The Seoul Journal of Medicine
Vol. 32, No. 4: 239-251, December 1991

Chronic Diarrhea in Infancy[+]
—Analysis of 68 Cases with Particular Reference to Differential Diagnosis and Management—

Cheol Ho Chang and Jeong Kee Seo*

Department of Pediatrics, Seoul National University College of Medicine, Seoul 110-744, Korea

=Abstract=**Sixty-eight cases of chronic diarrhea in infancy over a 5-year period have been analysed with particular reference to differential diagnosis and management. A diagnosis was established in 63, the most common diagnoses being lactose intolerance (30.9%) and milk allergy (26.5%). Other diagnoses included intestinal lymphangiectasia, short bowel syndrome, Salmonella enteritis, inflammatory bowel disease, congenital chloridorrhea, adrenogenital syndrome, and ganglioneuroma. A systematic diagnostic approach for such specific disease entities was presented. Despite intensive investigation a diagnosis could not be established in 5 (7.3%) infants. For differential diagnosis and treatment, we observed the responses to fasting and change of formula. 54 (79.4%) of the infants responded to more than 24 hours of fasting, 48 (88.9%) of whom showed good responses to the changes of formula. The age of onset of diarrhea, body weight on admission, and laboratory findings did not influence the outcome of infants with chronic diarrhea, but only the interval period from onset to diagnosis did influence it.**

Key Words: *Chronic diarrhea, Infancy*

INTRODUCTION

Diarrheal diseases continue to be the leading cause of morbidity and mortality in the world today, with estimates of 3 to 5 billion cases per year (an average of roughly one per person per year) (Walsh *et al.* 1979). The burden is especially severe on children under the age of 5 years in Asia, Africa, and Latin America, with approximately 500 million episodes of diarrhea leading to 5 to 18 million deaths per year (Rhode *et al.* 1976).

A major factor of this increased susceptibility to diarrheal disease in the young particularly under the one year of age seems to be immaturity of the GI defence system according to the recent research.

Infants have been shown to be more susceptable to various enteric pathogens and macromolecular penetrations because of the immature intestinal barrier at the surface of the intestinal mucosa.

One of the recent studies has shown that the newborn rat enterocyte appears to have a strikingly increased response to toxin when compared to enterocytes from adult controls when fluid secretion and adenylate cyclase activation are examined (Seo *et al.* 1989).

The important pathogenetic mechanism of persistent diarrhea secondary to acute gastroenteritis might be associated with increased cow's milk protein penetration through the damaged mucosa in addition to decreased disaccharidase activity.

[+] This work was supported by a research grant of Seoul National University Hospital (1990).

* Author for correspondence.

Chronic diarrhea is defined as diarrhea lasting more than 3 weeks and accompanied by a failure to thrive in many cases. Chronic diarrhea in infants and children often challenges the physician's diagnostic talents and therapeutic means. The clinical spectrum of chronic diarrhea is of considerable latitude, ranging from relatively benign problems to life-threatening illness when accompanied by severe nutritional deficiencies. Chronic diarrhea in infancy is not so common, but is one of the diseases that are difficult to manage in clinics. For proper management of patients with chronic diarrhea, it is necessary to understand the etiologies and pathophysiologic mechanisms of it.

Because few reports have dealt with chronic diarrhea in our country, we performed a clinical study on 68 infants with chronic diarrhea, paying particular attention to the etiologies, management, and outcomes.

MATERIALS AND METHODS

Between January 1987 and June 1991, 68 patients were admitted to Seoul National University Children's Hospital. A patient is defined as having chronic diarrhea in infancy if diarrhea develops in infancy and persists for longer than 3 weeks.

For the differential diagnosis and treatment of chronic diarrhea, we observed the responses respectively after trying, first, fasting (longer than 24 hours) with fluid therapy (including TPN), next, WHO ORS (oral rehydration solution), and then special milk formulas (lactose-free and/or cow's milk protein-free). In addition, laboratory tests (CBC, LFT, stool examination, stool culture, etc.), radiologic tests, and endoscopy were performed.

RESULTS

Clinical features: Diarrhea began at less than 3 months of age in the majority (78%) of the patients. In 75% of patients, 5 to 20 bowel movements per day were passed during attacks. Only 5.9% of patients reported less than 5 per day. In 32 infants (47.1%), the character of the stools was watery diarrhea. Mucoid diarrhea was reported in 16 (23.5%) of 68 patients. Blood was reported to be present in the stools of 6 infants, 4 of which had inflammatory bowel diseases. On admission to the hospital, 53 infants (78%) weighed less than the 3rd percentile for their age. None of the patients weighed more than the 50th percentile for their age.

Diagnosis: The commonest diagnoses were lactose intolerance (30.9%) and milk allergy (26.5%). Other causes of chronic diarrhea included conditions such as intestinal lymphangiectasia, short bowel syndrome, Salmonella enteritis, inflammatory bowel disease, congenital chloridorrhea, adrenogenital syndrome and ganglioneuroma. In 5 cases, no cause for the diarrhea could be established (Table 1).

Table 1. Diagnosis of 68 infants with chronic diarrhea

Diagnosis	No. of cases	%
Lactose intolerance	21	30.9
Milk allergy	18	26.5
Intestinal lymphangiectasia	5	7.3
Short bowel syndrome	5	7.3
Salmonella enteritis	4	5.9
Inflammatory bowel disease	4	5.9
Congenital chloridorrhea	3	4.4
Adrenogenital syndrome	2	3.0
Ganglioneuroma	1	1.5
Unknown	5	7.3
Total	68	100.0

Response to fasting and change of formula: For the differential diagnosis and treatment of chronic diarrhea, we observed the responses after trying, first, fasting for more than 24 hours. 54 (79.4%) of the infants responded to fasting, in whom the frequency of diarrhea decreased remarkably or the diarrhea stopped. For the responders, we tried changes of formula (lactose-free and/or cow's milk protein-free) and 48 (88.9%) of 54 infants showed good responses (Fig. 1).

