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SEASONAL GASTROENTERITIS AND MALABSORPTION AT AN AMERICAN MILITARY BASE IN THE PHILLIPPINES

II. MALABSORPTION FOLLOWING THE ACUTE ILLNESS

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Jones, T. C. (Rockefeller University, New York, N. Y. 10021), A. G. Dean and G. W. Parker. Seasonal gastroenteritis and malabsorption at an American military base in the Philippines. II. Malabsorption following the acute illness. *Am J Epidemiol* 95: 128–139, 1972.—In two epidemics of gastroenteritis at Clark Air Base in the Philippines, intestinal malabsorption was documented during the acute illness and for varying periods thereafter. The acute illness subsided in 1–5 days, but in 22% of 234 patients it was followed by prolonged symptoms of fatigue, nausea, abdominal discomfort, loose stools and weight loss. Xylose absorption was frequently abnormal during the first few days of illness, but lactose tolerance, intestinal lactase and sucrase levels, and intestinal morphology usually were normal. After the first week, tests of intestinal function usually were abnormal in patients with persistent symptoms and also, with a lesser frequency, in those who had become asymptomatic after the acute illness. The prolonged illness resembled tropical sprue and appeared to respond to therapy with tetracycline and folic acid. No epidemiologic differences were found between patients who recovered quickly from the acute gastroenteritis and those who had prolonged symptoms except that the latter group was slightly older. A single cause, of unknown nature, apparently produces annual seasonal epidemics with a spectrum of symptoms and signs ranging from acute gastroenteritis to mild tropical sprue. The epidemics at Clark Air Base provide a unique opportunity to study the etiology of tropical sprue and its relationship to acute gastroenteritis.

diarrhea; enteritis; gastroenteritis; lactose intolerance; malabsorption syndromes; sprue, tropical; xylose

Introduction

For many years epidemics of acute gastroenteritis of unknown cause have occurred annually in the period from March through July at Clark Air Base of the U. S. Air

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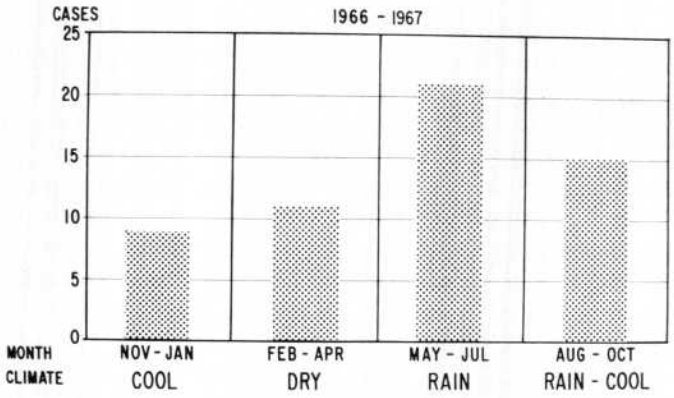

FIGURE 1. Cases diagnosed as tropical sprue and admitted to Clark Hospital in 1966 and 1967, by season and by date of admission.

Force, in Central Luzon, Republic of the Philippines (1). The epidemics occur among American military men and dependents of all ages living under relatively good hygienic conditions and are unusual not only because they lack known microbial cause, but also because they give rise to a high percentage of cases with prolonged symptoms resembling those of mild tropical sprue. Clark Hospital records for 1966 and 1967 showed a seasonal variation in the number of "tropical sprue" cases similar to that of acute gastroenteritis (figure 1). Because of the apparent clinical and epidemiologic associations between acute diarrhea and prolonged malabsorption, a study was made of the relationship between the two illnesses.

The results suggest that intestinal malabsorption, weight loss, fatigue, abdominal discomfort and prolonged diarrhea do follow an attack of epidemic gastroenteritis at Clark in many instances, and that this epidemic syndrome presents many of the features of tropical sprue.

MATERIALS AND METHODS

During two epidemics from March to July in 1968 and 1969, the symptoms and clinical laboratory abnormalities of patients were studied during and after an episode of acute gastroenteritis. In the 1968 study period, data were collected from 190 consecutive patients reporting to a general screening clinic with diarrhea of recent onset. Patients returning to clinic three or more weeks after the initial illness with persistent symptoms were re-examined. In 1969 a prospective evaluation of patients seen in the clinic within three days after onset of symptoms was conducted. Fifty-four patients agreed to an initial evaluation and repeat tests six weeks later and gave informed written consent to the procedures involved. Of these, 44 returned for follow-up interviews and laboratory testing of varying degrees of completeness.

