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

I. CLINICAL AND EPIDEMIOLOGIC INVESTIGATIONS OF THE ACUTE ILLNESS

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Dean, A. G. (Pacific Research Section, NIAID, NIH, P.O. Box 1680, Honolulu, Hawaii 96806), and T. C. Jones. Seasonal gastroenteritis and malabsorption at an American military base in the Philippines. I. Clinical and epidemiologic investigations of the acute illness. *Am J Epidemiol* 95: 111–127, 1972.—Seasonal epidemics of acute gastroenteritis affecting 5,000–6,000 of 36,000 Americans occur annually at Clark Air Base. In the 1969 epidemic the illness was usually afebrile, with nonbloody diarrhea, abdominal cramps, constitutional symptoms, and sometimes vomiting. One-fifth of the patients had symptoms lasting more than 2 weeks, often with accompanying intestinal malabsorption. The epidemic occurred during the hottest season of the year but before the heaviest rainfall, and lasted 5 months. The incidence of disease was uniform on and off base, and among men, women and children. The secondary attack rate in families was not significantly greater than the overall attack rate. Among Americans, previous attacks or higher rank (greater age) were not protective, but local Filipinos working on the base had a significantly lower incidence. The illness was not confined to new arrivals. Sources of meals, recent trips, and consumption of water, soft drinks, milk and locally made beer did not seem causally related. The water supply appeared to have been well chlorinated and free of coliform bacteria.

No microbiologic cause for the epidemic was found, but the suggestion is made that a waterborne, temperature-dependent agent may be responsible. Two hypothetical possibilities—blue-green algae and bacteriophage—are discussed.

diarrhea; enteritis; epidemiology; gastroenteritis; malabsorption syndromes; seasons; sprue, tropical; temperature

Introduction

Numerous surveys of acute diarrheal disease in children have established that, by present methods, a microbiologic cause cannot be identified in over one-half of endemic

Abbreviation: PFN, person-fortnight.

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cases (1–4). Many careful studies of epidemic gastroenteritis in adults also have not detected pathogens (5–8) and apparently a large proportion of all diarrheal disease is not due to presently identifiable causes.

Seasonal epidemics of acute gastroenteritis have occurred annually at Clark Air Base in the Philippines at least since 1963 (9), and American troops in the Philippines as long ago as 1940–1941 experienced the same seasonal pattern of diarrhea (10). Each spring (March–July) an estimated 5,000–6,000 of the 36,000 Americans (1968–1969 population) attached to Clark Air Base have diarrhea lasting a few days, and a significant proportion have symptoms persisting for several weeks or months and accompanied by intestinal malabsorption (11). Numerous attempts to discover a causative bacterial, helminthic, protozoal, or viral pathogen in the stools of patients have failed, and these epidemics appear to be an excellent example of gastroenteritis of unknown cause, as well as a possible model for the malabsorption which develops in Americans living in Southeast Asia (12–14).

The regularity of the epidemics, with abundant cases in adults, on a base served by a single medical facility—Clark Hospital—made possible a prospective clinical, epidemiologic, and microbiologic study during the Spring 1969 epidemic. This report describes the clinical aspects and epidemiology of the 1969 outbreak. Intestinal malabsorption following the acute illness is described elsewhere (11). Microbiologic investigations, including viral studies, and attempts to transmit the illness by feeding stool suspensions to human volunteers, will be reported separately (15).

Materials and methods

Except for school nurses and a single corpsman stationed in the headquarters buildings, all of the medical facilities available to U.S. military personnel and dependents attached to the base are housed at Clark Hospital. During the period March 17 to August 1, 1969, each of the 877 patients reporting to enlisted men's sick call with diarrhea was seen in a special clinic. All completed a four-page clinical and epidemiologic questionnaire giving name, age, rank, race, address of residence and work, travel in the previous three months, eating habits in the previous two weeks, clinical symptoms, date of onset, duration of illness, and other items. The oral temperature and body weight were measured and the patient was seen by a physician and given a brief physical examination and symptomatic treatment. All were asked to return in two weeks for follow-up and 32 per cent did so. Anyone with diarrhea visiting the Emergency Room or Family, Pediatric, or Obstetrics and Gynecology Clinics was also asked to complete the questionnaire, bringing the total number of persons studied to 1265.

Fifty-five men with acute diarrhea volunteered to undergo further study. In each case one of us examined the patient during the acute phase of the illness, and stool, serum and throat washings were collected. Stool specimens were cultured and examined microscopically in the Clark Hospital laboratory. Portions of each specimen were placed immediately in Cary-Blair and Ramakrishnan-Venkatraman bacteriologic transport media, 10 per cent formalin, and polyvinyl-alcohol fixatives and sent to the Center for Disease Control in Atlanta, Georgia, for further bacteriologic and parasitologic examination. Sections of jejunal biopsies obtained from 11 patients were stained by the method of Brandborg et al. (16) and examined for *Giardia lamblia* by Dr. Jack Welsh, Department of Medicine, University of Oklahoma.

The 1265 clinic patients who completed the questionnaire and had diarrhea—defined as at least three "soft or mushy" or two "watery" stools in a day—comprised the "Clinical Study" group for epidemiologic purposes. Two prospective door-to-door sur-

Intelligence Center, Dept. of Health, Manila, Republic of the Philippines, for the data on the incidence of diarrhea in the Philippines.

veys were also conducted with the aid of personnel assigned by the various Air Force units and Red Cross volunteers. The "Work Area and Barracks" survey covered two sets of barracks and five geographically scattered work areas selected as typical of the base as a whole (figure 1). The "Family Study," conducted by Red Cross volunteers in their own neighborhoods, surveyed private homes both on and off base. The period studied, mid-April to mid-June, coincided with the peak of the epidemic. Individuals present in the prospective study groups were given a short questionnaire every two weeks for eight weeks of the epidemic period, and information concerning presence or absence of illness and other epidemiologic parameters was obtained. Anyone having diarrhea in the previous two weeks was asked to fill out the more detailed form used in the clinical study. At the end of the prospective survey in June, all respondents who had not yet completed the longer form were asked to do so in order to provide baseline information on the nondiarrheal population. In the Work Area and Barracks Study, 3061 two-week periods were covered, and in the Family Survey, 1985. The data were transferred to IBM cards and processed on a mechanical sorter with occasional help from an IBM

