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EPIDEMIOLOGY, DIAGNOSIS, AND IMPACT OF SHIGA DYSENTERY IN CENTRAL AMERICA

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PESTILENCES, with wars and famines, have decimated mankind throughout the centuries. Some of them such as smallpox, cholera and dysentery were adequately described long ago solely on clinical grounds, thus providing a historical record for the present. The fearful attitude toward pestilence that has existed for millenia has changed during this century to overconfidence that such scourges will not strike again. But the present cholera pandemic, the recent Central American epidemic of Shiga dysentery, and the outbreak of typhoid in Mexico are clear indications that as long as poverty, malnutrition and low sanitation remain as components of the ecosystem of many nations, diseases like those will reappear to threaten society.

Shiga dysentery, long-forgotten, occurred in a series of village outbreaks in the eastern part of Guatemala bordering on Mexico during the end of 1968 and the beginning of 1969, eventually developing into a regional epidemic which affected seven countries. These outbreaks were very similar one to the other, and were explosive, characteristically affecting persons of all ages, thus suggesting the involvement of an etiologic agent different from those already known in the region.

Clinical Manifestations

Shiga dysentery in Central America was characterized by abrupt diarrhea that within 24 to 48 hours contained pus, blood and mucus. A few patients recovered in one or two days; others underwent an acute and often fulminant course; while still others remained chronically ill for months. The clinical manifestations observed in outbreaks are illustrated in Table 1.[21] Abdominal pain, cramps, bloody diarrhea, fever, and tenesmus were present in most severe cases. When dysentery became established, intestinal discharges consisted almost wholly of mucus, pus, and red blood which appeared in spots, striae or large masses (like "red currant jelly"). Later, bowel discharges appeared less mucoid, more liquid and purulent, and with a dull red color. Stools were passed at frequent intervals, were odorless and of small volume, as classically described by Manson-Bahr.[19] Neurological and joint manifestations were not recorded in this epidemic. Chronic cases, particularly in adults, were characterized by recurrent diarrhea with malabsorption, flatulence, abdominal distention, loose foul stools, weakness, and occasionally emaciation and malnutrition. The case fatality rate ranged from eight to 15 percent.[11] Death could occur within a few days or weeks after onset and on occasion was sudden. Cause of death has been ascribed to dehydration and exhaustion. However, bowel discharges were not as voluminous as in cholera, food poisoning, and other varieties of diarrhea. Malnutrition undoubtedly played a role since

most autopsy cases revealed overt malnutrition in a rate in excess of the usual prevalence in the area.[5] The profound signs of toxicosis and exhaustion and the intense pain and tenesmus exhibited by some patients were striking. Rapid improvement was observed shortly after administration of an effective antibiotic.[11, 21]

Table 1

CLINICAL MANIFESTATIONS RECORDED IN THREE GUATEMALAN VILLAGES, 1969

	Persons	
	With diarrhea n = 356	*Without diarrhea n = 206*
Abdominal pain	302 (85)*	28 (14)*
Cramps	259 (73)	6 (3)
Blood and mucus	250 (70)	0
Fever	219 (61)	12 (6)
Tenesmus and/or rectal pain	190 (53)	0
Vomiting	109 (31)	4 (2)
Stools in 24 hours		
10 to 40 or more	177 (50)	0
4 to 9	143 (40)	5 (2)
less than 4	36 (10)	201 (98)

*Percentage in parentheses

Etiology and Diagnosis

The organism responsible for the Central American epidemic is a virulent strain of *Shigella dysenteriae* 1 (Shiga bacillus).[21] Study of more than 200 strains isolated from four Central American countries revealed that their biochemical properties are identical to those of the original Shiga-Krüse bacillus.[21, 24] Nevertheless, the Central American epidemic strains differ in that they possess the multiple drug resistance factor (Table 2) first discovered in Japan in the '50's.[34] The *in vitro* resistance to drugs correlates with clinical behavior. The responsible episome is transferable *in vitro* to receptor *Escherichia coli* strains and to other enterobacteriaceae.[13] Recently it has been found in *Salmonella typhi* strains causing the serious typhoid epidemic in Mexico,[1] as well as in other *Shigella* serotypes that exhibit an unusual virulence.[13] The epidemic strains of *Shigella dysenteriae* 1 are not readily isolated from SS agar, a characteristic that seems related also to the drug-resistance episome.[33] The organism is easily isolated when MacConkey or Tergitol-7 with triphenyl tetrazolium chloride (T7T) are used; approximately two-thirds of all isolations can be made from T7T agar.[21, 24]