The following tests of intestinal function were used: 25-gm, 5-hour urinary D-xylose excretion; 50-gm lactose tolerance test with venous blood samples at 0, 15, 30, 60, 90 and 120 minutes; duodenojejunal biopsy (Crosby capsule); and small bowel x-ray series. Dr. Jack Welsh of the University of Oklahoma did disaccharidase assays on intestinal biopsy specimens preserved at −70 C, using previously described techniques (2). Hematocrit, leukocyte counts and blood smear examination and liver function tests were obtained for nearly all patients during the second study period and, in some cases, serum calcium, cholesterol, and triglyceride, and prothrombin time were also measured. Tests were recorded as abnormal based on recorded values for Americans in the U. S. or in Southeast Asia: less than 4.5 gm/5 hours urine for D-xylose (3), less than 20 mg per cent maximum rise in venous blood

sugar for lactose tolerance (4), less than 12.5 units per milligram of protein for lactase, less than 27 units per milligram for sucrase (4), and greater than 4:1 for sucrase-lactase ratio (4).

The biopsy specimens were described in detail by evaluation of formalin-fixed hematoxylin- and eosin-stained sections for villus shape, morphology of surface epithelial cells and degree of infiltration of the lamina propria. During the 1968 study this was performed by Dr. R. Lawrence Smith of the Clark Hospital Department of Pathology. Dr. Jack Welsh interpreted specimens obtained during the 1969 study. The specimens were graded as normal, slightly abnormal, or 1+, 2+ or 3+ abnormal based on the above observations. Special stains for *Giardia lamblia* were done in 1969.

Dr. William Bender, of the Department of Radiology, at Clark Hospital reviewed all small bowel x-ray studies and graded them systematically on the basis of the degree of dilation, segmentation, fragmentation, edema and moulage. An x-ray impression was recorded as normal or 1+, 2+ or 3+ abnormal based on the degree of alteration of the small bowel pattern. The grading of both x-rays and biopsies was done without reference to the clinical history.

In the 1968 study, stool bacterial cultures and parasitologic examinations were performed by the Clark Hospital Laboratory, using routine methods. In 1969 duplicate specimens were sent in appropriate holding media and fixatives to the Center for Disease Control (CDC) in Atlanta, Georgia, and fresh stools were also examined by the Clark Hospital Laboratory. Virologic studies, a search for enteropathogenic or enterotoxin-producing *Escherichia coli*, and attempts to transmit the illness to human volunteers were also carried out and will be reported separately (5).

Results

"Tropical sprue" at Clark Air Base prior to 1968. Figure 1 shows the cases of tropical sprue diagnosed at Clark Hospital during a two-year period (1966–1967), as determined by retrospective review of charts listing "sprue" as the discharge diagnosis. The minimum criteria for acceptance as probable cases were prolonged illness, weight loss, varying symptoms of fatigue or malaise and at least one abnormal test of intestinal function. Fifty-six cases met these criteria and demonstrated the seasonal fluctuation in the illness shown in figure 1. This figure does not represent the incidence of tropical sprue at Clark because 1) many patients with similar symptoms were not hospitalized but were treated as outpatients, and 2) complete documentation of cases with tests such as stool fat and intestinal biopsies was not done. None of the cases followed during 1968 and 1969 progressed to a classical picture of late tropical sprue. This may be due partly to the use of tetracycline and folic acid. A few cases of advanced tropical sprue were seen during this period but they had apparently acquired the disease during the 1967 gastroenteritis epidemic. One such case is described below in order to document the presence of severe tropical sprue at Clark.

Case report. L. J. B., a 20-year-old white male, was well until June of 1967 when he had an episode of watery diarrhea lasting three days. The illness resolved spontaneously, and he did not seek medical attention. However, during the 16 months following the diarrhea he noted intermittent nausea, food intolerance, occasional vomiting, progressive weakness and weight loss amounting to 40 lb. He was seen in medical clinic in September 1968, diagnosed as having tropical sprue, and placed on tetracycline and folic acid. Three days later he returned because of bilateral ankle edema and increased abdominal girth. His therapy was discontinued and he was admitted to the hospital for complete evaluation.

He had been in the Philippines for one month at the time that the illness began. He smoked, drank occasionally, and denied having milk or food intolerance in the past. His normal weight had been 170 lb.