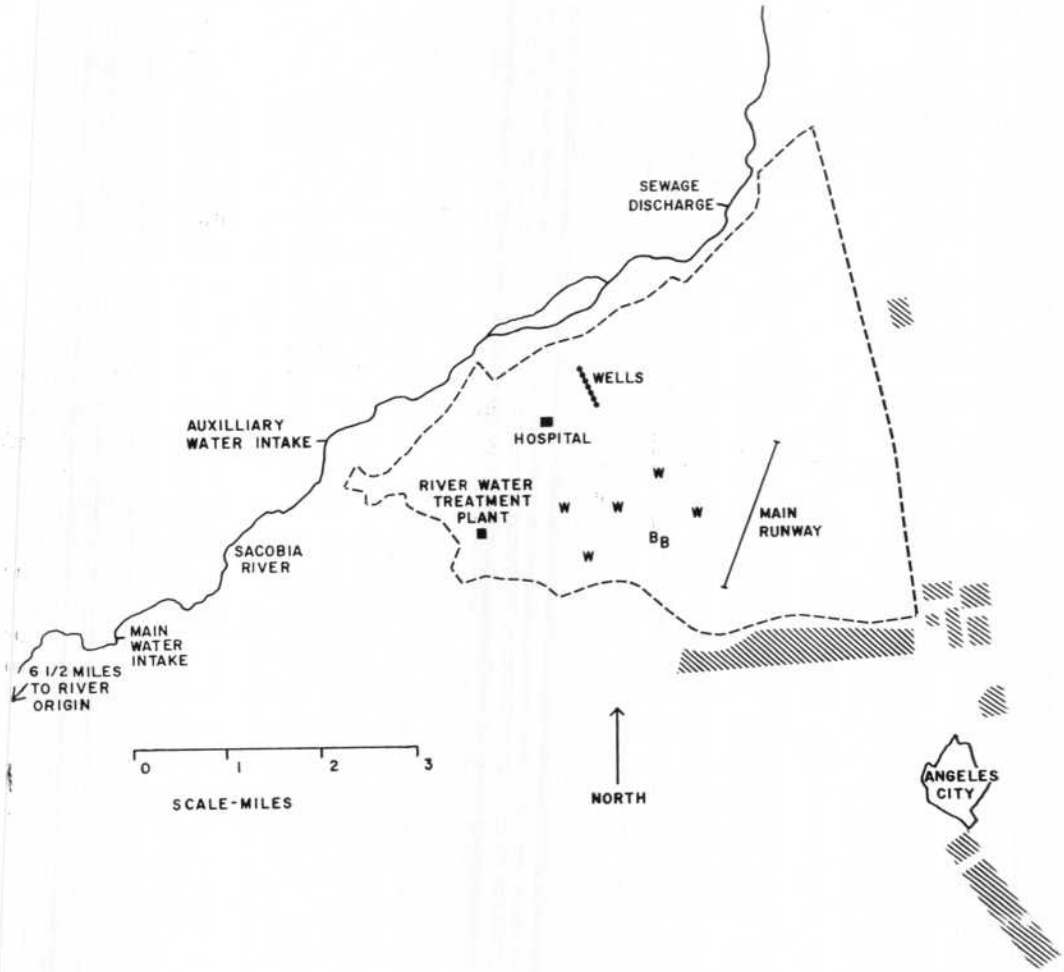

FIGURE 1. Clark Air Base. – – –, boundaries of base. *B*, barracks area in prospective study. *W*, work area in prospective study. *Shaded areas* indicate main off-base housing areas for military personnel.

360 model 20 computer. Many of the questions applied to "the past two weeks," and in the subsequent discussion the term person-fortnight (PFN) is used to indicate the number of persons at risk over the two weeks prior to questioning.

Cultures of the base water supply were done by the Base Bioenvironmental Engineering Department by routine methods using a commercially available Millipore-filter concentration technique which samples 100 ml of water per determination. Mosquito collections were made by the same department using light traps placed at four scattered areas on base.

Results

Clinical manifestations

The acute illness described by 823 enlisted men was characterized by the sudden onset of diarrhea associated with abdominal cramps, nausea and malaise. Headache, chills, vomiting, myalgia and fever occurred less commonly. An estimate of the percentage of symptoms associated with diarrhea was obtained by subtracting their frequency in a control population of nondiarrheal military men in the Work Area and Barracks Study from the frequency in diarrhea patients (table 1). Using these results, 18 per cent of patients reported weight loss associated with the diarrhea, averaging 7.8 pounds. Symptoms of stuffy nose, sore throat, and cough were reported equally by the gastroenteritis and control groups. Twelve per cent of adult diarrhea cases had oral temperatures over 99.4 F (as measured in the clinic), but the frequency of fever in the nondiarrheal control population is not accurately known. Among patients with diarrhea, the frequency of fever was equal in those with and without cough, sore throat or rhinitis.

Table 1

Frequency of various symptoms in men with and without diarrhea in the 1969 epidemic

Symptom	% of respondents having symptom in previous 2 weeks		
	Among 823 diarrhea cases (Clinical Study)	Among 2268 control questionnaires (Work Area and Barracks Study)	Difference (indicating symptoms associated with diarrhea)
Diarrhea	100		
Abdominal pain (cramps)	68	6	62
Nausea	47	3	44
Weakness or dizziness	48	9	39
Fatigue	68	28	40
Chills	30	3	27
Headache	51	22	29
Vomiting	28	2	26
Myalgia	41	11	30
Weight loss	23	5	18
Fever	14	2	12
Cough	17	17	0
Sore throat	15	13	2
Runny or stuffy nose	21	19	2

The severity of symptoms ranged from a few loose bowel movements to illness requiring hospitalization. The most acutely ill patients had 15–20 watery, nonbloody stools per day, vomited for three to four days, had severe malaise and headache and required intravenous fluid replacement. Serious complications were not observed. Diarrhea was more severe and frequent during the first few days of the illness, but was usually controlled by diphenoxylate hydrochloride (Lomotil). Over one-half of 826 adult cases had had diarrhea for less than one week at the time of the last visit (most for one to three days), but 14 per cent had had diarrhea for eight to 14 days and 22 per cent for over two weeks. A number of cases lasted for months. Weakness and fatigue often continued for many days after cessation of the diarrhea.

