57] and has been suspected in other cases of intrauterine viral disease. Other manifestations, such as microcephaly, hepatomegaly and bone changes, may be present.

IMMUNOLOGIC CAUSES OF CHRONIC DIARRHEA

Diarrhea is well recognized in some of the more severe immunoglobulin deficiencies,[58-60] but it has become increasingly significant that a number of infants with chronic diarrhea actually have transient or persistent abnormalities of IgA production or transient IgG deficiency. We have recently evaluated our active patients with chronic diarrhea and found that one third have had such immunoglobulin disorders. This is a significant finding in view of the fact that recent reports consider transient deficiencies a rarity.

Congenital Agammaglobulinemia

Bruton-type agammaglobulinemia is transmitted through an X-linked pattern and affects only males. The disease has its onset during the 1st year of life and is characterized by a decrease in all of the immunoglobulins, and defective antibody formation. Typically these children have recurrent infections from the encapsulated pyogenic organisms. Gastrointestinal complaints, which are not common, result in prolonged, incapacitating diarrhea. In

such cases there may be lactose or glucose intolerance, steatorrhea and even *Giardia* infestation. Small bowel biopsy studies may show subtotal villous atrophy. Mucosal invasion seems to be a factor in pathogenesis and jejunal culture for aerobes and anaerobes can help in selecting an antibiotic for treatment. Intramuscular injection of immunoglobulin every 3–4 weeks is helpful in maintaining γ-globulin levels but does not always affect the diarrhea.

Hereditary Thymic Aplasia or Swiss-Type Agammaglobulinemia

Thymic-dependent and thymic-independent tissues are affected by this disease, which is inherited as an autosomal or as an X-linked recessive trait. In most cases, all of the immunoglobulins are absent and so are lymphocytes in the peripheral smear. Antibody and delayed hypersensitivity tests are negative. The illness becomes obvious during the first few months of life, with recurrent monilial infections and respiratory disease. Some patients are referred early with persistent, unremitting diarrhea which is unresponsive to bowel rest. Why they are symptomatic while still protected by maternal antibody remains to be studied. Radiologic examination shows no thymic or adenoid tissue and there is also absence of tonsillar tissue. Rectal biopsy may be helpful as an early diagnostic tool before immunoglobulin determinations are diagnostic because it may show an absence of plasma cells and lymphocytes.

Treatment consists of supportive therapy and hyperalimentation. Irradiated blood must be used if transfusions are required, to avoid graft-versus host reactions, which are likely to occur in these children.

Dysgammaglobulinemia and Nodular Lymphoid Hyperplasia of the Small Bowel

Nodular lymphoid hyperplasia of the small bowel may occur with isolated IgA deficiency or with acquired hypogammaglobulinemia, but it is most often found in this syndrome, in which all levels of γ-globulins are depressed. The etiology is unknown and the disease has not been reported in members of the same family. It is often discovered during evaluation for chronic diarrhea associated with mild-to-moderate steatorrhea. Lactose intolerance, secondary milk and gluten sensitivity and *Giardia lamblia* infestation are often concurrent findings. Radiologic examination findings are classical for this disease, including mucosal nodules measuring 1–3 mm in diameter, scattered uniformly through the small bowel and into the cecum. These consist of lymph follicles with large germinal centers.

The particular risk of this disorder lies in the fact that nearly one third of the original patients have developed lymphoma or carcinoma within the gastrointestinal tract. Treatment is difficult; some improvement can be noted after long-term tetracycline therapy. Fresh frozen plasma has been beneficial in the past, but in view of the current knowledge of immune reactions in these patients, it can no longer be recommended.

IgA Deficiency

Isolated IgA deficiency occurs in approximately 1 of 500 individuals and in most it causes no symptoms. Some patients are susceptible to viral illnesses and others develop diarrhea. As mentioned before, IgA is the major immunoglobulin in the intestine and its deficiency predisposes to both infection and protein sensitization. Patients are also susceptible to *Giardia* infestation. Treatment with a hypoallergenic diet is often sufficient to prevent diarrhea, but in some cases bacterial overgrowth in the small bowel causes persistent symptoms and requires evaluation and treatment.