On physical examination he appeared well developed but thin. The conjunctival and mucous membranes were pale. There was no mucosal erythema or ulceration. The chest and heart ex-

aminations were normal. The liver was palpable 3 cm below the costal margin, and the edge was firm. The spleen was not palpable. The abdomen was distended, and shifting dullness was detected. Two plus edema to the knees was present. He weighed 130 lb.

The patient was placed at bed rest and tests of hematopoietic, hepatic, renal and intestinal function were initiated. Pertinent results were: hematocrit, 26 per cent; hemoglobin, 11.7 gm%; white blood cell count, 4600/mm^3; urinalysis, normal; total protein, 5.0 gm; albumin, 3.2 gm; bilirubin, 0.9 mg per cent; serum glutamic oxaloacetic-acid-transaminase, 78 Reitman-Frankel units; serum glutamic pyruvic transaminase, 65 Reitman-Frankel units; bromsulphalein, 18.5 per cent retention at 45 minutes; fasting blood sugar, 100 mg per cent; blood urea nitrogen, 7 mg per cent; D-xylose excretion, 4.1 gm/5 hours; lactose tolerance test, 3 mg per cent maximum rise/2 hours; liver biopsy, normal; bone marrow biopsy, erythroid hyperplasia consistent with partially treated megaloblastic anemia; small bowel x-ray, fragmentation and flocculations in small intestine consistent with malabsorption; small bowel biopsy, villus broadening and mononuclear cell infiltration of lamina propria; stool fat, 23.7 gm/100 gm of stool. Other tests, including purified protein derivative, peritoneal fluid culture, chest x-ray, electrocardiogram, and stool examination for parasites and bacteria, were normal.

The patient was started on therapy with tetracycline, 250 mg four times daily, and folic acid, 5 mg three times daily. His weight rapidly increased during the next three weeks to 165 lb during which time his ankle edema and ascites disappeared. After four weeks of therapy his hematocrit had risen to 40 per cent, total protein to 7.9 gm, D-xylose excretion to 6.0 gm, and maximum rise in venous blood sugar after lactose load to 40 mg per cent. A repeat intestinal biopsy showed some mononuclear cell infiltration, but was otherwise interpreted as normal. At the end of five weeks of therapy he weighed 169 lb and was asymptomatic. Because of the severity of his illness he was returned to the United States for continued convalescence. The discharge diagnosis was stage III tropical sprue with anemia, hypoproteinemia and edema.

Clinical observations, 1968 and 1969. The symptoms of patients with the acute diarrheal illness, as described previously (1), consisted of nonbloody diarrhea, abdominal cramps, nausea and malaise, usually without fever. In those who developed a more prolonged illness, the most characteristic symptoms were 5- to 15-lb weight loss, marked fatigue, intermittent abdominal discomfort and sometimes loose stools. Some had persistent nausea. A few patients described their stools as bulky and foul smelling. In 1968, when 190 patients with acute diarrhea were followed, 39 returned to clinic more than three weeks after onset with the above complaints. In 1969, during the prospective study of 44 patients, 12 noted persistent symptoms. The incidence of prolonged symptoms (greater than three weeks) following acute diarrhea during the two epidemic periods was 21 and 27 per cent.

Although antispasmodics and antiemetics controlled the acute symptoms of diarrhea and nausea in most patients, they were not effective for the complaints of weight loss, fatigue and abdominal discomfort. Administration of tetracycline and folic acid was associated with relief of these symptoms in 28 of 32 patients so treated in 1968 and three of three patients treated in 1969. The fatigue, abdominal discomfort and loose stools improved in three to five days. Seven patients in 1968 and nine in 1969 improved spontaneously, usually during a one- to two-month period. A controlled study of the effectiveness of different medications was not done.

Except for tests of intestinal function, essentially all of the clinical laboratory determinations done during the 1969 study gave normal results both initially and after one month or more of symptoms. The hematocrit remained normal and no consistent abnormalities were seen in the red cells in peripheral blood smears.

Microbiologic findings. During the two years of the study 162 acute stool specimens were cultured for bacterial pathogens and 121 were examined parasitologically by the Clark Hospital Laboratory. In 1969, 48 and 55 of these were submitted to CDC for bacteriology and parasitology, respectively.

Salmonella panama, Shigella sonnei, and an Arizona species were each found in a single stool. Two stools contained members of the Providence group and five, *Proteus rettgeri* or *mirabilis. Strongyloides stercoralis* was found in one stool, *Ascaris lumbricoides* in one, *Trichuris trichuria* in four, *Giardia lamblia* in three (one the patient with *S. sonnei*) and *Dientamoeba fragilis* or unidentified amoebae in five. Only in the four cases with Salmonella, Shigella, Arizona or Strongyloides and possibly the two others with Giardia, was a likely cause for the diarrhea identified.