In addition to occasional fever, physical examination showed hyperactive bowel sounds in 50 per cent, diffuse abdominal tenderness in 41 per cent, and varying degrees of "toxicity"—75 per cent appearing completely well, 25 per cent moderately ill, and only 0.6 per cent markedly toxic. Pharyngitis was found in 10 per cent, but was not statistically associated with the presence of

diarrhea by history and is viewed as an incidental finding. Enlargement of lymph nodes, liver or spleen was rarely detected.

Laboratory tests done on randomly selected patients by the hospital laboratory included hematocrit, white blood cell count, differential blood count, platelet count, prothrombin time, serum calcium, cholesterol, glutamic and pyruvic transaminases, and blood urea nitrogen. Six of 40 patients had elevated white blood cell counts during the first week of the illness, but the differential count remained near normal. Four patients of 20 were noted to have atypical lymphocytes in blood smears made one week or more after onset of diarrhea. All four patients had had normal smears earlier in the illness. The results of other routine tests were within normal limits. Laboratory tests measuring intestinal function are presented in detail elsewhere (11).

Cultures of 55 stools and microscopic examinations of 48 identified one patient with *Salmonella panama*, one with *Shigella sonnei*, one with an Arizona species, and two with Providence group organisms. *Trichuris trichiura* eggs were found in two stools, Ascaris ova in one, *Dientamoeba fragilis* in four, and unidentified or questionable amoebae in two. *Giardia lamblia* trophozoites were seen in the same stool yielding *S. sonnei*, but in none of the other acute specimens. Eight frozen jejunal fluids were later examined for Giardia with negative results, and no Giardia were found in 14 jejunal biopsies from 11 patients. As will be reported elsewhere (15) no one serotype of *E. coli* appeared to predominate in the stools of the patients. Attempts to demonstrate viruses in the stools of patients were negative in most cases, and mycoplasmas were not found. Six stool suspension supernatant fluids have been fed to 34 volunteers (15). One of these men had soft and liquid stools on the seventh and eighth days after inoculation, but the significance of these symptoms in a single man has not yet been investigated by attempts at further passage.

Epidemiologic features

The area and population at risk. Clark rests on a flat plain between two mountain ranges in central Luzon, 50 miles north of Manila. The climate is hot, with a dry period from November to March—sometimes with no measurable rainfall in January, February or March. The rainy season usually begins in April or May and lasts five or six months, reaching a peak in August.

The base is approximately four miles in diameter. In 1969 essentially all of the 19,000 military personnel worked inside the base limits during the day, but approximately one-third of these men and two-thirds of the 17,000 dependents lived in rented homes in nearby Angeles City, often several miles from the base (figure 1).

Men assigned to the base stay two years if accompanied by dependents and 18 months if not. Extension beyond this period is unusual except for the 700 U.S. civilians, many of whom stay for longer periods.

Americans at Clark make frequent trips to other areas in the Philippines and Southeast Asia for both military and recreational purposes. In 1969 the base accommodated about 1200 transient personnel nightly, and hundreds more passed through the air passenger terminal daily.

Temporal distribution of cases. Figure 2 shows the number of enlisted men with diarrhea seen in military sick call and the emergency room from March through July, 1969. The figure presents dates of onset obtained from questionnaires for cases seen between March 17 and July 31, supplemented by records of numbers of clinic visits in early March and emergency room visits in March and early April. Questionnaires were obtained from nearly all enlisted cases between the second week in April and the end of July and surveillance was uniform during this period.

Figure 3 shows the number of cases of "gastritis," gastroenteritis, and diarrhea seen in the emergency room throughout 1969 and 1970. Definite seasonal peaks are pres-