INFLAMMATORY BOWEL DISEASE

Although inflammatory bowel disease merits a section in its own right, it must be included in the differential diagnosis of chronic diarrhea in young children because of its increasing frequency and severity among toddlers as well as adolescents.

Ulcerative Colitis

This inflammatory disease affects the mucosa of the rectum and colon causing mucoid, bloody diarrhea. It is extremely rare in children under 2 years; only 3% of our patient group had such an early onset. Most of the cases resembling ulcerative colitis in infancy are actually due to milk or soy protein allergy. Ulcerative colitis has been reported in several offspring of mothers with the disease but this is unusual.

Although a number of hypotheses have been proposed as to the cause of colitis, no one factor has yet been identified.[3, 61] Infectious and allergic origins have been suggested, each having some support. A hereditary explanation cannot be overlooked: there is a 25% family incidence in patients with inflammatory bowel disease and also an apparent family incidence of ulcerative colitis and Crohn's disease. It seems most likely that in the genetically susceptible person some inflammatory insult sets the stage for the development of a later immune reaction. Psychogenic agents are not responsible for creating the disease but they are often involved in its recurrence.

Pathologic findings are nonspecific inflammatory changes involving the rectum, rectosigmoid and eventually part or all of the remaining colon. Extension into the appendix and terminal ileum occurs in 10% of patients. In fulminant disease, mucosal ulcerations can erode through the muscularis and into the serosa, causing collar-stud or rose-thorn ulcerations. As scarring develops in the mucosa, normal tissue is heaved into pseudopolyps. Eventually the colon becomes shortened and rigid, with its diameter narrowed and the absorptive function destroyed. Microscopically the surface epithelium shows areas of destruction with a decrease in goblet cells. The lamina propria is infiltrated with polymorphonuclear, round and eosinophilic cells and the glandular pattern is disrupted. Crypt abscesses are common.

In the infant and young child the disease is either mild and short-lived or severe and unrelenting. Diarrhea without blood may be present for weeks before typical stools are passed. If there is significant rectal disease, tenesmus is marked. Cramping is a complaint of older children. The eventual complications of untreated disease are anemia and hypoproteinemia. Extracolonic manifestations such as uveitis, arthritis and erythema nodosum are rare.

Physical examination shows evidence of weight loss and tenderness to palpation over affected areas of colon. Barium enema examination may show disease or, if the disease is rather superficial, no abnormality may be found. Sigmoidoscopy and rectal biopsy studies are essential in making the diagnosis.

Treatment of patients with mild-to-moderate disease consists in administration of salicylazosulfapyridine (Azulfidine) 125 mg 4 times a day for infants to 3–4 gm/day for older children. More severe disease or that which does not respond to therapy is managed with prednisone, 1.5–2 mg/kg. Patients with toxicity or who are severely ill are hospitalized, given steroids or adrenocorticotropic hormone (ACTH) intravenously and are treated with hyperalimentation to place the bowel at rest. Surgical intervention is obviously indicated if there is any sign of toxic megacolon or after failure to improve with maximum therapy for 14 days. The risk of carcinoma is formidable in long-standing disease; in ulcerative colitis of 10 years' duration the incidence of carcinoma approximates 15%.

Long-term treatment is variable but Azulfidine has been shown to decrease recurrence rates of disease and should be continued indefinitely. Steroid therapy is continued in large dosage until clinical and laboratory abnormalities return to normal; then it is tapered gradually over the following 4–6 weeks.