No Giardia were found in 11 acute and three follow-up intestinal biopsies especially stained for the organism.

Intestinal function during the acute illness and in patients with prolonged symptoms. During the first week after the onset of diarrhea, D-xylose tests were obtained from 79 patients, lactose tolerance tests from 26, intestinal biopsies from 13, disaccharidase determinations from 9, and small bowel x-ray studies from 2 patients. The distribution, mean and percentage abnormal are recorded in table 1. The D-xylose was found abnormal in 54 per cent. This could not be attributed solely to the presence of diarrhea, since many patients who had frequent watery stools excreted normal amounts of D-xylose. On the other hand, lactose tolerance, intestinal biopsy morphology and disaccharidase determinations were normal or only slightly altered at this stage. One patient demonstrated abnormal small bowel x-ray patterns during the acute illness.

Some patients were tested during the second week of illness (table 2). Of 27 D-xylose tests, 74 per cent were abnormally low, a slightly higher percentage than noted during the first week. Two of three small bowel x-rays were interpreted as abnormal—one mildly, one markedly. In contrast to studies done during the first week of symptoms, six of eight intestinal biopsies were abnormal—one with slight alteration, three recorded as 1+, one 2+, and one 2+ to 3+. Five of eight lactose tolerance tests, four of six intestinal lactase levels and three of six intestinal sucrase levels were abnormally low during the second week.

Tests of intestinal function done after at least two weeks of symptoms (usually three to six weeks) are recorded in table 3. Most of these patients demonstrated defects in xylose absorption, lactose intolerance, low lactase enzyme levels, abnormal small bowel histology and abnormal patterns on small bowel x-ray studies. The percentage of patients with abnormal sucrase-lactase ratios remained constant, indicating that the abnormality was not one of progressive isolated lactase deficiency. Lactase enzyme

TABLE 1

Laboratory data during the first 7 days after the onset of diarrhea

Test or procedure	No. of patients tested	Results		
		Mean ± SD	Range	% abnormal
25-gm xylose excretion (gm excreted in 5 hr)	79	4.7 ± 3.3	0–12.5	54
50-gm lactose tolerance (mg% rise in venous blood glucose)	26	37 ± 15	6–63	8
Intestinal lactase (units/gm of protein)	9	15 ± 7	5.8–29	33
Intestinal sucrase (units/gm of protein)	9	56 ± 29	12–113	11
Sucrase-lactase ratio	9	5.5	1.2–19	33
Intestinal biopsy	13		0 to slight abnormality	23
Small bowel x-ray	2		0 to 3+ abnormality	50

TABLE 2

Laboratory data 7 to 14 days after onset of diarrhea

Test or procedure	No. of patients tested	Results		
		Mean ± SD	Range	% abnormal
25-gm xylose excretion (gm excreted in 5 hr)	27	3.1 ± 2.1	0.2–9.2	74
50-gm lactose tolerance (mg% rise in venous blood glucose)	8	28 ± 23	7–65	63
Intestinal lactase (units/gm of protein)	6	17 ± 21	3.9–18	66
Intestinal sucrase (units/gm of protein)	6	48 ± 43	8.9–120	50
Sucrase-lactase ratio	6	4.2	1.5–14	17
Intestinal biopsy	8		Slight to 2+ to 3+ abnormality	75
Small bowel x-ray	3		1+ to 3+ abnormality	67

TABLE 3

Laboratory data 3 weeks or more after onset of diarrhea, in patients with continuing symptoms

Test or procedure	No. of patients tested	Results		
		Mean ± SD	Range	% abnormal
25-gm xylose excretion (gm excreted in 5 hr)	41	3.8 ± 3.4	0.2–12.0	76
50-gm lactose tolerance (mg% rise in venous blood glucose)	20	15 ± 10	0–34	70
Intestinal lactase (units/gm of protein)	8	9.8 ± 9.9	0.9–34	87
Intestinal sucrase (units/gm of protein)	8	33 ± 26	13–92	50
Sucrase-lactase ratio	8	7.0	3–32	25
Intestinal biopsy	8		1+ to 2+ abnormality	100
Small bowel x-ray	19		1+ to 3+ abnormality	74

abnormality was, however, seen more commonly than low values of sucrase, maltase or alkaline phosphatase. Thus, though significant abnormalities were present during the second week of the illness, a further increase in frequency of abnormalities of intestinal function was seen in those with symptoms lasting two weeks or longer (figure 2).