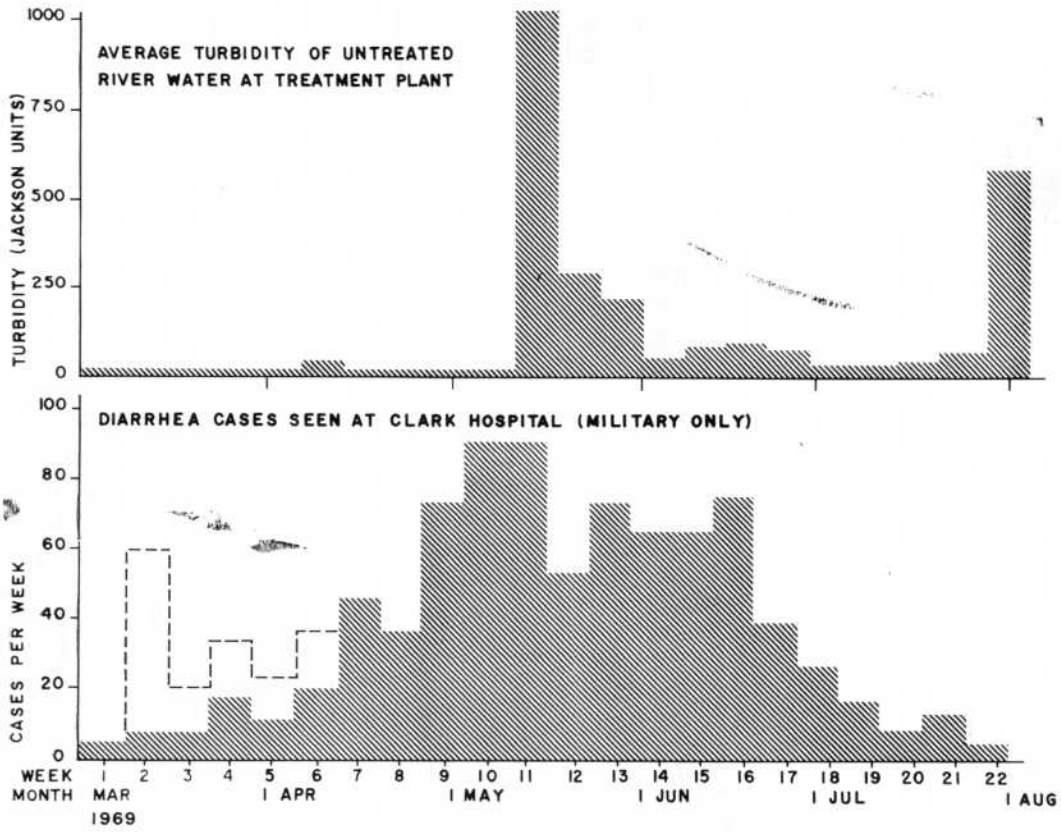

FIGURE 2. Number of diarrhea cases in enlisted military personnel seen at Clark Hospital, March through July, 1969, compared with turbidity of untreated river water. In the lower graph, the *shaded area* shows the date of onset of diarrhea for cases who filled out questionnaires. – – –, indicates the date of first clinic visit for those who did not fill out questionnaires.

ent, the epidemics beginning at about the time of the spring-summer rainy season, but waning before the period of heaviest rainfall. The period of the epidemic is the hottest time of the year, as shown in figure 3, and the epidemic curve rises and falls more in synchrony with the average daily maximum temperature than with the rainfall. High turbidity of the incoming river water at the treatment plant (figure 2), used as an indicator of rainfall over the watershed, occurred after the periods of highest incidence. Relative humidity, although not shown in the figures, closely paralleled the rainfall.

Geographic distribution of cases. Of enlisted military clinic cases, 331 lived off base and 522 on base. Using the official figure of 65 per cent of the base's total complement of 16,759 men quartered on base to calculate denominators, the attack rates were 5.6 per cent off base and 4.8 per cent on base. Since a number of men actually live "unofficially" off base, the real ratios probably were even more similar. In the Work Area Study 60 per cent of 185 men with diarrhea and 57 per cent of 288 unaffected men lived on base, again an insignificant difference. In the Family Study the overall attack rate was 6.8 per cent per two-week period off base and 9.9 per cent on base of 1824 person-fortnights evaluated, the difference being statistically significant at the 95 per cent level. However, this difference is primarily due to the lower incidence in women and children (6.9 per cent per PFN) off

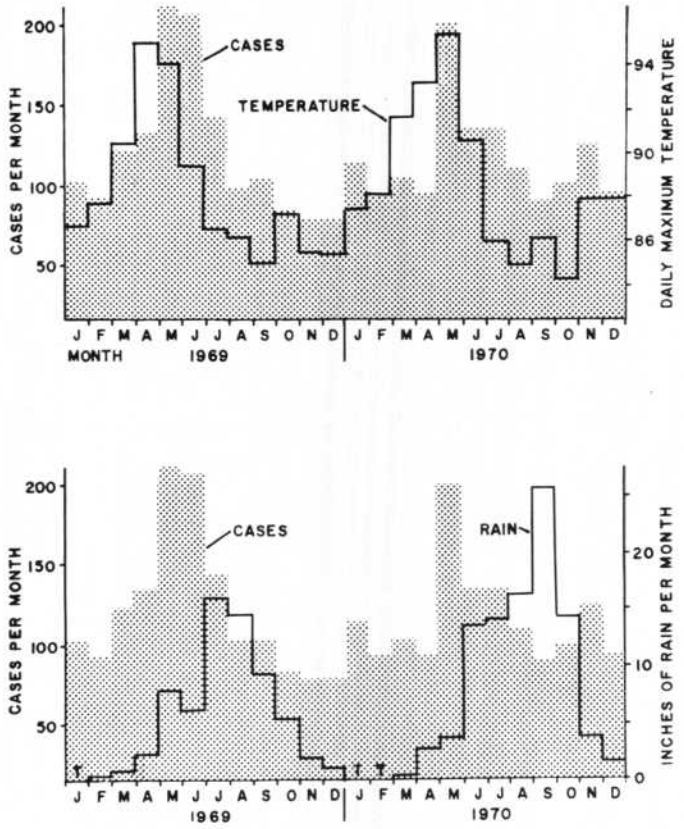

FIGURE 3. Cases of diarrhea seen in Clark Hospital Emergency Room in 1969 and 1970, compared with monthly rainfall and average daily maximum temperature. *T*, trace, or less than measurable amount of rainfall.

base than on (11 per cent), and may simply reflect the fact that many of the wives of men living off base are Filipino. Local Filipinos had a much lower attack rate than Americans.

The average time of onset for 446 clinic cases living off base and 532 quartered on base differed by less than one day, and the general time of appearance of cases both on and off base and in various buildings seemed quite random. Cases of diarrhea were scattered uniformly throughout the major barracks areas on base, and pin maps made for place of work and residence did not disclose any significant localization of cases. By dividing the number of enlisted military clinic cases living in an area by the number of officially registered housing units in the area, an index of attack rates was obtained for 32 off-base housing subdivisions. Unusually high rates were found in several areas near the main gate of the base, but these are thought to be areas where large numbers of men live in unregistered housing, thus yielding a falsely low denominator for calculating rates. The rates in the remainder of the areas were quite uniform, and areas several miles from the base (figure 1) did not have a significantly lower incidence of diarrhea.

Age, sex and race. The incidence of diarrhea in various categories of family members is shown in table 2. Essentially all heads of household were male military personnel and spouses were female. The higher incidence among women in the family study must be interpreted with the knowledge that women usually were the ones to complete

TABLE 2

Incidence of diarrhea in household members during the 1969 epidemic as determined from questionnaires in the Family Study

Household members	No. of questionnaires	% with diarrhea in previous 2 weeks
Heads of household	383	11
Spouse	395	19
Children		
0–4 yr	150	7
5–9 yr	269	11
10–14 yr	270	7
15–19 yr	159	9
	848	9
Domestic servants	290	2
Total	1916	10

the questionnaires for the entire family and hence were more likely to report minor episodes of diarrhea for themselves than for their husbands. In the Clinical Study Group, men were disproportionately represented, possibly because access to hospital facilities may be more convenient for military personnel than for dependents. In the Family Study, children of different age groups had similar incidence rates. Overall, the actual incidence was probably very uniform in both sexes and all age groups.