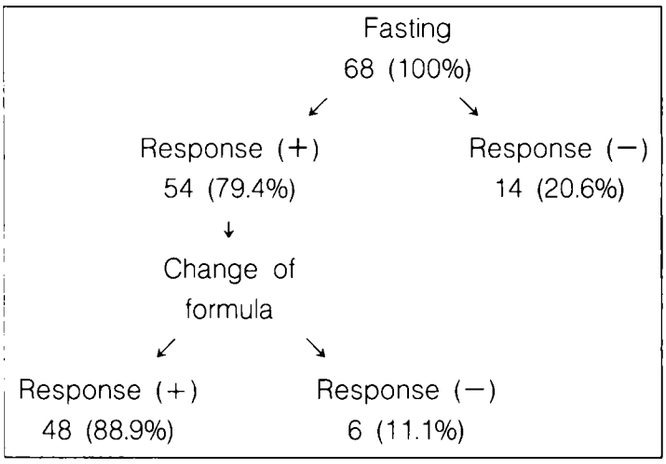

Fig. 1. Response to fasting and change of formula.

Diagnostic investigations (Table 2): In this study, lactose intolerance was defined by improvement after discontinuance of milk and a trial with a lactose-free formula. The stool pH of test was not helpful in diagnosis of lactose intolerance and the test for reducing substance in stool and the breath hydrogen test were not performed. Milk allergy was defined by improvement after discontinuance of milk and recurrence of symptoms with rechallenge. The diagnosis of intestinal lymphangiectasis was suspected in a child with persistent loose stools, hypoalbuminemia (edema), hypoglobulinemia, lymphocytopenia, steatorrhea, and a failure to thrive. Increased intestinal loss of protein from the intravascular compartment was measured by intravenous administration of labeled macromolecule or random fecal α_1-antitrypsin concentration. In our series, 5 cases of intestinal lymphangiectasis were diagnosed by fecal α_1-antitrypsin (3 cases), ^{129}I-albumin excretion (2 cases), endoscopic biopsy (2 cases), and lymphangiography (1 case). Short bowel syndrome developed after a small bowel resection due to necrotizing enterocolitis (3 cases) and jejunal atresia (2 cases). In 4 patients who were diagnosed as Salmonella enteritis, Salmonella grew in the stool culture. Inflammatory bowel disease was suspected in infants with intractable bloody and mucoid diarrhea, and was confirmed by colonoscopic biopsy which revealed Crohn's disease (2 cases) and inflammatory bowel disease of undetermined type (2 cases). Congenital chloridorrhea was considered when diarrhea was associated with metabolic alkalosis, hypokalemia, and hypochloremia. Diagnosis was definite if the chloride content of the fecal fluid was high. Values in our series were between 126 and 167 mEq/L, which were more than the sum of sodium and potassium. In contrast, the chloride content of the urine was very low. On rare occasions, we have seen two infants with adrenogenital syndrome presented with an acute fulminating diarrhea during the first month of life. Additional clues to this diagnosis may be found at physical examination (pigmentation and virilization). Adrenal insufficiency should also be suspected when the usual therapeutic measures fail to control the vomiting and diarrhea or, when there are characteristic electrolyte abnormalities (low sodium and high potassium). We experienced one patient with VIPoma (tumor secreting vasoactive intestinal peptide) who was a 5-year-old girl and had a ganglioneuroma in the suprarenal area.

Table 2. Diagnostic investigations

Diagnostic tests	Clues	Final Diagnosis
Stool α_1-antitrypsin	Hypoproteinemia	Intestinal
Lymphangiography	Lymphopenia	Lymphagiectasis
Colonoscopy and biopsy		IBD*
Stool chloride amount	Hypochloremia	Congenital
	Metabolic alkalosis	Chloridorrhea
Progesterone level	Hyperkalemia	CAH**
Abdominal CT	Hypokalemia	Ganglioneuroma
Stool culture		Salmonellosis

* IBD: Inflammatory bowel disease

** CAH: Congenital adrenal hyperplasia

She had no diarrhea after resection of the ganglioneuroma.

Factors influencing the outcome of infants with chronic diarrhea (Table 3): Accurate weights were available at the time of follow-up (more than 3 months) in 35 of the 68 patients. In order to find the factors influencing the outcome of the infants with chronic diarrhea, we divided 35 patients into two groups; Group I consisted of 22 infants showing some degree of weight gain (increase in the percentile of body weight for age) and group II consisted of 13 infants showing no weight gain (no change in the percentile of body weight for age). The mean interval period from onset to diagnosis was 2.7 months in group I and 6.2 months in group II ($p < 0.05$). The mean age of onset of diarrhea was 1.8 months in group I and 3.2 months in group II ($p > 0.05$). The number of infants with a weight below the 3rd percentile for their age was 18/22 in group I and 13/13 in group II ($p > 0.05$). The number of infants with one of the following laboratory findings — hemoglobin <10.0 gm%, albumin <3.0 gm%, cholesterol <70 mg% — was 8/22 in group I and 9/13 in group II ($p > 0.05$).

Table 3. Factors influencing the outcome of infants with chronic diarrhea

	Group I	Group II	P value
Interval from onset to diagnosis (mo)	2.7 ± 1.9	6.2 ± 4.1	<0.05
Age at onset (mo)	1.8 ± 1.5	3.2 ± 2.8	>0.05
Body weight (<3P) on admission	18/22	13/13	>0.05
Lab findings (Hb<10, Alb<3, Chol<70)	8/22	9/13	>0.05

DISCUSSION

Infants with chronic diarrhea often present major problems of diagnosis and management. The clinician's dilemma is usually centered around deciding whether or not the child with persistent or recurrent diarrhea has an organic disease requiring investigation and treatment. The differential diagnosis of chronic diarrhea in children is extensive and there is no substitute for a meticulous clinical assessment. Chronic diarrhea may be secondary to a number of congenital and acquired disorders of the gastrointestinal tract,of the liver and of the pancreas, but it can also reflect an underlying metabolic or endocrine problem, infections elsewhere, improper diet, or a drug reaction.