Crohn's Disease

Crohn's disease, formerly seen only in adolescents, is now occurring in children as young as 4 years. There is a paucity of information concerning the disease in infants and it is not certain whether the reported cases pertain to the same disease as in older children. In all centers, however, there is a unified impression that the disease is affecting younger children in a more severe form than that seen a decade ago.[62]

As with ulcerative colitis, the etiology remains unclear. However, a transmissible agent is suggested in Crohn's disease on the strength of the finding that injection of tissue into experimental animals has resulted in development of disease 12–36 weeks later.

Crohn's disease differs from ulcerative colitis both pathologically and clinically in that it is transmural and segmental and may involve both large and small bowel. Ulceration, polypoid change, stenosis and proximal progression of disease are characteristic. There is hyperplasia of perilymphatic histiocytes, dilatation of lymphatics, thickening of the mesentery and enlargement of lymph nodes. Biopsy specimens are characterized by ulceration, dense round cell infiltration of the lamina propria and presence of granulomas.

In infants, the onset has been reported as early as the 2d day of life. The acute form is heralded by intestinal obstruction and the chronic one by increasing abdominal distention, anorexia and diarrhea. Since in infants the disease involves primarily the terminal ileum, little blood is detected in the stool. In older children the symptoms depend on the site of involvement: those with colonic disease have diarrhea resembling that of ulcerative colitis. Children with only terminal ileal disease have pain as a more dramatic symptom than diarrhea and those with diffuse small bowel disease have diarrhea and often enteric protein loss. Fever, arthritis and arthralgias as well as erythema nodosum are associated with ileocolitis more than with other forms. In several adolescent patients, anorexia has been the only initial complaint.

Diagnostic findings are an elevated erythrocyte sedimentation rate and presence of anemia and hypoalbuminemia. Examination of the colon and small bowel will usually reveal the characteristic radiologic abnormalities of Crohn's disease: nodular or stenotic changes in the ileum, with evidence of rigidity or segmental colitis in the colon.

Treatment is similar to that used for ulcerative colitis. Azulfidine has not been shown to be effective in small bowel disease in adults, but has resulted in clinical improvement in children and is worthy of initial trial to avoid steroids. The long-term prognosis is less encouraging than in ulcerative colitis. The incidence figures for carcinoma are approximating those in ulcerative coli-

tis. Surgical resection of diseased bowel is not curative, however, and recurrence of disease above or near the area of surgical anastomosis may be expected. This is more frequent in cases of ileocolitis than in other forms of disease. Patients with growth failure have responded to several months of intravenous hyperalimentation, which suppresses disease activity but is not curative. Surgical resection of diseased bowel was originally looked upon with favor as treatment of growth failure but more recent results in very young or in older children have been disappointing; growth did not occur or was only transient after the operation. Surgery to promote growth is best performed between 12 and 16 years of age in patients whose epiphyses are still open and who have a retarded bone age.

ENDOCRINE AND METABOLIC DIARRHEAS

Disorders of Protein and Amino Acid Absorption

These are extremely rare and with limited applicability to the chronic diarrheal syndromes. *Familial protein intolerance*[63] is characterized by the onset of vomiting and diarrhea between 3 and 13 months of age and by generalized malabsorption in some infants. With progression of the disease, hepatomegaly, growth retardation and, in a few, mental retardation occur. The levels of BUN and ammonia are low, but ammonia values rise after protein ingestion. Plasma levels of arginine, leucine, lysine and trypsin are low and there is impaired absorption of lysine and hyperdibasicaminoaciduria.

Treatment consists in administration of a low protein diet supplemented with arginine, which promotes growth but does not control diarrhea. *Methionine malabsorption*[64] is signaled by diarrhea and convulsions and may be suspected by the finding of intermittent increased excretion of α-hydroxybutyric acid in the urine. Other amino acid disorders are usually not accompanied by diarrhea.