Of the military cases seen at the hospital, 14 per cent were Negroes, and 84 per cent Caucasians. No figures were available for the racial composition of the base population. Negroes comprised only 7 per cent of the Work Area and Barracks Study, but within this study group the incidence of diarrhea was *lower* in Negroes than in Caucasians. It is likely that social factors influenced the accuracy of reporting in different directions in the two groups and that race is not a highly significant factor in determining the incidence of the disease.

The 5800 Filipino civilians working on base rarely reported with diarrhea to the clinic designated to serve them, and among Filipino domestic servants in the Family Study the incidence was 2 per cent of 290 questionnaires as opposed to 11.7 per cent of the 1626 questionnaires for Americans (table 2). The comptroller's office, the only work area studied employing large numbers of Filipino personnel, had an incidence of 10.4 per cent per PFN among American military but only 3.5 per cent among the Filipino civilians. Local adult Filipinos, then, had a significantly lower incidence than did Americans.

Length of stay in the Philippines, previous diarrhea, and rank. With the above evidence of immunity among the local population, one might expect to find a similarly low incidence among Americans with longer residence at Clark, previous attacks of diarrhea at Clark, or many years of service overseas (roughly correlated with increasing rank among Air Force enlisted men), but this was not the case. As shown in table 3, cases were not confined to new arrivals, and the risk of acquiring diarrhea remained nearly the same throughout the 1.5- to 2-year stay. Table 4 shows that previous diarrhea at Clark apparently did not protect

TABLE 3

Date of arrival at Clark of men with and without diarrhea in the 1969 epidemic

Date of arrival at Clark	% of 810 diarrhea cases (Clinical Study)	% of 331 controls (Work Area and Barracks Study)
1966 or before	0.5	0.3
1967	18	18
1968	50	53
1969	32	28

TABLE 4

History of a previous diarrhea attack at Clark in men with and without diarrhea in the 1969 epidemic

Date of previous attack	% of 841 diarrhea cases (Clinical Study)	% of 319 controls (Work Area and Barracks Study)
1966 or before	0.1	
1967	1	1
1968	10	5
1969	5	3
Total (including those not giving date)	22	12

against further attacks and that such patients may even have been more susceptible than others, possibly because of constitutional or genetic factors. The higher ranking Air Force enlisted men have generally had several tours of duty overseas in areas where gastroenteritis is prevalent, but as shown in table 5, rank had no apparent connection with the incidence of diarrhea.

Transmissibility and incubation period. Several indicators of person-to-person transmissibility were available. Comparing diarrhea cases with controls with respect to the size of their families or number of men living in the same barracks room showed no significant difference. In the Family Study 80 families had at least one case of diarrhea of the 150 surveyed. In the 1826 person-fortnights surveyed, 165 cases of diarrhea occurred, a rate of 9.0 per cent. Among 699 PFN in persons living in households where a case had occurred one or more days previously during the study, the secondary attack rate was 10.3 per cent, the difference between the two figures being less than one standard error ($p > 32$ per cent). If cases occurring on the same day as the primary case are included, the secondary attack rate becomes 12.2 per cent and the difference between this and the primary attack rate is significant at the 1.8 per cent level, suggesting that some clustering of cases in households did occur, but not sequential transmission from person to person. The identity of the first case in affected families (man, women or child) simply reflected the composition of the population, indicating that no one group was bringing the disease home to others in the household.

TABLE 5

Rank of enlisted men with diarrhea in the 1969 epidemic compared with rank of total base enlisted population obtained from personnel records

Rank	% of diarrhea cases (Clinical Study)*	% of estimated population on base†
E1–E4 (airman basic, sergeant)	57	57.5
E5–E9 (staff sergeant, chief master sergeant)	43	42.5

* Total number of men, 796.

† Estimated population, 16,800.

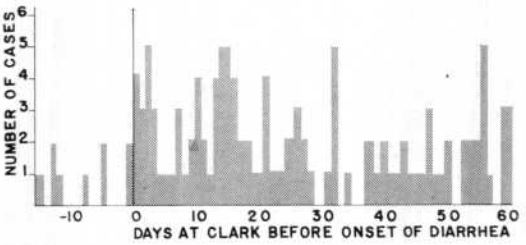

FIGURE 4. Days spent at Clark Air Base prior to onset of diarrhea for military personnel and dependents arriving from the U.S. and having onset of diarrhea within 60 days of arrival. The cases were seen in diarrhea clinic at Clark Hospital, March through July, 1969. Those with diarrhea prior to arrival at Clark are shown to the left of zero on the horizontal axis.

Although the apparent lack of secondary cases excludes the determination of the incubation period in families, data on the length of stay at Clark before acquiring diarrhea are available (figure 4). The picture is blurred by a few cases acquired before arrival at the base, represented in figure 4 to the left of zero on the horizontal axis, but it appears likely that the incubation period is quite short, probably no more than a day or two.

Travel, meals and beverages. Personnel stationed at Clark travel a great deal, and it was found that 48 per cent of 363 healthy men had made trips within the previous three months to other parts of the Philippines, Southeast Asia or the U.S. This percentage was not significantly different from the 49 per cent of 874 in the diarrheal group, and there was no significant difference found in the areas visited by the two groups.

There was no difference between diarrheal and control populations with regard to sources of meals as shown in table 6. Unfortunately for epidemiologic purposes, very few of the men ate at only one dining hall, but among those who did, no one dining facility was disproportionately represented.

The number of meals taken off base (mostly in Angeles City), also shown in table 6, did not seem to be of significance.

Specific questions were asked about beverages, with the results for water shown in table 7 by way of example. Similarly detailed data showed no meaningful difference between control and diarrhea cases among military men in the two prospective studies with regard to consumption of soft drinks, milk, or locally made beer.

Comparison with diarrheas elsewhere in the Philippines and Southeast Asia. Air Force figures for the previous 1.5 to 2.5 years for gastrointestinal visits to Air Force clinics at various bases in the Philippines and Southeast Asia were not adequate to exclude a seasonal pattern of diarrhea in these other areas, but did seem to indicate that the Clark epidemics were more sharply localized to a particular time of the year than outbreaks at the other bases.