Larcher *et al.* (1977) reported 82 cases of protracted diarrhea of four or more loose stools per day for longer than 2 weeks with infants suffering from a failure to thrive. Of these, 33% had celiac disease, 12% had secondary disaccharide intolerance (possibly postinfectious), and 11% had cows' milk protein intolerance. Other diagnoses included primary sucrase-isomaltase deficiency, Shwachman's syndrome, ulcerative colitis, ganglioneuroma, defective opsonization, Staphylococcal pneumonia, and Hirschsprung's disease. In 28%, however, despite intensive investigation no diagnosis could be established. Avery *et al.* (1968) reported 20 infants with intractable diarrhea, whose onset was before 3 months of age. Twelve of these had identifiable pathological entities sufficient to explain their protracted diarrhea; disaccharide intolerance (3 cases), cystic fibrosis (2 cases), Salmonella enteritis (1 case), ulcerative colitis (1 case), perinephric abscess (1 case), urinary tract infection (1 case), adrenal insufficiency (1 case), ileal stenosis (1 case), Hirschsprung's disease (1 case). Eight of the 20 infants had no identifiable cause for diarrhea of such severity and refractoriness, and these babies were termed non-specific enterocolitis. Sunshine *et al.* (1977) reviewed the subject and cited 42 additional cases, in which the largest category (48 %) consisted of a nonspecific enterocolitis secondary to an infectious gastroenteritis or cows' milk protein intolerance. Lloyd-Still analysed 108 children referred for outpatient evaluation of chronic recurrent diarrhea, the commonest diagnoses were chronic nonspecific diarrhea (58.4%), and postinfectious diarrhea (22.2%). Other diagnoses included celiac disease (8.4%), milk allergy (6.5%), and primary sucrase isomaltase deficiency (4.6%). In our series, the commonest diagnoses being lactose intolerance (30.9%) and milk allergy (26.5%), most of which were postinfectious origin. A variety of

other diagnoses was established such as intestinal lymphangiectasis, short bowel syndrome, Salmonella enteritis, inflammatory bowel disease, congenital chloridorrhea, adrenogenital syndrome, ganglioneuroma. No patient had celiac disease contrasted with 33.2% (the commonest diagnosis) in the reported series of Larcher *et al.* (1977). Sallon and Deckelbaum (1988) reported that in less-developed areas, Cryptosporidium was a major pathogen, not only in acute but also in chronic childhood diarrhea, and that it might play an important role in the interaction between diarrhea and malnutrition. We experienced one patient with Cryptosporidium who was a 18-month-old boy who had an inflammatory bowel disease.

Diarrhea is an extremely common cause of morbidity in infancy. Occasionally, it becomes protracted, leading to vicious cycle of malabsorption, malnutrition, and failure to thrive. Although many mechanisms may contribute to diarrhea, a similar pathophysiologic syndrome of mucosal atrophy, inflammation, and malabsorption results. Attention should be paid to recognition of malnutrition as well as etiologic diagnosis. On admission at this hospital 53 (78%) weighed less than the 3rd percentile for their age and 3 were clinically marasmic; 12 weighed less than their birthweight. None of the patients weighed more than the 50th percentile for their age. Therefore, we found that the majority of the infants with chronic diarrhea suffered from the vicious cycle of malabsorption, malnutrition, and failure to thrive. Larcher *et al.* (1977) reported that all 17 infants weighed less than the 3rd percentile for their age in whom a firm diagnosis could not be established and diarrhea presented at varying intervals after birth. And 15 were clinically marasmic; 8 weighed less than their birthweight.

Although novel technics have been applied to the diagnosis of chronic diarrhea, a well-taken history (eg, history of feeding) offers important clues to define channeling and to identify priorities in the work-up of the patient. A careful history of travel, illnesses, medications, development, family history, and especially social situation can sometimes provide the only clue to the origin of the diarrhea. Much important information is gained by plotting the infant's growth curve with serial measurements of weight, height, and weight for height: normal growth is not likely to be associated with a process of a severe nature. The widely used Gomez classification (Gomez *et al.* 1955) defines mild (grade I) malnutrition as between 75% and 90% of standard weight for age; moderate (grade II) as between 60% and 75%; and severe (grade III) as less than 60% weight for age. Values less than 80% of standard weight for height, or values below the fifth percentile of the new National Center for Health Statistics (NCHS) standards have been widely used as the criteria for chronic malnutrition.

On physical examination, the general appearance of a child with chronic diarrhea can often separate those with benign nonspecific loose stools and those with chronic malabsorption and malnutrition. The clinical picture of severe marasmus includes lethargy, emaciation, muscle wasting, hypotonia, and sunken cheeks, but these signs may be more subtle in mild or moderate malnutrition. Occasionally, edema, a distended abdomen, and "flaky paint" dermatitis are seen, classic signs of kwashiorkor (Sinatra and Merritt 1981).

Laboratory examination of the stool is often overlooked, but usually provides far more information than most biochemical serum tests in the diagnosis of chronic diarrhea. With no equipment other than a microscope, the liquid portion of the stool sample can easily and quickly be tested for weight, acidity, sugars (reducing substances), occult blood, fat globules, leukocytes, ova, and parasites.

Biochemical tests of nutritional status tend to be too expensive and limited for most situations, but a good initial screen might include a complete blood count with differential and red cell morphology, serum electrolytes, total protein, and albumin. In a hospital setting, serum carotene, calcium, phosphorous, iron, transferrin, zinc, copper, thyroxine, cholesterol, triglycerides, or liver function tests might be among those considered for further investigation. Stool culture, multiple samples for ova and parasites, and a 72-hour collection for fecal fat can be done on an inpatient or outpatient basis, although this may be difficult in infants.

One of the most important tools for the investigation of chronic diarrhea and failure to thrive is hospitalization for observation of stool pattern and

weight gain. It is best to leave the infant on the diet currently producing the diarrhea. Daily weights, careful intake and output records, and serial measurements of stool weight, pH, and reducing substances, will quantitatively document the severity of the diarrhea and malabsorption. Occasionally, an upper GI contrast series with small bowel follow-through, a barium enema, ultrasound studies, a small bowel biopsy and duodenal aspirate, sigmoidoscopy, or colonoscopy may be necessary to reveal the underlying cause.