Disorders of Lipid Metabolism

Abetalipoproteinemia is inherited as an autosomal recessive disorder and is characterized by an inability to synthesize β-lipoprotein which leads to secondary central nervous system, red cell and retinal disturbances, as well as defective chylomicron formation.[65] Malabsorption is noted in early infancy and within several years patients become ataxic, with nystagmus, strabismus and retinal lesions. There is mild anemia, with acanthocytes present in the peripheral blood smear and decreased plasma levels of cholesterol, triglycerides and phospholipids. Serum contains no chy-

lomicrons after a fatty meal. The small bowel biopsy sample is relatively normal but the villi contain lipid droplets. Steatorrhea is due to defective fat transport from mucosa to lymphatics.

Treatment consists of a low fat diet with medium-chain triglyceride supplementation.

Wolman's Disease[66]

This cholesterol storage disease occurs in early infancy and has been fatal in all of the reported cases. The etiology is unknown but there is absence of acid lipase in the liver and spleen, which contain deposits of cholesterol, its esters and triglycerides. Lipid storage occurs within the reticuloendothelial cells and the epithelial cells of the intestine. There is loss of villus structure with infiltration of lipid-filled histiocytes. The adrenal glands are calcified and enlarged. Foamy histiocytes are present in the thymus, bone marrow and peripheral blood smear. The gray matter of the brain contains increased cholesterol and there is faulty myelination within the white matter. The infants develop chronic diarrhea during the first few weeks of life and there is progressive enlargement of the liver and spleen. The outcome is fatal and there is no known therapy for this illness.

Acrodermatitis Enteropathica

In this disorder, severe skin lesions are the prominent symptoms along with diarrhea.[3, 55] An autosomal-recessive inheritance has been suggested because other siblings have been affected in two thirds of the reported cases. Typically the illness is noted only in bottle-fed infants or in those weaned from the breast. Allergy and disorders of lipid metabolism were initially postulated as etiologic factors, but the disease is now conclusively related to zinc deficiency.

In a few cases acrodermatitis has been diagnosed during the 1st month of age, but in most children symptoms are florid by 9 months. Skin lesions begin as moist, bullous or pustular eruptions around the mouth and anus and are symmetrically distributed over mouth, buttocks, hands and feet. As the lesions become chronic, they assume a plaque-like, scaling appearance. The nails are often dystrophic and there is associated photophobia and alopecia. Diarrhea is loose and associated with malabsorption.

Breast milk was curative in early cases; later it was noted that many patients responded to a trial of diiodohydroxyquin. Now it seems that it was the zinc in the tablets rather than the drug itself which is therapeutic. Current treatment consists of supplemental zinc.

Hypoparathyroidism

Steatorrhea and chronic diarrhea are unusual complications of hypoparathyroidism. They are directly related to the degree of hypocalcemia and respond to the administration of parathyroid hormone. Magnesium deficiency may also play a role in this disorder.

Hyperthyroidism

Diarrhea may be a manifestation of hyperthyroidism but in most patients other clinical signs are evident. Suppressive therapy for the underlying disease is curative.

Familial Chloride Diarrhea

This congenital diarrhea is characterized by systemic alkalosis and marked intestinal chloride loss.[67] It is probably inherited as an autosomal recessive trait (several siblings in a family may be affected).

Of the reported cases, more than half of the dozen infants passed no meconium and presumably had intrauterine diarrhea. Diarrhea is usually present on the 1st day of life but in a few cases it was not reported until several weeks of age. There is abdominal distention and ileus and the stools resemble water. The babies are hypotonic and have hyponatremia, hypokalemia, hypochloremia and alkalosis. The stool chloride initially ranges between 30 and 100 mEq/L but reaches 150 mEq/L, totalling more than the sum of K and Na ions. Urinary aldosterone and plasma renin levels are elevated and juxtaglomerular hyperplasia, renal calcification and increased urinary potassium losses eventually occur. The treatment is based on administration of supplemental potassium, 2 – 14 mEq/day in a dosage sufficient to maintain plasma electrolytes.