Intestinal function in asymptomatic convalescent patients. During the 1969 study, 32 of 44 patients became asymptomatic within two weeks and had no further fatigue, nausea, abdominal discomfort or weight loss. The results of follow-up tests done on these patients are shown in table 4. Eight of 13 (62 per cent) demonstrated persistently abnormal D-xylose excretion, three with values of 2.0 gm or below. Lactose intolerance was noted in three of 12 patients tested (25 per cent). Two patients had intestinal biopsies and these showed broadened villi with cuboidal cells and leukopedesis; one also had infiltration of the lamina propria. Although abnormalities of intestinal function were somewhat less frequent in asymptomatic patients than in those with continuing symptoms (figure 2),

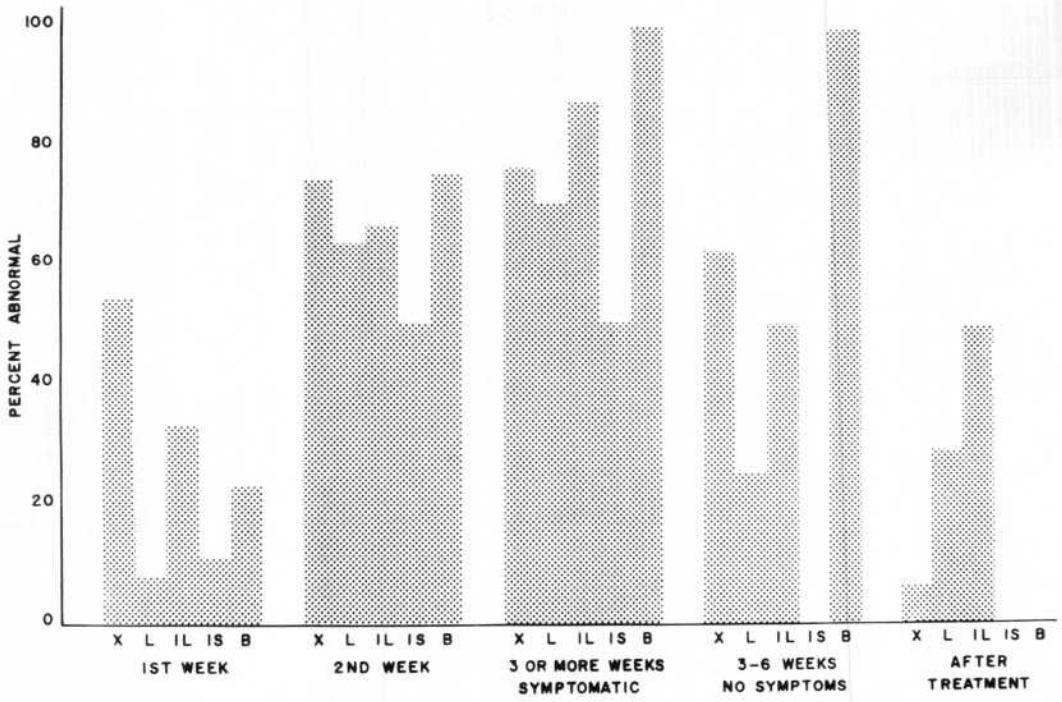

FIGURE 2. Summary from tables 2–5 showing the percentage of intestinal function tests abnormal one, two and three or more weeks after onset of acute gastroenteritis in patients with and without continuing symptoms, and in treated patients one to four months after therapy. *X*, xylose excretion; *L*, lactose tolerance; *IL*, intestinal lactase; *IS*, intestinal sucrase; *B*, intestinal biopsy morphology.

TABLE 4

Laboratory data 3 to 6 weeks after onset of diarrhea, in patients who had become asymptomatic

Test or procedure	No. of patients tested	Results		
		Mean ± SD	Range	% abnormal
25-gm xylose excretion (gm excreted in 5 hr)	13	4.9 ± 3.2	1.5–12.0	62
50-gm lactose tolerance (mg% rise in venous blood glucose)	12	31 ± 28	4–60	25
Intestinal lactase (units/gm of protein)	2	12	11–14	50
Intestinal sucrase (units/gm of protein)	2	61	29–93	0
Sucrase-lactase ratio	2	5.4	2.0–8.7	50
Intestinal biopsy	2		Slight abnormality	100
Small bowel x-ray	0			

a few had marked alterations in these tests for long periods in the absence of any symptoms.