Chronic watery diarrhea and, frequently, failure to thrive, are recognized with increasing regularity as the result of intestinal disaccharidase deficiencies. These enzyme deficiencies may occur as "primary," isolated, and hence, probably hereditary disorders, or they may occur secondary to insults from a disease of the small intestinal mucosa. Generally, the onset of the diarrhea follows the introduction of either lactose- or sucrose- and starch-containing foods. In addition to obtaining adequate clinical information, stools of patients with chronic diarrhea should be screened for reducing substances (Townley 1966; Davidson *et al.* 1970) since their increased presence, associated with a stool pH of around 5, is indicative of carbohydrate maldigestion and/or malabsorption. Presence of lactose in breast-fed infants is usually a normal occurrence up to 4 weeks of age (Davidson *et al.* 1970). Disaccharides in infants' diarrheal stools may be also analyzed by either paper (Barr *et al.* 1964) or thin layer chromatography (Raadsveld *et al.* 1971). A quantitative analysis of disaccharidase activities (Dahlqvist 1968) can be done on small pieces of biopsied small intestinal mucosa to identify the nature and extent of the disaccharidase deficiencies. Recently hydrogen breath test has shown to be the most accurate and reliable method for the diagnosis of lactose intolerance.

Although recognized since the time of Hippocrates, cow's milk intolerance has been a topic of increasing interest as the effects of widespread use of cow's milk-based formulas in infant nutrition have become apparent. The manifestations of cow's milk allergy are protean; in addition to diarrhea and a variety of other gastrointestinal symptoms, they may include respiratory, dermatologic, hematologic, neurologic, and cardiovascular signs and symptoms. From a series of children with cow's milk allergy, Lebenthal lists presenting symptoms as diarrhea, 88%; vomiting, 44%; abdominal pain or colic, 39%; atopic dermatitis, 33%; rhinitis, 31%; asthma, 31%; urticaria, 13%; and anaphylaxis, 12%. Cow's milk allergy usually occurs before the age of 6 months, but diagnosis is not always clearly documented, leading to reports of incidence ranging from 0.3% to 7.5% (Bahna and Heiner 1978; Gerrard *et al.* 1973). This is partly due to the difficulty of fulfilling the strict criteria of Goldman *et al.* (1963): (1) symptoms subsiding after milk elimination; (2) symptoms occurring within 48 hours following a trial feeding of milk; (3) three such positive challenges similar in onset, duration, and clinical features; and (4) symptoms subsiding following each challenge reaction. In as much as many workers (Walker-Smith 1975; Walker-Smith *et al.* 1978) feel that three challenges are impractical, an alternative approach to diagnosis is serial intestinal biopsies after a single challenge, yielding a mucosal villous atrophy of varying severity which resolves on milk-free diet (Iyngkaran *et al.* 1978; Shiner *et al.* 1975). However, in view of the diverse pathogenesis and manifestations of the disease, abnormal morphologic findings during small bowel biopsy are neither specific nor consistently detectable (Hill *et al.* 1979; Shiner *et al.* 1975). A large number of immunologic tests have been reported to be variably abnormal in cow's milk intolerance, including skin tests (Goldman *et al.* 1963), hemagglutinin and milk precipitin antibodies (Freier *et al.* 1969), secretory coproantibodies, eosinophilia, elevated serum immunoglobulin E (IgE) levels, and positive radioallergosorbant test (RAST) (Wraith *et al.* 1979), immune complexes, leukocyte histamine release, lymphoblast transformation, and lymphokine production (Bahna 1978). However, most of these tests have poor sensitivity and specificity, and no single simple test that can easily be performed has gained wide acceptance. Cow's milk allergy may be due to early exposure to cow's milk protein at a time when there is excessive intestinal antigenic uptake of macromolecules (Galant 1976; Walker and Isselbacher 1974); thus it may be prevented by breast-feeding through the first months of life.

Increased macromolecular transport may also occur after an episode of infectious diarrhea (Gruskay and Cooke 1955), producing a secondary cow's milk intolerance (Harrison *et al.* 1976; Iyngkaran *et al.* 1979). This may prolong the duration of mucosal damage during refeeding, leading to secondary lactase deficiency, lactose malabsorption, malnutrition, and failure to thrive (Kuitunen *et al.* 1975). The main fractions of protein in cow's milk, β-lactoglobulin, α-lactalbumin, albumin, casein, and γ-globulin, are all demonstrably antigenic, and may be processed by partial digestion into as many as 100 or more additional different antigenic protein fragments (Eastham and Walker 1968).

A diagnosis of intestinal lymphangiectasis might be suspected in a child with persistent loose stools, hypoalbuminemia (edema), hypoglobulinemia, steatorrhea, and failure to thrive (Amirhakimi *et al.* 1969). Intestinal lymphangiectasis should be thought of in the presence of chylous ascites and/or peripheral lymphedema; lymphocytopenia invariably is present when chyle is lost either into the intestinal lumen or into the peritoneal cavity (Camiel *et al.* 1970). Increased intestinal loss of protein from the intravascular compartment can be measured after the intravenous administration of labeled macromolecule: ^{51}Cr-albumin (Waldmann *et al.* 1969), ^{67}Cu-ceruloplasmin (Waldman *et al.* 1967) and ^{59}Fe-dextran (Jarnum *et al.* 1968). Recently random fecal α_1-antitrypsin concentration has been employed to detect protein-losing enteropathy in children with various gastrointestinal mucosal disorders (Thomas *et al.* 1981), acute diarrhea (Maki *et al.* 1982), and Crohn's disease (Thomas *et al.* 1983). Other studies have shown a close relationship between fecal clearance of α_1-antitrypsin and enteric protein loss measured by ^{51}Cr excretion (Bernier *et al.* 1978; Florent *et al.* 1981; Hill *et al.* 1981). A small intestinal peroral suction biopsy is usually diagnostic.

Recently, with the advancement of the technology, smaller calibered pediatric gastrofiberscope has been widely used and partly replaced blind peroral small intestinal suction biopsy, and found to be useful for the diagnosis of intestinal lymphangiectasis.

Extensive ileal resection causes marked steatorrhea by two principal reasons: firstly, there is marked bile acid malabsorption resulting in a small, inefficient bile acid pool, particularly if the liver is unable to compensate for bile acid loss by new synthesis; secondly, the decrease in surface area for the absorption of fatty acid is perhaps a more critical factor for the development of marked steatorrhea. It is interesting that the diarrhea of patients with large ileal resection and steatorrhea is associated with an increased fecal output of hydroxy-fatty acids, which probably have a causal relationship to the diarrhea. Diarrhea and steatorrhea ,then, should respond well to the substitution of dietary medium-chain triglycerides for long-chain triglycerides and this has been demonstrated.