Hormonal Tumors

Watery Diarrhea, or the Watery Diarrhea, Hypokalemia, Hypochlorhydria (WDHH) Syndrome

Profuse watery diarrhea, otherwise termed the Verner-Morrison syndrome, occurs primarily in middle-aged females but is now being reported in children, the youngest of whom was 5 years old. Because it is usually associated with either pancreatic hyperplasia or tumor, it is also termed "pancreatic cholera."[68-69]

Diarrhea is intermittent at onset but becomes unrelenting. Cramping and pain are unusual but because of significant water and electrolyte losses, patients complain of muscle weakness, lethargy, nausea and vomiting. Surprisingly, steatorrhea is ei-

ther mild or absent. A few patients have noted flushing of the face and upper trunk. Stool volumes range between 3 and 10 L/day and there are hypokalemia and acidosis due to potassium and bicarbonate loss. Patients become easily dehydrated and may develop prerenal azotemia, hypokalemic renal tubular and myocardial damage. Studies of gastric secretion show hypochlorhydria and decreased pepsin levels; half of the patients show no response to histamine stimulation, although parietal cells are present in normal numbers. In a few cases, hypersecretion and elevations of serum gastrin are associated findings. Hypercalcemia is present in nearly half of the patients, as are hyperglycemia and abnormal glucose tolerance.

The secretory diarrhea takes place in the small bowel beyond the duodenum. Although colonic absorption is normal, the colon cannot cope with the volume and electrolyte load presented. Secondary hyperaldostonerism results in colonic sodium absorption and potassium excretion.

Although the etiologic lesion lies in the pancreas, no one agent has yet been identified. Secretin has been proposed as a responsible hormone, but most patients have normal secretin levels. Increased levels of plasma and tumor VIP (as mentioned before, a neurotransmitter substance synthesized by cells in the intestine and nervous system) have been reported in patients with this syndrome. Others, however, have had normal levels. Human pancreatic polypeptide (HPP), produced by endocrine cells in the exocrine tissue and within the islets, is elevated in approximately half of the pancreatic endocrine tumors. Prostaglandin E_2(PgE_2), as VIP, may be elevated and can induce all of the changes of the WDHH syndrome.[70] Certain increases in one or more of these substances could be explained by the concept of the amine precursor uptake decarboxylase (APUD) tumor. APUD cells synthesize or secrete peptide or amine hormones and are all derived from the neuroectoderm of the neural crest.

The diagnosis is suggested by the clinical findings of severe watery diarrhea and hypokalemia. Malabsorption is minimal and the small bowel biopsy usually normal. Plasma levels of VIP, PgE_2 and HPP as well as secretin should be examined. Since more than two thirds of patients have pancreatic tumors, particularly of the non-beta islet-cell type, and 10% have ectopic tumors in the adrenals or lungs, intravenous pyelography studies and laminograms of the chest are indicated. Tumors have not always been identified by computerized axial tomography scans or angiographic studies. The final diagnostic test remains surgical exploration.

Cure is accomplished only by complete tumor resection. Most pancreatic adenomas are large and readily detectable; they can be located in the body as well as the head. If the tumor is malignant and not totally resectable, palliation is accomplished by

resection of as much tumor as possible. Rebound gastric hypersecretion may be a postoperative problem. If symptoms persist after operation, several drugs may be used to control them, such as adrenal steroids, streptozocin injected intra-arterially and, if prostaglandins are elevated, indomethacin.