Incidence figures from the Naval Dispensary at Subic Bay about 30 miles southeast of Clark, which serves about 4000 naval, marine, and retired military personnel, were obtained for April 1966 to May 1969, and demonstrated a yearly rise in diarrhea cases at about the same time as the Clark epidemics, in March through August. Physicians at the dispensary described the diarrhea as usually idiopathic in spite of the routine practice of taking cultures and doing parasitologic exams. Moderate numbers of amebiasis cases and only occasional salmonella and shigella infections were seen.

Cases of gastroenteritis and colitis as reported to the Philippine Government for both Pampanga Province (where Clark is located) and the entire Philippines for 1966–1969 show definite peaks in May through August, corresponding in time of onset to the Clark epidemics but lasting later into the summer. No information is available on the nature of these cases or on the reliability of reporting, but presumably many salmonella, shigella and enteropathogenic *E. coli* infections are included.

Environmental factors. In a seasonal epidemic of this magnitude and widespread distribution, attention naturally focuses on the water and food supplies and some thought must be given to possible arthropod vectors.

Approximately 3,300,000 gallons of water per day are provided to the base by the Sacobia River, and 2,200,000 gallons by a series of wells on base (figure 1). The river, really a large stream, originates about 9.5 miles from the base on the slopes of 5650-foot Mt. Pinatubo, and, as disclosed by personal inspection from a helicopter, flows in a deep ravine through forests nearly uninhabited by man, the only exceptions being a few small Filipino gardens at some distance from the streambed and, 7 miles up-

TABLE 6

Source of meals for preceding two weeks of men with and without diarrhea in the 1969 epidemic

Source of meals	% of 808 diarrhea cases (Clinical Study)	% of 316 controls (Work Area and Barracks Study)
All meals on base	20	18
Most but not all meals on base	40	40
All meals at home	3	1
Most but not all meals at home	33	33
Most meals not at home or on base	8	9
Meals off base and outside of military homes		
None	56	51
1 or 2	25	22
>2	20	27

TABLE 7

Amount of water consumed in the preceding two weeks by men with and without diarrhea in the 1969 epidemic*

Water consumed in preceding two weeks (glasses per day)	% of 874 diarrhea cases (Clinical Study)	% of 395 controls (Work Area and Barracks Study)
None	5	4
1	15	12
2	21	22
3	23	24
4–6	24	26
>6	12	10

* Including iced tea, Kool-Aid.

stream, the Jungle Survival School run by the base.

The river bed is sandy and the water, particularly during rains, picks up large amounts of silt. This is removed to some extent by a series of baffles at the water inlet, 1.5 miles above the base, whence the water travels to the treatment plant through pipes. Treatment is carried out on base by settling, flocculation, sand filtration, and chlorination before distribution to several storage tanks. The process is monitored by a small laboratory at the treatment plant and records of volumes, pH, residual chlorine, chemicals added, and chemical analyses are maintained.

Water from the wells is chlorinated separately from the river water and pumped to storage tanks without further treatment. A single distribution system is fed by the two water sources and an unknown amount of mixing of well and river water occurs before it flows from the tap. The general tendencies are that the eastern half of the base receives more well water, the western half more river water.

Of the five work and two barracks areas in the prospective survey (figure 1), the two westernmost areas would be expected to receive a higher proportion of river water from the tap than would the four to the east. The incidence of diarrhea during the eight weeks of the study was higher in the two western areas (14.9 per cent versus 10.6 per cent per person-fortnight) than in the others, with the area in the middle being 10.4 per cent. The difference is 3.1 times its standard error ($p = .002$), but other nonrandom errors in the sample may have contributed.

Homes off base are supplied with water of uncertain bacteriologic quality from the Angeles City water system, but most off-base families obtain their drinking water from the base system in 5-gallon carboys, which are filled from taps at several points on base.

During the epidemic, on May 14 and 15, heavy rainfall occurred both on base and in the watershed, causing such an excess of sediment in the river water that it emerged from taps on base with the appearance of dilute skim milk. The turbidity of the incoming water at the treatment plant was over 5000 Jackson units rather than the usual 10 to 20, and of the treated water, 175, as opposed to the usual figure of 5 units. However as seen in figure 2, the incidence of diarrhea, rather than rising after this event, tended to dwindle somewhat. Apart from the gross increase of solids in the water, no significant chemical or bacterial contaminants were detected in samples of tap water taken on the day of highest turbidity.

Between March 3 and June 30, 204 cultures of base tap water at widely scattered sampling points were made. All were negative for coliform bacteria, although untreated river water occasionally contained *E. coli*. The combined residual chlorine, as measured daily with orthotolidine in treated river water, was always between 2.0 and 6.0 parts per million. The pH of raw river water was usually 8.0–9.0 and of treated water 7.4–9.2, not significantly different from the pH at other seasons of the year.

During the epidemic 10 samples of both raw and treated water were sent to the Environmental Health Laboratory at McClellan Air Force Base in California for complete chemical water analysis, and no significant deviations from the USPHS Drinking Water Standards (17) were found, other than a high turbidity in the untreated water.

Almost all food eaten by Americans attached to the base is either sold through the commissary or consumed in base dining facilities. Incoming food, whether purchased in the Philippines or imported, is inspected by the Base Veterinary Department. All meat, frozen foods, canned and packaged goods, and a large proportion of the fruits and vegetables come from the U.S. At suitable seasons fresh fruits and vegetables are purchased from Filipino farms approved by the Veterinary Department. The most important of these local purchases in cost and volume, and *a priori* perhaps the suspect, is

lettuce. Figures were obtained for lettuce purchased and it was found that the months of the epidemic did not coincide with the largest purchases or with any change in the source of lettuce. Further, purchases were made from different sources at different times for sale in the commissary (primarily to families) and for use in the base dining halls (restricted to military personnel). Hence, if one source of lettuce had been involved in the epidemic, differences should have been seen in the two populations, and this was not the case.