Infectious diarrhea due to various strains of Salmonella continues to be a public health problem. Because the highest specific attack rates are for infants and children, pediatricians should be continuously aware of this problem. Further, most contact cases may be found among young children, and it should be remembered that frequently pets, such as dogs and turtles, as well as animal feeds may be carriers of Salmonella organisms. In spite of previous antibacterial treatment, recurrent Salmonellosis should be borne in mind and a search for this etiology should be pursued in a patient with a past history of Salmonellosis. Diarrhea due to Salmonellosis can be bloody and associated with systemic manifestations such as fever, rash, arthritis, spondylitis.

The prevalence of inflammatory bowel disease among children has not been ascertained and the etiology is still unknown. Ulcerative colitis may occur in any age group and has been observed in newborns and early infancy. Crohn's disease is considered quite rare below the age of 8 to 9 years, but has to be looked for and differentiated from ulcerative colitis when chronic diarrhea, intermittently bloody stools, weight loss, crampy abdominal pains, and fever are present. Colonoscopy and radiologic examination of the colon are helpful for correct diagnosis, but exact differentiation of ulcerative colitis and Crohn's disease is not always possible as in our two infants who showed the pathologic, radiologic, and clinical characteristics of both disease entities.

Congenital chloridorrhea is a rare condition,

for it has been described in less than 10 patients. It is characterized by watery diarrhea which may be present soon after birth or develop in the months to follow. It is considered when diarrhea is associated with metabolic alkalosis, hypokalemia, and hypochloremia. Diagnosis is definite if the chloride content of fecal fluid is high. Values of chloride are between 50 and 150 mEq/L during the first months and reach 110 to 180 mEq/L subsequently. Normal stools contain 6 to 17 mEq/L of chloride anions. Values of chloride in diarrheal stools in other disorders never approach the figures noted in this condition. In fact, in the acidic liquid stools of this familial entity, chloride is more than the sum of sodium and potassium. In contrast, the urine is practically chloride-free. There seems to be a defect in the double ion exchange model (Na^--H^-; Cl^--HCO_3^-) in the ileum, in that there is a normal Na^--H^- exchange, but a poor Cl^--HCO_3^- exchange because chloride cannot be transported against an electrochemical gradient. Consequently, the content of chloride in the stool is very high, that of bicarbonate low, and consequently the pH of the stools tends to be low. A high (>60 mV) transmural electrical potential difference of the rectum (negative to the mucosa) should be diagnostic for this condition, provided that one component of the potential difference is chloride dependent.

Watery diarrhea syndrome (WDS) has been reported in all age groups (Bloom *et al.* 1980; Hansen *et al.* 1980; Mekhjian and O'Dorisio 1987; Mitchel *et al.* 1976), and virtually all patients have presented with watery diarrhea and hypokalemia. Several patients have presented with incontinence. Fecal losses while fasting have been at least 20 ml per kilogram per day and in most cases exceed 50 ml per kilogram per day (Long 1983). Fecal osmolarity is entirely accounted for as twice the sum of the concentrations of sodium and potassium. Steatorrhea is not a feature of the syndrome (Mekhjian *et al.* 1987). Hypochlorhydria is seen in about 70 percent of patients, hyperglycemia in 20 to 50 percent, and hypercalcemia in 20 to 50 percent. Flushing is present in about 20 percent and is frequently intermittent, indicating that hormone release by the tumor is also sporadic (Mekhjian *et al.* 1987). In the pediatric age group, most of the VIPomas so far described are ganglioneuromas or ganglioneuroblastomas (Long 1983). The tumors have been found in the neck, thorax, and suprarenal and pelvic areas. Surgery offers the only possible cure for VIPoma. It has been estimated that 70 percent of childhood VIPomas are resectable (Long *et al.* 1981; Long 1983). Preoperative stabilization of fluid and electrolyte balance is critical. It has been shown that with successful resection, VIP levels fall to normal within hours postoperatively (Funato *et al.* 1982). Recently we experienced a five year old girl with VIPoma in whom a ganglioneuroma in the suprarenal area was found and resected with complete recovery from the persistent diarrhea.

The basic principles of the treatment of diarrhea are nutritional, replenishing not only sodium, potassium, and water losses, but also, protein, calorie, and other nutrient stores. Although complex calculations of sodium and potassium maintenance and deficit requirements were made (Smith and Etteldorg 1961; Weil 1969), less attention was paid to protein and calorie needs, and infants were subjected to a prolonged fast for 'bowel rest.' This concept has been questioned (Chung 1948; Chung and Viscorova 1949), and recent evidence suggests that both gut villous morphology and disaccharidase activity improved faster when stimulated by early enteral feedings than with prolonged 'bowel rest' and intravenous alimentation (Greene *et al.* 1975). The somewhat traditional concept of 'resting the bowel' of infants with diarrheal states continues to be attractive, but there is no clear evidence that this approach is therapeutically beneficial. On the contrary, there is now clear evidence that intramural substrates exert a trophic effect on the small intestinal mucosa and that this effect may be mediated by certain gastrointestinal hormones such as gastrin.

Oral glucose-electrolyte solutions have been used increasingly as initial therapy in diarrhea and dehydration due to a wide variety of infectious agents (Santosham *et al.* 1982). They contain simple monosaccharides and minerals which are usually absorbed by active transport across partly damaged gut mucosal surfaces without normal villi (Hirschhorn and Denny 1975). However, the caloric

value of clear liquids is low, and they contain no protein source that can be used to heal damaged gut epithelium. Therefore, clear liquids alone should not be used for more than a few days without the provision of additional calorie or nitrogen sources.

Oral elemental diets containing simply monosaccharides, amino acids, and safflower oil (eg, Pregestimil) are essentially completely predigested and are usually well tolerated by infants no matter how badly the gut is damaged (Sherman *et al.* 1975). However, as their high osmolarity may provoke an osmotic diarrhea, elemental diets must usually be diluted for use in infants. Other elemental formulas containing casein hydrolysates (short-chain polypeptides), medium-chain triglycerides (eight- to ten-carbon synthetic fatty acids which can be absorbed without bile acids or micelles), and sucrose or glucose polymers instead of lactose, can be tailored to the individual patient's absorptive capacities as tested by tolerance or breath tests. These elemental formulas, claimed to be hypoallergenic, are also useful if the problem involves milk or soy protein allergy. If bolus feedings cannot be tolerated, a slow continuous drip through a nasogastric tube may be tried.