Case report. One such patient, D. D., had the sudden onset of 4–5 watery stools per day on May 14, 1969. He had headache, chills, weakness and fatigue for several days and loose stools for 10 days, after which he was entirely well. During the illness his weight fell initially from 147 to 142 lb, then gradually returned to normal. He had had no previous history of gastrointestinal symptoms or milk intolerance. On days 2 and 3 of the illness, xylose excretion was 1.6 gm/5

hours and a lactose tolerance test showed a 30 mg percent maximum rise. An intestinal biopsy on day 2 was morphologically normal; intestinal lactase was 18.8 units and sucrase was 37.2 units. Repeat studies 23 to 28 days after onset of diarrhea—11–16 days after becoming asymptomatic—resulted in: xylose excretion of 3.0 gm/5 hours; a lactose tolerance test with a 10 mg per cent rise in venous blood sugar; an intestinal biopsy interpreted as showing questionable villus change, cuboidal epithelial cells and leukopedesis; and intestinal lactase of 10.6 units and sucrase 92.6 units per milligram of protein. A glucose-galactose tolerance test was done at this time and produced a 51 mg per cent rise in venous blood sugar. On day 80 after onset of diarrhea, a lactose tolerance test showed a 25 mg per cent maximum rise, and on day 90 xylose excretion was 2.5 gm/5 hours. This patient therefore demonstrated persistent xylose malabsorption during a three-month period, evidence of slight morphologic changes in intestinal morphology and apparently a transient acquired isolated lactase deficiency after becoming asymptomatic.

Intestinal function after treatment. Some of the 32 patients treated with tetracycline and folic acid had repeat studies of intestinal function one to four months following therapy, at a time when weight had returned to normal and all symptoms had disappeared (table 5). Seventeen D-xylose tests revealed a mean of 7.1 gm/5 hours urine, with 6 per cent abnormally low; seven lactose tolerance tests revealed a mean of 27 mg per cent with two abnormally low; two disaccharidase assays revealed one abnormally low lactase (9.5 units per milligram of protein) with a sucrase-lactase ratio of 4.5. The sucrase and maltase levels were within normal limits. Three patients who had had biopsies interpreted as abnormal prior to therapy had repeat biopsies which were considered to be normal. Therapy, therefore, in addition to causing subjective symptomatic improvement, may have rendered more likely the return of xylose absorption, lactose tolerance and intestinal morphology toward normal.

Case report. R. D. N., age 30, illustrates the apparent efficacy of treatment. He developed diarrhea on June 1, 1968. By June 19 he had lost 17 lb and complained of bulky stools and fatigue. Xylose excretion was 1.7 gm, the lactose tolerance test gave a rise of 8 mg per cent, intestinal lactase was 4.6 units per milligram of protein, and an intestinal biopsy was interpreted as 1+ abnormal. He was treated with tetracycline, 250 mg four times daily for 10 days, and folic acid, 5 mg three times per day for 30 days, with improvement of symptoms beginning on the third day of treatment. When restudied 118 days after onset, he was asymptomatic, had regained the weight lost and had D-xylose excretion of 6.4 gm, a lactose tolerance test rise of 27 mg per cent, intestinal lactase of 27.3 units and a normal biopsy.

Epidemiology of prolonged symptoms. The epidemiologic characteristics of the

TABLE 5

Laboratory data 1 to 4 months after treatment with tetracycline and folic acid in patients with prolonged symptoms

Test or procedure	No. of patients tested	Results		
		Mean ± SD	Range	% abnormal
25-gm xylose excretion (gm excreted in 5 hr)	17	7.1 ± 2.0	4.0–10.1	6
50-gm lactose tolerance (mg% rise in venous blood glucose)	7	27 ± 12	10–44	29
Intestinal lactase (units/gm of protein)	2	18	10–27	50
Intestinal sucrase (units/gm of protein)	2	55	42–69	0
Sucrase-lactase ratio	2	3.5	2.5–4.5	50
Intestinal biopsy	3			0
Small bowel x-ray	0			

acute illness during the 1969 epidemic have been described (1). Cases of acute gastroenteritis were evenly distributed among the population of the base in both sexes and all age groups. The epidemic occurred near the onset of the rainy season in the period of highest temperatures and waned before the heaviest part of the rainy season. Local Filipinos working on base had a lower incidence of illness than Americans. No evidence of person-to-person transmission was found and the most likely source of a causative agent or toxin appeared to be the water supply, even though almost daily cultures of the water did not detect coliform bacteria, and chlorination was well maintained. No cause for the epidemic was found in careful bacteriologic, parasitologic and virologic studies of the patients' stools.