Medullary Carcinoma of the Thyroid

This tumor is an extremely rare lesion in children, associated at times with multiple endocrine neoplasia (MEN) and particularly with pheochromocytoma (MEN-IIb). When these tumors are also accompanied by hyperparathyroidism, the syndrome is termed MEN-II. Diarrhea is due to tumor elaboration of prostaglandin E_2, serotonin and histaminase, as well as the characteristic hormone, thyrocalcitonin (TCT). Diagnosis is established by elevations of these circulating hormones and presence of a cold nodule detected by thyroid scan. Challenging tests use infusion of calcium or pentagastrin or bolus injection; a rise in TCT greater than 1 ng/ml is considered positive. Even before laboratory diagnosis is established, medullary carcinoma may be suspected in the patient with typical physical features: prominent mandible, puffy lips, neuromas of the tongue and a Marfanoid habitus. Barium enema studies may show several colonic diverticula and a rectal biopsy examination reveals an increase in ganglion cells.[71]

Treatment consists in total lobectomy and if there is metastatic disease, also a radical neck dissection.

Ganglioneuroma

This fully differentiated tumor is relatively benign, growing slowly and causing few local symptoms. Unfortunately it is far less common than its relative, the neuroblastoma. These tumors arise from the sympathetic chain, anywhere from the base of the skull to the pelvis, and are found most often in the posterior mediastinum or within or near the adrenal gland. The benign tumor contains adult ganglion cells but one fifth of ganglioneuromas contain some anaplasia, in which case they may metastasize.[3, 72]

Catecholamines are synthesized from dihydroxyphenylalanine and dopamine. Epinephrines are converted to vanillylmandelic acid (VMA) and 3-methyldopamine to homovanyllic acid (HVA). Norepinephrine is in greatest concentration so that excretion of its metabolite, VMA, is greatest in the urine. Hypertension, often associated with these tumors, is a direct consequence of increased norepinephrine.

Many of these tumors are asymptomatic in older children, but in the infant and young child they cause chronic watery diarrhea associated with significant abdominal distention. Secretory in type, diarrhea leads to hypokalemia and hyponatremia.

The diagnosis must be suspected in any child with long-standing watery diarrhea. Presence of calcified mass in the posterior

chest or abdomen should suggest the diagnosis. Measurement of urinary catecholamines and particularly of VMA is the most reliable diagnostic test, although catechols are not always elevated early in the disease. One or more metabolites may be increased and all must be measured. Some tumors also produce prostaglandins, which may be measured in the blood.

The only definitive treatment is surgical removal of the tumor. If this is not possible, the diarrhea may at times be decreased by the use of steroids.

Neuroblastoma

This is the most common tumor in infancy and probably in childhood. It is complex both in its variable histologic presentation and in clinical course. For every tumor identified in the young child there are presumably as many as 4 others in newborns which disappear without ever becoming apparent. Nearly half of all neuroblastomas are diagnosed in children under 2 years old.[3, 55]

The sympathetic nerve cells composing the tumor vary in maturity from the anaplastic sympathogonioma to the well-differentiated neurocytoma. Although most tumors arise from the adrenal medulla, 40% of those in the newborn arise from other sympathetic ganglia. Nodular and encapsulated, these tumors vary in color from yellow to red or purple, depending on the degree of hemorrhagic necrosis present. Metastases occur early and are frequently found in liver, long bones, skull, meninges and bone marrow. Unilateral proptosis is secondary to invasion of the soft tissue of the orbit and may be the first sign of tumor. One third of neonatal tumors metastasize to the skin as subcutaneous nodules.

Immunologically these tumors are fascinating: they may undergo spontaneous dissolution even after they have metastasized. Infiltration of tumor by plasma cells or lymphocytes is considered a good prognostic sign.

Clinically these tumors present as progressive enlargement of the abdomen associated with few other symptoms. Less often they cause chronic diarrhea through production of catecholamines or other hormones. Diagnosis is established by (1) palpation of the characteristic mass that extends across the midline; (2) intravenous pyelographic studies, which reveal a downward displacement of one of the renal calyces; (3) presence of tumor cells in the marrow; and (4) by increased urinary excretion of catecholamines.