Larcher *et al.* (1977) proposed that the 'chicken-based feeding regimen' is a highly effective form of dietary treatment in those infants with chronic diarrhea. It contains a hypoallergenic protein source, essential fatty acids, and excludes the saccharides lactose and sucrose; carbohydrate is included in the form of glucose polymer, Gastrocaloreen. The formula provides all the essential nutrients required for optimal growth, is a relatively low osmolar feed, is well tolerated by infants, and is cheap.

Although oral elemental formulas will be sufficient in most cases, occasionally total parenteral nutrition may be necessary if diarrhea and malabsorption continue (Gunn *et al.* 1977). Parenteral nutrition may be life saving in marasmic infants and, unless there is a rapid response to dietary treatment, should probably be started at an early stage. Peripheral administration of protein dextrose solutions with fat emulsions have been used to provide maintenance calories. However, this does not allow the large amount of extra calories to be administered, up to 200 kcal/kg/d or more, which an extremely malnourished infant or child might require for growth. Therefore, placement of a central venous catheter for infusion of hypertonic solutions becomes necessary for treatment of prolonged diarrhea or severe malabsorption problems. The presence of an indwelling catheter for prolonged periods has raised appropriate concern over the high rates of infection observed in early studies, but the use of silastic catheters, strict aseptic technique, and increased experience has lowered complications to acceptable levels. Complications of parenteral nutrition, however, are far more likely to occur in severely malnourished infants, particularly septicemia and hypophosphatemia. Hypophosphatemia may result in hemolytic anemia, and peripheral hypoxia leading to convulsions and sometimes coma, and may also result in defective phagocytic function, and thus predispose to sepsis during parenteral nutrition.

Drug treatment of chronic diarrhea in children is usually not warranted. No advantage has been found in giving antibiotics in diarrhea due to E. coli, Salmonella, or nonspecific infections (Garcia *et al.* 1974); Shigella is the specific exception. Intestinal paralytic agents, such as diphenoxylate-atropine (Lomotil), may relieve symptoms by decreasing fluid transit through the gut, but without reducing secretion. The excess water will instead tend to pool in distended loops of bowel, masking dehydration and delaying the usual excretion of infectious organisms. Absorbants such as kaolin-pectin suspension (Kaopectate) may actually cause increased sodium and potassium losses. Bismuth subsalicylate (Pepto-Bismol) has recently been shown to be of use in traveller's diarrhea, possibly by enhancing the mucosal barrier or by affecting prostaglandins, but the large quantities necessary may put young infants at risk for toxic salicylism. Other common antidiarrheal agents are probably useless and may actually prolong diarrhea and be hazardous in young children (Portnoy *et al.* 1976).

In the present series of patients, the age of onset of diarrhea, body weight on admission, and laboratory findings did not influence the outcome of infants with chronic diarrhea. Only the interval period from onset to diagnosis did influence the outcome.

Larcher *et al.* (1972) reported that overall mortality was 5%, much improved over the earlier experience of Avery *et al.* (1968) of 45% mortality, and this improvement was attributed to the use of an elemental chicken-based formula. Sunshine *et al.* (1977) reported that mortality was 28%. Other reports of persistent diarrhea in infants claim much reduced morbidity and mortality with improved methods for delivery of oral or intravenous alimentation. In this study, three infants expired, and the mortality was 4.4%, which was similar to the report of Larcher *et al.* (1977).

Rehabilitation from severe chronic diarrhea with protein-calorie malnutrition requires a long, expensive hospitalization, with not inconsiderable morbidity and mortality. If diarrhea does develop, proper attention to the infant's nutritional needs by the mother and the physician and avoidance of prolonged iatrogenic starvation on clear liquids or diluted formulas will prevent further deterioration into the vicious cycle of malnutrition, infection, and malabsorption.

Increasing evidence is being accumulated on the anti-infective properties of breast milk (Welsh and May 1979) and specific protection against Salmonella, rotavirus, and E. coli has been demonstrated. Even in the United States, fewer hospitalizations and infectious illnesses were found in infants breast-fed for prolonged periods. Obviously, cow's milk intolerance will not be a problem in exclusively breast-fed infants, but there is some evidence that other allergic illness is also prevented.

Conclusively chronic diarrhea in infancy is most commonly caused by lactose intolerance and milk allergy. Systemic diagnostic measures should be embarked upon as soon as chronic diarrhea is recognized in order that any treatable underlying condition may be identified and dealt with before changes in the intestinal tract become irrevocable. Diagnosis of chronic diarrheal disease should include a careful dietary history, attention to signs of malnutrition and specific tests. Management is chiefly directed at providing adequate nutrition through oral elemental diets or total parenteral nutrition. About 70% of infants with chronic diarrhea responded to fasting and change of formula. The outcome of infants with chronic diarrhea was influenced significantly by the interval period from onset to diagnosis. Therefore, early referral to experienced centers is most important for the sake of the infant's future normal growth and development.