There are seven main dining facilities and four large clubs serving military personnel. Approximately 20 snackbars and cafeterias run by the post exchanges are also spread over the base. All of these are inspected by the Base Veterinary Department. In talking with the food inspectors and visiting various facilities on base, it was apparent that refrigeration problems in the kitchens are chronic during the hot season (April and May) and that a number of unsatisfactory conditions were being uncovered by inspections. However, in view of our inability to connect diarrheal illness with any one food facility, this had to be regarded as a potential hazard, but probably not the cause of the great majority of diarrhea cases which occurred.

According to a survey conducted in 1964–1965 (18) maximum mosquito populations occur in the May-June-July season, the predominant species being *Culex tritaeniorhynchus summorosus*. Four light traps are operated routinely on the base and the total numbers of mosquitoes caught are recorded. In 1969 the number of mosquitoes was considerably greater in March and in June than in April and May, in contrast to the number of diarrhea cases. This does not mean, however, that figures for an individual species would be accurately represented by the total for all species over the whole season.

No counts were performed on the fly population, but by personal observation at the time of the study, flies were not numerous enough to constitute a significant nuisance, or to be particularly evident either on base or off base.

In the Work Area and Barracks Study, Americans working in air-conditioned buildings completed 650 forms and those without air conditioning 1521. The incidence of diarrhea (11.7 and 13.2 per cent per PFN) differed by less than one standard error in the two groups.

Discussion

The majority of diarrhea cases worldwide have no detectable cause by present methods (1–8), and the Clark epidemics appear to be almost a pure example of such an illness. Several different patterns of "diarrhea of unknown cause" have been described in the literature, none of which typifies the Clark experience.

"Travellers' diarrhea," at least some of which is due to *E. coli* pathogenic for adults (19), occurs in aliens soon after arrival in a new area (20, 21). The epidemics at Clark resemble "travellers' diarrhea" in their prevalence among aliens, but not in their uniform incidence during the two-year tour of duty.

"Nonbacterial gastroenteritis," shown by Gordon and others to be transmitted to human volunteers by a filtrable agent, occurred in New York, Cleveland, and in many parts of Japan in 1946–1955 (22–28). In a New York mental institution transmission of this disease appeared to be from person to person by the fecal-oral route (22), whereas data from an epidemic in Hokkaido seemed to point to an iced confection sold at athletic meets as the common source (27). The term "nonbacterial gastroenteritis" might be applied to the Clark epidemics if the disease is viewed as endemic in the local population and epidemic in Americans. Transmissibility to human volunteers, one of the principal characteristics of "nonbacterial gastroenteritis," has yet to be established with the Clark material, however.

"Winter vomiting disease" (29) is characterized by its brief course, a high incidence of vomiting, often with diarrhea, and high

person-to-person transmissibility, usually occurring in the winter season. It has recently been transmitted to human volunteers by filtered stool suspensions (30). Several of these features distinguish it clearly from the Clark epidemics.

Numerous other reports have been published on diarrhea outbreaks of unknown cause, some related to contaminated water (6–8) and some to eating clams or oysters (31, 32). At least one waterborne epidemic had a high rate of secondary person-to-person spread (6).

Prolonged diarrhea may follow acute gastroenteritis due to *Giardia lamblia* (33, 34) or *Capillaria philippinensis* (35). We believe that the absence of Giardia in acute stools, our failure to find it in eight (frozen) jejunal fluids, and its absence on special staining of jejunal biopsies in 11 patients essentially rules out this organism. Further, although waterborne Giardia epidemics have been reported (33), they are not described as temperature-related and are more connected with breaches in sanitary practice such as broken sewer and water lines than with season. The endemic area of human *C. philippinensis* infection is only a few hours drive to the north of Clark. Capillaria ova have not been seen in any stools examined at Clark however, despite careful search with this organism in mind, and it is most unlikely that the characteristic ova would have been missed.

As will be described in detail elsewhere (15), laboratory studies for most other known causes of diarrhea were essentially negative in the Clark epidemic. The common enteropathogenic bacteria were found in only three of 55 cases and noncholera vibrios in none. The parasites seen might be found in almost any healthy population. Serologic identity could only rarely be demonstrated among strains of *E. coli* from different patients, and no enterotoxin-producing *E. coli* were found. Viral studies did not reveal a likely causative agent. Transmission to human volunteers has not been conclusively demonstrated in spite of administration of six patients' stools to 34 volunteers, definite diarrhea having occurred in only one case. In view of these findings, it is reasonable to hypothesize that an unusual or entirely unknown agent is responsible for the epidemic. The rest of the discussion will center on its possible characteristics as indicated by the epidemiologic data.

The generalized distribution of cases both on and off base indicates either that a source common to nearly every American in the area must be involved or that the disease is transmitted rapidly from person to person. If the epidemic is propagated by a common source such as water, the prolonged epidemic curve indicates continuous or repeated exposure, since a long and variable incubation period is ruled out by the recent arrival on base of many of the cases.

The similar incidence in men, women and children, with random distribution of first cases in the family among these three groups, means that the acquisition of the illness is not work-related or school-related. It is probable, therefore, that it is acquired in family homes and barracks with at least as high a frequency as at work or school.

The seasonal pattern of the illness, corresponding to the period of maximum temperature and preceding the period of heavy rainfall, may indicate involvement of a temperature-sensitive causative agent or vector. Philbrook and Gordon, in a review of diarrheal disease among American troops during World War II (10), suggest that it is largely a tropical disease rather than one of temperate and polar climates. Their figures for North Africa and Middle East (necessarily lumping together diarrheas of known and unknown cause, but undoubtedly including a high percentage of the latter) show a definite peak in the hot season. The high incidence in these two relatively dry, thinly populated areas suggests that neither rainfall nor density of the local population plays an essential role. High temperature then may be the important factor, as is apparently the case at Clark, where the temperature curve essentially parallels the in-

cidence of diarrhea. The data indicating a similar incidence of diarrhea in air-conditioned and non-air-conditioned buildings show that the effect of temperature is probably not directly on the host but on an environmental factor such as water, food, arthropods, etc.

The water supply is *a priori* a possible vehicle for the illness. The distribution of cases, which showed only a modest difference between the two sides of the base, would still be consistent with river water being the source, because of the interconnections between the two systems. The water supply as a vehicle would account for the cases off base, since most families obtain their drinking water from the base supply. One would expect a later onset off base, since most families have two water carboys, keeping one for current use and the other in reserve, consuming their water perhaps several days after it is drawn from a tap on the base. This was not the case, however; the difference in average date of onset on and off base was less than a day.