Complete surgical removal may be accomplished in cases of localized disease; when this is not possible, clips should be placed in the remaining tumor for radiation therapy. Although the tumor is considered radiosensitive, there are conflicting data regarding postradiologic survival rates. Vincristine and cyclophosphamide have been used extensively alone or in combination but do not seem to have affected survival rates. Newer agents, such as

adriamycin, dimethyltriazenoimidazole-carboxamide and a chloroethyl derivative, have shown some encouraging results.[73] The presence of bone metastases is uniformly discouraging. Tumors secreting small amounts of HVA have had a more benign course than those secreting large amounts and those secreting epinephrine and norepinephrine metabolites were more often benign than tumors secreting dopamine.

NONSPECIFIC DIARRHEAS

Hypercaloric Diarrhea

It is well known that excessive feeding in the infant may cause either diarrhea or vomiting. When infants eat ravenously and their intake exceeds 160 cal/kg/day, there is a strong likelihood that diarrhea will be the end result. Mothers often misinterpret a strong sucking reflex as a sign of hunger and overfeed their babies. In such cases, substitution of sugar water or juice or even a pacifier is indicated.

Increased Sugar Loading

Occasionally a healthy child passes loose stools that have an acid pH. Disaccharide tolerance tests are normal; eventually, history reveals that the mother is supplementing the diet with large amounts of table sugar or juices. A simple restriction of dietary sugars is curative.

Diarrhea and Systemic Infection

Abdominal pain and diarrhea are frequently associated with upper respiratory infections, such as pharyngitis and otitis media, and with urinary tract infections. The mechanism is unknown but it is postulated that the disturbance represents a nervous system response varying with the maturity of the child. Similarly, mothers refer their children for teething-associated diarrhea. Although we have no physiologic explanation, the constellation of symptoms is reported too often to be purely coincidental.

Well-Water Diarrhea

Well water may cause diarrhea in infants and small children due to a high concentration of sulfates or nitrates that does not seem to affect the adults. The condition is treated by use of water-softeners or changing the water source.

IRRITABLE BOWEL OF CHILDHOOD

Many support the existence of this disease entity in childhood but I have reservations in making such a diagnosis in the toddler. Onset of diarrhea is typically between 8 months and 3 years of age, when the child passes 3–10 loose, mucoid stools per day. Sigmoidoscopic examination shows a pale, edematous rectal mucosa; an increase in goblet cells is noted in the rectal biopsy sample.[74] Adult members of the family often have irritable bowel and there may be an early history of colic. There is no associated malabsorption and growth and development are unaffected by diarrhea. Improvement sometimes followed treatment with diiodohydroxyquin but this drug is now disapproved for use in children because of the complication of optic atrophy.

Recently, Cohen et al.[75] have noted that many of these patients had been receiving high-protein, low-carbohydrate and low-fat diets. During evaluation of absorption and with administration of a 50-gm fat diet, diarrhea subsided. The authors conclude that this diarrhea is often iatrogenically produced (particularly by the use of low-fat diets for the prevention of atherosclerosis) and attribute it to a lack of dietary fat which plays a role in delaying gastric emptying and slowing intestinal transit. Although many of their patients had been drinking hyperosmolar carbohydrate beverages, restriction of these alone did not control the diarrhea.

Until we have something better to offer, this type of dietary manipulation seems a valuable therapy, particularly for the older toddler, for whom toilet training becomes an important item in life.

DIAGNOSTIC STEPS IN THE EVALUATION OF CHRONIC DIARRHEA

The causes of chronic diarrhea are obviously multiple but if such criteria as age and a good dietary and travel history are considered, a logical diagnostic approach emerges. Most diarrheas in infants and young children are due to the postgastroenteritis syndrome, chronic infection or infestation, and/or gastrointestinal allergy. More unusual are celiac disease, cystic fibrosis, immune deficiency and irritable bowel. In older children, chronic diarrhea is far less common; in these cases, inflammatory bowel disease, late-onset lactose intolerance and irritable bowel syndrome must be considered as the most common causes of diarrhea. Endocrine abnormalities, celiac disease and occasionally parasitic infestation are less frequent causes.