REFERENCES

Amirhakimi GH, Samloff IM, Bruson MF. Intestinal lymphangiectasia. Am. J. Dis. Child. 1969, 117: 178-185

Avery GB, Villavicencio O, Lilly JR. Intractable diarrhea in early infancy. Pediatrics 1968, 41: 712-722

Bahna SL. Control of milk allergy: A challenge for physicians, mothers, and industry. Ann. Allergy 1978, 41: 1-9

Bahna SL, Heiner DC. Cow's milk allergy. Adv. Pediatr. 1978, 25: 1-7

Barr S, Bickel H. Oligosaccharides in infants' feces. J. Clin. Pathol. 1964, 17: 273-274

Bernier JJ, Florent CH, Desmazures CH. Diagnosis of protein losing enteropathy by gastrointestinal clearance of alpha-1-antitrypsin. Lancet 1978, 760-764

Bloom SR, Long RG, Bryant MG. Clinical biochemical and pathological studies on 62 VIPomas. Gastroenterology 1980, 78: 1143-1156

Camiel MR, Benninghoff DL, Alexander LL. Lymphocytopenia with lymph extravasation from abnormal lymphatics: its occurrence with chylous ascites and chylothorax. Lymphology 1970, 4: 147-151

Chung AW. The effect of oral feeding at different levels on the absorption of food stuffs in infantile diarrhea. J. Pediatr. 1948, 33: 11-20

Chung AW, Viscorova B. The effect of early oral feeding versus early oral starvation on the course of infantile diarrhea. J. Pediatr. 1949, 35: 14-21

Dahlqvist A. Assay of intestinal disaccharidases. Anal. Biochem. 1968, 22: 99-107

Davidson AGF, Mullinger M. Reducing substances in neonatal stool detected by clinitest. Pediatrics 1970, 46: 632-635

Davidson GP, Cameron DJS. The spectrum of cow's milk allergy in childhood. Acta Pediatr. Scand. 1979, 68: 847-854

Eastham EJ, Walker WA. Effect of cow's milk on the gastrointestinal tract: A persistent dilemma for the pediatrician. Pediatrics 1968, 40: 354-360

Florent C, Desmazures C, Aymes C. Intestinal clear-

ance of alpha-1-antitrypsin. A sensitive method for the detection of protein-losing enteropathy. Gastroenterology 1981, 81: 777-780

Freier S, Kletter B, Gery I. Intolerance to milk protein. J. Pediatr. 1969, 75: 623-630

Funato M, Fujimura M, Shimada S. Rapid changes of serum VIP after removal of ganglioneuroblastoma with watery diarrhea-hypokalemia-achlorhydria syndrome in a child. J. Pediatr. Gastroenterol. Nutr. 1982, 1: 131-135

Galant SP. Biological and clinical significance of the gut as a barrier to penetration of macromolecules. Clin. Pediatr. 1976, 15: 731-738

Garcia de Olarte D, Trujillo H, Agudelo N. Treatment of diarrhea in malnourished infants and children, a double-blind study comparing ampicillin and placebo. Am. J. Dis. Child. 1974, 127: 379-385

Gerrard JW, Mackenzie JWA, Goluboff N. Cow's milk allergy: Prevalence and manifestations in an unselected series of newborns. Acta Pediatr. Scand. 1973 (suppl.234)

Goldman SA, Anderson DW, Sellers WA. Milk allergy: I. Oral challenge with milk and isolated milk proteins in allergic children. Pediatrics 1963, 32: 425-450

Goldman SA, Sellers WA, Halpern SR. Milk allergy: II. Skin testing of allergic and normal children with purified milk proteins. Pediatrics 1963, 32: 572-579

Gomez F, Galvan RR, Cravioto J. Malnutrition in infancy and childhood with special reference to kwasiorkor. Adv. Pediatr. 1955, 7: 131-137

Greene HL, McCabe DR, Merenstein GB. Protracted diarrhea and malnutrition in infancy: Changes in intestinal morphology and disaccharidase activities during treatment with total intravenous nutrition or oral elemental diets. J. Pediatr. 1975, 87: 695-672

Gruskay FL, Cooke RE. The gastrointestinal absorption of unaltered protein in normal infants and in infants recovering from diarrhea. Pediatrics 1955, 16: 763-780

Gunn T, Brown RS, Pencharz P. Total parenteral nutrition in malnourished infants with intractable diarrhea. Can. Med. Assoc. J. 1977, 17: 357-364

Hansen LP, Lund HT, Fahrenkrug J. VIP-producing ganglioneuroma in a child with chronic diarrhea. Acta. Pediatr. Scand. 1980, 69: 419-424

Harrison M, Kilby A, Walker-Smith JA. Cow's milk protein intolerance: A possible association with gastroenteritis, lactose intolerance and IgA deficiency. Br. Med. J. 1976, 1: 1501-1509

Hill RE, Herez A, Corey ML. Fecal clearance of alpha-1-antitrypsin: a reliable measure of enteric protein loss in children. J. Pediatr. 1981, 99: 416-418

Hirschhorn N, Denny KM. Oral glucose-electrolyte therapy for diarrhea: A means to maintain or improve nutrition. Am. J. Clin. Nutr. 1975, 28: 189-195

Iyngkaran N, David K, Robinson MJ. Cow's milk protein-sensitive enteropathy. Arch. Dis. Child. 1979, 54: 39-46

Iyngkaran N, Robinson MH, Prathap K. Cow's milk protein-sensitive enteropathy: Combined clinical and histological criteria for diagnosis. Arch. Dis. Child. 1978, 53: 20-27

Jarnum S, Westergaard H, Yssing M. Quantitation of gastrointestinal protein loss by means of ^{59}Fe labelled iron dextran. Gastroenterology 1968, 55: 229-241

Kuitunen P, Visakorpi JK, Savilahti E. Malabsorption syndrome with cow's milk intolerance: Clinical findings and course in 54 cases. Arch. Dis. Child. 1975, 50: 351-358

Larcher VF, Shepherd R, Francis DEM, Harries JT. Protracted diarrhea in infancy. Arch. Dis. Child. 1977, 52: 597-605

Lebenthal E. Cow's milk protein allergy. Pediatr. Clin. North Am. 1985, 22: 827-839

Lloyd-Still JD. Chronic diarrhea of childhood and the misuse of elimination diets. J. Pediatr. 95: 10-13, 1979.