The failure to correlate incidence of diarrhea with intake of various beverages seems fairly strong evidence against a water-, milk-, or bottled-beverage-borne epidemic unless items consumed "in the past two weeks" do not reflect accurately the single ingestion possibly required for infection, or the incidence of disease is not highly dose-related—perhaps because host characteristics are more important.

The lack of significance of the place where meals were taken and the similar attack rates in both men and dependents make food an unlikely source. It is difficult to imagine an item of food carrying a microorganism which would reach such a large population so randomly over such a long period of time, and exactly at the same season each year.

The widespread, nearly random distribution of the illness, with a peak incidence in the hot season and lack of person-to-person transmission would be in accord with mosquito-borne illness, the main counterargument being that no gastrointestinal illness has been shown to be carried by such an insect. However, agents of other enteric diseases (e.g., salmonellosis and viral hepatitis) do circulate in the blood, and the hypothesis that Australia-antigen-positive hepatitis is transmitted by mosquitoes is currently being investigated (36). Perhaps attempts to transmit the Clark illness by transfer of serum would not be unreasonable.

The failure to find an elevated secondary attack rate in the family study may indicate that the disease is not transmitted from person to person. On the other hand if one assumed rapid and universal infection, with a high percentage of asymptomatic cases, the same pattern might result. With a very rapidly spreading agent one might not see progression of disease from group to group on base, but the length of the Clark epidemic indicates that infection is *not* occurring rapidly, and makes this hypothesis seem unlikely. It is hard to see how an illness could be contagious enough to affect people living nine miles apart synchronously and still take five months to run its course in this same population. It seems probable therefore that, if person-to-person transmission occurs at all, another mode of transmission—perhaps the water supply—participates in the initiation of the epidemic.

Our data on rainfall and turbidity of the water supply are sufficient to set aside any simple theory of washdown of contaminants from the watershed by the first rains of the season, since the epidemic was already in progress before the rains began. Our tentative hypothesis is that the epidemic was caused by something in the water of the Sacobia River, that high temperature is necessary for development of the infectious or toxic agent, that it is chlorine-resistant, able to subsist in water of pH 8–9 and originates in a watershed nearly uninhabited by man. This would explain the widespread almost simultaneous distribution of the disease, the subsidence of the epidemic with the dilution of the river water by the heavy

rains, and the yearly occurrence of the epidemic during the hot season.

From the data at hand one would like to be able to point either to an infectious organism or to a toxin as the cause of the epidemic. An infectious agent would more easily explain the variable and often prolonged course of the illness. The fact that stool specimens have not caused illness in human volunteers could be due to lability of the agent on freezing, or the absence of the agent from centrifuged supernatant fluid. Nontransmissibility within families in the epidemic would have to be due to either 1) low infectivity and good sanitation or 2) universal infection but a low percentage of symptomatic cases. Possible agents range from multicellular parasites to an undescribed pathogenic bacterium or virus.

A chemical or biologic toxin would be more compatible with the apparently short incubation period, and with nontransmissibility of the disease. Considering the negative chemical analysis of the water, there is no evidence for poisoning by a simple inorganic compound. If a toxin is responsible, the variable length of illness means that self-propagating changes in the bacterial intestinal flora and/or the intestinal wall would have to occur in some cases or (if one presumes the toxin to be present over a long period of time) that most cases recover by some adjustment affording temporary immunity.

As a source of toxin, fresh water algae might be considered. Several blue-green algae growing on lakes and ponds are known to cause fatal poisoning in animals (37) and epidemics of gastroenteritis in humans have been circumstantially connected with heavy growth of algae in water sources (38, 39). Such growth would be closely connected with high temperatures and sunlight. Although in cases so far reported, the growth of algae has been heavy and the water has been noticeably altered in odor and taste, it is conceivable that not all toxic species have been described, and that special conditions at Clark favor the growth of one of these.

Since neither a toxin nor any known pathogenic infectious agent easily explains all of the data, bacteriophage might form the basis for another speculative hypothesis. A phage might grow in bacteria found in the river; *E. coli*, for example, are occasionally cultured from the untreated river water. Production of vegetative phage is, at least with some phages, dependent on temperature (40), and one might expect higher titers to be produced in the hot season. It is conceivable that some phages are chlorine-resistant and could survive in the base water system. Once ingested, a large amount of phage might lyse susceptible enteric bacteria, releasing toxins and causing temporary gastrointestinal and constitutional symptoms. The phage could either be eliminated in a few days or set up lysogenic infection, lysing only part of the bacteria infected and producing continued symptoms (or no symptoms) until finally eliminated, perhaps months later, by a change in intestinal ecology. The effects of phage would be highly dependent on the strains of bacteria resident in the gut and might even stimulate humoral immunity after repeated infection, either mechanism being adequate to explain the resistance of adult Filipinos to its effects.

Conclusion

Taking all of the evidence together, we conclude that the Clark diarrhea epidemics are probably waterborne. The epidemiologic data stand against person-to-person transmission unless infection is universal and usually asymptomatic. Other than the seasonal pattern there is little evidence for or against mosquito transmission. Foodborne transmission does not seem likely.

Although neither the epidemiologic data nor extensive microbiologic studies have produced clear evidence of the nature of the agent involved, the suggestion is offered that high temperatures may affect the concentration of either a toxin or an infectious organism in the water of the Sacobia River. The hypothetical models of toxin-producing al-

gae and bacteriophage are discussed. Although neither hypothesis is put forward with a great amount of conviction, neither conflicts with the evidence at hand, and both offer possibilities for experimental verification.

The epidemics at Clark appear to offer a unique opportunity for study of acute diarrhea of unknown cause. Their predictable recurrence, the large number of cases in adults under good hygienic conditions, and the structured military setting offer unusual advantages for research. It is likely that knowledge gained at Clark will be applicable in other areas, where complex extraneous factors, such as the presence of large numbers of enteroviruses, may make studies more difficult.

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