In both 1968 and 1969 adult patients with prolonged symptoms were slightly older than those who recovered in a few days. In 1969, 605 clinic patients with diarrhea of less than 14 days duration (at the last clinic visit) were compared by means of questionnaires with 175 patients having diarrhea for 14 days or more. The average ages were 27.4 and 29.0 years, respectively, differing by twice the standard error of the difference in the mean ($p = .045$). Whether the difference is related to age-dependent responses of the intestinal tract or to other factors is not clear. It should be noted that pediatric cases with prolonged diarrhea and malabsorption did occur, although this study dealt only with adults.

In the 1968 epidemic, 252 men with diarrhea of less than five days duration and 39 with diarrhea lasting more than two weeks were compared by means of questionnaires. No significant differences could be found between the two groups with respect to location of residence, date of arrival at Clark, history of previous diarrhea, number of meals recently eaten off base, or initial clinical symptoms. The only differences found were those that would be expected to be associated with the somewhat greater age of those with prolonged symptoms, such as higher rank and greater tendency to eat meals at home. Thus the epidemiologic data was in accord with the clinical impression that acute gastroenteritis and the sprue-like illness are clinical variations of the same basic disease process and may share a common etiology.

Discussion

Changes in intestinal function associated with acute diarrheal diseases were documented by Lindenbaum in Pakistan (6). He found that D-xylose and vitamin B_{12} absorption tests were abnormal in Pakistani patients with cholera, salmonellosis, shigellosis, staphylococcal food poisoning and idiopathic "acute gastroenteritis." During the acute illness, over 90 per cent of his patients showed altered absorption of xylose or vitamin B_{12}. Seventy per cent of patients studied the week following the end of diarrhea still malabsorbed D-xylose. In about one-third of patients who malabsorbed xylose when first studied, this test remained abnormal 2½ weeks or more after cessation of the diarrhea. A similar pattern was seen with vitamin B_{12} absorption tests. Nothing was known of the absorptive status of the patients before their acute illness, however, and, as Lindenbaum has shown (7), malabsorption is common in the Pakistani population.

Disaccharide malabsorption during acute infectious diarrhea in children is mentioned by Sunshine and Kretchmer (8). Persistent monosaccharide malabsorption and clinical intolerance to disaccharides were also found in 23 of 403 cases of infantile diarrhea in Mexico (9). The malabsorption of carbohydrates was associated with the presence of aerobic bacteria in the upper small intestine in most of these cases.

In the present study intestinal malabsorption prior to the onset of acute diarrhea cannot be entirely excluded, but the increasingly abnormal tests of intestinal function with the passage of time after onset suggest a relationship between the acute illness and malabsorption. With the lactose tolerance

test, for example, 92 per cent of our patients initially had normal results but two weeks after onset of diarrhea only 30 per cent were normal. Similarly, the percentage of abnormal biopsies increased from 25 to 100 per cent and xylose malabsorption from 54 to 76 per cent. It seems likely that many or most of the abnormalities developed during and after the acute diarrheal episode.

In a tropical setting and having seen a few patients with classical symptoms of tropical sprue, it appeared reasonable to physicians at Clark Hospital to use the term "sprue" to describe patients experiencing weight loss, fatigue and abdominal discomfort following the annual epidemics of diarrhea. Klipstein and Baker (10) suggest as a working definition of tropical sprue that it is a syndrome occurring in the tropics and includes "all persons who have malabsorption of two or more unrelated substances for which no etiology can be ascertained." The patients at Clark with prolonged malabsorption not only satisfy this definition, but have other features of sprue such as weight loss, fatigue, abnormal intestinal biopsies and an apparent clinical response to tetracycline and folic acid. This, plus the occasional occurrence of more severe full-blown cases, lends support to the identification of the Clark cases as examples of "tropical sprue."

Tropical sprue has been known to occur in the Philippines for a long time (11–13), although the scarcity of published reports suggests that it is much less common there than on the Indian subcontinent. Indeed, while the British Army in India during World War II had over 1000 cases of sprue (14), the occurrence of three cases among a larger number of American troops in the Pacific and Southeast Asia was unusual enough to warrant publication (12). One of these cases arose in the Philippines. Three cases of sprue in American Air Force personnel or dependents stationed in the Philippines in 1963–1965 were reported by Sparberg et al. (13). All had normal intestinal biopsies and had lost 30 lb in weight, and two of the cases had glossitis and severe anemia.