Long RG. VIPomas in childhood. J. Pediatr. Gastroenterol. Nutr. 1983, 122-126

Long RG, Bryant MG, Mitchell SJ. Clinicopathological study of pancreatic and ganglioneuroblastoma tumors secreting VIP. Br. Med. J. 1981, 282: 1767-1770

Maki M, Harmolnen A, Vesikari T. Fecal excretion of alpha-1-antitrypsin in acute diarrhea. Arch. Dis. Child. 1982, 57: 154-156

Mekhjian HS, O'Dorisio TM. VIPoma syndrome. Semin. Oncol. 1987, 14: 282-291

Mitchell CH, Crast FW, Griffin R. Intractable watery diarrhea, ganglioneuroblastoma and vasoactive intestinal peptide. J. Pediatr. 1976, 89: 593-595

Portnoy BL, Dupont HL, Pruitt D. Antidiarrheal agents in the treatment of acute diarrhea in children. JAMA 1976, 236: 844-850

Raadsveld CW, Klomp H. Thin-layer chromatogra-

phic analysis of sugar mixtures. J. Chromatog. 1971, 57: 99-106

Rhode JE, Northup RS. Taking science where the diarrhea is. Ciba Found. Symp. 1976, 42: 339

Sallon S, Deckelbaum RJ. Cryptosporidium, malnutrition, and chronic diarrhea in children. Am. J. Dis. Child. 1988, 142: 312-315

Santosham M, Daum RS, Dillmann L. Oral rehydration therapy of infantile diarrhea. N. Engl . J. Med. 1982, 306: 1070-1078

Seo JK, Chu SHW, Walker WA. Development of intestinal host defense: an increased sensitivity in the adenylate cyclase response to cholera toxin in suckling rats. Pediatric Research 1989, 25 (3): 225-227

Sherman JO, Hamly CA, Khachadurian AK. Use of an oral elemental diet in infants with severe intractable diarrhea. J. Pediatr. 1975, 86: 518-526

Shiner M, Ballard J, Brook CGD. Intestinal biopsy in the diagnosis of cow's milk protein intolerance without acute symptoms. Lancet 1975, 2: 1060-1068

Shiner M, Ballard J, Smith ME. The small intestinal mucosa in cow's milk allergy. Lancet 1985, 1: 136-142

Sinatra FR, Merritt RJ. Iatrogenic kwasiorkor in infants. Am. J. Dis. Child. 1981, 135: 21-26

Smith HL, Etteldorf JN. Parenteral fluid regimens in the treatment of severe diarrhea in infants. J. Pediatr. 1961, 51: 1-7

Sunshine P, Sinatra FR, Mitchell CH. Intractable diarrhea of infancy. Clin. Gastroenterol. 1977, 6: 445-450

Thomas DW, Sinatra FR, Merritt RJ. Random fecal alpha-1-antitrypsin concentration in children with gastrointestinal disease. Gastroenterology 1981, 80: 776-782

Thomas DW, Sinatra FR, Russel JM. Fecal alpha-1-antitrypsin excretion in young people with Crohn's disease. J. Pediatr. Gastroenterol. Nutr. 1983, 2: 491-496

Townley RRW. Disaccharidase deficiency in infancy and childhood. Pediatrics 38: 127-141, 1966.

Waldmann TA, Morell AG, Wochner RD. Measurement of gastrointestinal protein loss using ceruloplasmin labeled with ^{67}copper. J. Clin. Invest. 1967, 46: 10-20

Waldmann TA, Wochner RD, Strober W. The role of gastrointestinal tract in plasma protein metabolism; studies with ^{51}Cr-albumin. Am. J. Med. 1969, 46: 275-285

Walker-Smith J. Cow's milk protein intolerance: Transient food intolerance of infancy. Arch. Dis. Child. 1975, 50: 347-356

Walker-Smith J, Harrison M, Kilby A. Cow's milk sensitive enteropathy. Arch. Dis. Child. 1978, 53: 375-380

Walker WA, Isselbacher KJ. Uptake and transport of macromolecules by the intestine. Gastroenterology 1974, 67: 531-539

Walsh JA, Warren KS. Selective primary health care: An interim strategy for disease cotrol in developing countries. N. Engl. J. Med. 1979, 301: 967-972

Weil WB. A unified guide to parenteral fluid therapy: I. Maintenance requirements and repair of dehydration. J. Pediatr. 1979, 75: 1-8

Welsh JK, May JT. Anti-infective properties of breast milk. J. Pediatr. 1979, 94: 1-7

Wraith DG, Merrett J, Roth A. Recognition of food-allergic patients and their allergens by the RAST technique for clinical investigation. Clin. Allergy 1979, 9: 25-36

＝국 문 초 록＝

영아기 만성 설사
－ 감별진단과 치료에 대한 중점적 분석 －

서울대학교 의과대학 소아과학교실

장철호 · 서정기

영아기 만성 설사는 흔하지 않으나 임상에서 다루기 힘든 증상의 하나로 정확한 원인과 기전을 이해함으로써 적절한 치료가 가능하다. 저자들은 영아기에 발생한 만성 설사 환아 68명의 임상 상을 분석하여 향후 진단과 치료에 도움이 되고자 본 연구를 시행하였다.

영아기 만성 설사의 원인으로는 총 68명 중 유당 불내성과 우유 단백 알레르기가 각각 21례, 18례로 전체의 57.4%를 차지했으며, 그 외에 장임파관 확장증 5례, short bowel 증후군 5례, Salmonella 감염 4례, 염증성 장질환 4례, 선천성 chloridorrhea 3례, 부신 성기 증후군 2례, ganglioneuroma 1례 등이 있었다. 각 원인 질환에 대하여 체계적인 진단적 접근방법을 시도하였으며, 광범위한 검사에도 불구하고 5명의 환아에서는 특별한 원인을 찾을 수 없었다. 만성 설사의 원인 진단 및 치료를 위해서 첫 단계로 24시간 이상 금식 및 수액요법(TPN 포함)을 시행한 결과 환아의 79.4%에서 증상의 호전을 보였으며, 금식에 반응을 보였던 환아를 대상으로 다시 전해질 용액, 유당 또는 우유 단백이 제거된 특수 조제분유 등을 사용한 결과 54명 중 48명(88.9%)에서 증상의 호전을 보였다. 만성 설사 환아의 예후에 영향을 미치는 인자로서는 설사의 시작부터 진단까지의 기간이 중요한 것으로 나타났으며, 설사의 시작연령, 입원시 체중(백분위수), 검사소견(혈색소, 혈중 콜레스테롤, 알부민) 등은 예후와 무관하였다.

이상의 결과로 영아기 만성 설사는 다양한 원인에 의해 유발되며, 환아의 70%가 금식 및 조제 분유를 적절히 바꿈으로써 증상의 호전을 보였고, 향후 환아의 정상적인 성장과 발달을 위해서 조기진단 및 치료가 중요함을 알 수 있었다.