A number of screening tests may be easily obtained to provide direction for other diagnostic studies.

1. *Visual examination of the stool.* This is paramount in the order of tests because, often, what appears like diarrhea to a

mother is in fact a perfectly normal stool. Stool consistency, degree of mucus and color are helpful. Certainly, once examined, steatorrheal stools are well-remembered and unmistakable. The pale, putty-like stools of biliary atresia are similarly unique. Mucoid stools suggest colonic irritation from infection or allergy whereas those which are frothy suggest a disaccharide intolerance and watery stools indicate a secretory problem. Blood in the stools suggests infection, allergy or inflammatory bowel disease. Oil droplets occur primarily in cases of pancreatic insufficiency.

2. *Examination for bacterial and parasitic pathogens.*

3. *Examination for stool pH and reducing substances.* A stool pH less than 6 indicates disaccharide or monosaccharide malabsorption. A positive test for reducing substances (using Clinitest tablets) indicates lactose or glucose malabsorption. Treatment of the stool supernatant is done and the examination is repeated (if the test is negative) to detect sucrose malabsorption. Obviously, if these tests are positive, the appropriate carbohydrate tolerance test must be performed.

4. *Examination for occult blood.* Occult blood may be real or mimicked by the effect of a rapid transit of meat through the intestine. If there is any question, the test should be repeated after the patient has been on a meat-free diet for several days.

5. *Urinalysis and culture.* The name of this test is self-explanatory: a number of infants have chronic diarrhea in association with urinary tract infections that have to be identified.

6. *Blood studies.* Fat malabsorption is evaluated by serum carotene and cholesterol levels; protein malabsorption is assessed by serum albumin and globulin levels; and small bowel absorption, by serum folate. Complete blood count test with erythrocyte sedimentation rate is performed. Serum quantitative immunoglobulin studies are performed in all patients with diarrhea.

7. *Growth curves.* An integral part of the initial visit is the determination of the child's height and weight from birth, in order to detect a sudden deviation from normal that can indicate the onset of malabsorptive disease.

8. *Sweat chloride determination.* All patients with chronic diarrhea for which no definite cause has been determined should have this test.

At the end of this evaluation we should at least have some direction if a diagnosis has not been made. Low serum carotene and folate levels suggest intestinal disease, whereas low carotene and normal folate values point to the pancreas or biliary tract as sites of disturbance.

If absorptive studies are normal and examination of the stools has been nonrevelatory but there is a strong suggestion of allergy, we prefer to place the patient on a restricted diet and reevaluate the response after 2 weeks. If there is no improvement, patients are hospitalized for further studies consisting of small

bowel biopsy and aspirate of jejunal secretions for anaerobic culture, immunoglobulin levels, bile acids and parasite examination. Endocrine studies are also obtained at this point, as well as quantitative stool fat and nitrogen.

If there are indications of malabsorption, a similar approach is undertaken. If small bowel studies are normal, pancreatic function is examined by a secretin-pancreozymin test.

Children with a secretory type of diarrhea are examined for catecholamine and VIP production and tests of ileal function (Schilling test and bile acid measurements in the stool) are carried out.

At some point in the diagnostic evaluation of patients with persistent diarrhea, radiologic examination of the colon and of the upper gastrointestinal tract and small bowel is performed to rule out partial obstructive lesions as well as to identify patterns of malabsorption. Sigmoidoscopy and rectal biopsy studies are performed early in those with evidence of occult or gross blood in the stool but later in those in whom no lesion has been identified.

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Answers to Self-Assessment Questions

1. *a, d*
2. *a*
3. *a, c, e*
4. *b, c*
5. *a, c, d, e*
6. *All*
7. *a, b, d*
8. *b, e*
9. *b, c, d, e*
10. *b*
11. *b*
12. *b, c*
13. *b, c, e*
14. *a, b, e*
15. *a, b, d*