The relative rarity of this severe form of tropical sprue at Clark is in our opinion due to the infrequency with which American military patients tolerate the disease for long periods without seeking medical attention, and the frequent use of tetracycline or tetracycline and folic acid in the medical clinics. The advanced cases seen occasionally demonstrate that the potentiality for development of severe tropical sprue does exist at Clark.

Sprue at Clark is associated with the annual epidemic of gastroenteritis and appears to be both seasonal and epidemic. These features apparently are not characteristic of sprue in all areas of the world, for example in Puerto Rico (15), but resemble those of epidemic sprue in parts of India. Baker, Mathan and Joseph reported a dramatic epidemic in South India affecting over 100,000 people with a mortality of 10 per cent and have studied other epidemics of sprue in the same region (16, 17). Sprue epidemics have occurred elsewhere in India and in Burma (18, 19).

Although Keele and Bound (14), in their study of British Army troops in India, found that sprue was not associated with bacillary or amoebic dysentery, others have mentioned the connection between acute gastroenteritis and sprue. Stefanini (18) recorded a sudden onset of "explosive" diarrhea in 73 per cent of 1069 cases, and Mathan and Baker (17) apparently found the same mixture of brief and prolonged illness in Madras as is found at Clark. It seems quite possible that an association exists between sprue and a nonamoebic, nonbacillary form of gastroenteritis, both at Clark and elsewhere.

Sprue in British troops in India in 1943 and 1944 (14) showed a seasonal peak in May and June during the hot season and before the heaviest rains, just as seen at Clark. However, among Italian prisoners of war in India in 1942–1945 (18) the greatest incidence regularly occurred in the fall

(September–November) at the end of the rainy season. Many of the cases in the latter study had relapses during this same season in one or more successive years.

The cause of tropical sprue has remained elusive (21–23) and it is possible that more than one cause exists. The occurrence of the disease in epidemic form in India and the Philippines makes an infectious or toxic agent seem the most likely cause, but as yet no specific agent has been discovered.

Associations have been noted between sprue and poor nutrition or spoiled foods (18–20), certain houses (24, 25), and even dry wood termites (26). Our study of the acute diarrheal illness at Clark (1) suggested that the water supply might be the most likely source of a causative agent. This may well be the case with other epidemics of sprue, for although some of the groups involved (18, 19) had a common food supply, their water source may also have been shared by the group. A waterborne etiology would also help to explain the clustering of cases in certain houses in India and Ceylon (24, 25), where presumably the household all used the same water supply.

In other reported epidemics of sprue, the cases were often either indigenous peoples with marginal nutritional status and hygiene (17) or European troops under field conditions or with poor food supplies (18, 19). At Clark, it is unlikely that nutritional deficiency or spoiled foods could be a causative factor. The patients prior to onset have been well nourished and living on what could be considered a normal American diet. A dietary vitamin deficiency as a causative factor, as suggested by Ayrey (19), seems almost impossible in the Clark setting. There appeared to be no association of sprue with buildings, and, at least for personnel living on base, exposure to termites at Clark is quite limited.

Tropical sprue characteristically spares the dark-skinned races (27), although recently cases among natives of Haiti (28) and Nigeria (29) have been described. Although 14 per cent of the acute diarrhea patients at Clark in 1969 were Negro, only two of the 51 patients exhibiting prolonged symptoms were Negro. This could have been influenced by many factors, but prolonged symptoms did seem to be less common among Negroes. The Clark epidemics offer an unusual opportunity to study the racial incidence of sprue and investigate its physiologic basis, since diet and living conditions are essentially identical for both Negro and Caucasian Air Force personnel.

The only other host factor correlated with prolonged symptoms during this study was increased patient age, a slight but consistent finding. It may indicate that prolonged symptoms are related to variation in host response to intestinal injury.

In these annual epidemics of acute enteritis a similar intestinal insult appears in some patients to cause transient illness with rapid and complete recovery, and in others chronic enteritis indistinguishable from tropical sprue. In spite of extensive investigation the cause of the acute illness and the factors contributing to prolonged illness remain unknown. There seems little doubt, however, that further study of the acute illness and its sequelae could provide valuable information on the pathogenesis of malabsorption in classical tropical sprue.

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