The severe clinical manifestations of the disease, the failure of therapy with sulfonamides, chloramphenicol, and tetracyclines, and the problems regarding isolation of the epidemic strain on the traditional agar media, were factors that interfered with the establishment of an accurate diagnosis of the epidemic during the first nine months when the toll had been approximately 5,600 deaths.[24] Diagnosis was complicated because macrophages, leukocytes and other cells in the stools were often confused with amebae by public health laboratories, a mistake for which warnings had been issued in the past.[19] This particular situation was further aggravated by the knowledge of an existing high prevalence (30 percent overall) of *Entamoeba histolytica* in the Central American population.[24] Trophozoites could be expelled during the early phase of diarrhea in the shigellosis, although they were rarely found when dysentery was established.[21, 24] The epidemic was diagnosed as "amebiasis" or "amebiasis complicated with a viral agent."

Table 2

CHARACTERISTICS OF CENTRAL AMERICAN STRAINS OF THE SHIGA BACILLUS, 1969-1971

	Number of Strains	
	Tested	*With characteristic*
Non-fermenting xylose, rhamnose, mannitol, raffinose, sorbitol, and dulcitol; splitting glycerol	180	180
Agglutination with Shiga bacillus' serum	250	250
Penetration in guinea pig's conjunctiva	21	21
Enterotoxin production	6	6
Resistance to chloramphenicol, tetracyclines, streptomycin and sulfathiazole	180	180
Sensitivity to ampicillin, nalidixic acid, colistin, nitrofurantoin, trimethoprim-sulfamethoxazole	205	205

Once the observer becomes familiar with the disease, diagnosis is suspected on epidemiologic and clinical grounds, and is readily confirmed by isolation of the organism and demonstration of leukocytes, macrophages, and epithelial cells in the intestinal discharges. Isolation is not hard when the proper media are used and if plating is done at the bedside of the patient. The concentration of *shigellae* is of the order of 10^7 to 10^9 per gram of feces.[22]

Investigation of passive hemagglutinating antibody to the Shiga "O" polysaccharides[3, 4] is diagnostic because approximately 80 percent of the acute cases develop significant titers by the eighth to tenth day after onset. Antibodies appear to be IgM in view of their rapid rise (four to eight days) and fall (three to six months) (Figure 1), and their sensitivity to mercaptoethanol.[4, 24] These antibodies may not be related to actual immunity, but nevertheless have considerable value, particularly for the study of epidemics and for serosurveys in the general population.[4, 24, 26]

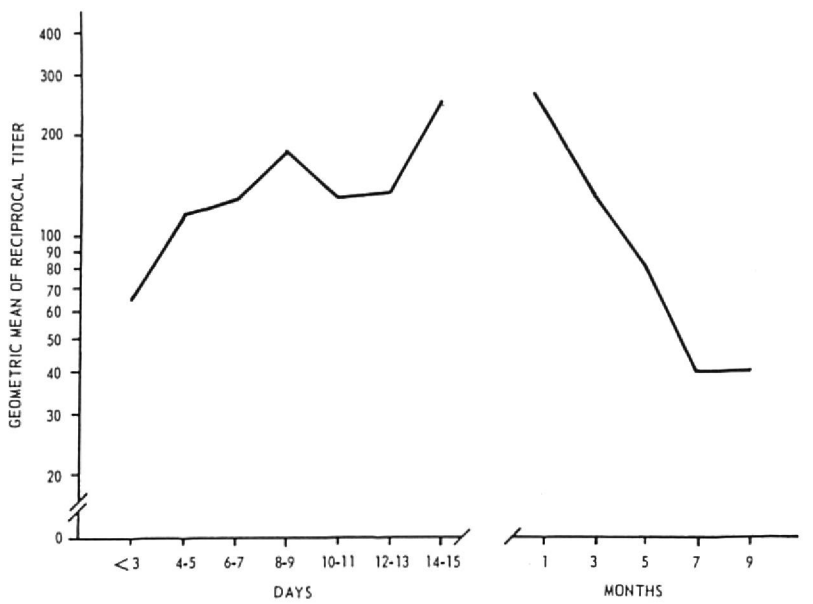

Figure 1—Indirect hemagglutinating antibody titers (geometric mean) to the Shiga Bacillus' "O" polisaccharide. Antibodies appear in significant titers soon after onset; maximum levels are observed within two weeks of onset; antibodies begin to fall three months after.[4]

Pathology

Extensive damage to the intestinal mucosa was common.[5, 21] In post-mortem specimens, the lesion often involved the whole colonic mucosa and occasionally the terminal ileum; in very rare cases other segments of the small intestine were affected.[5] The primary lesion consisted of whitish nodules of a few millimeters in diameter surrounded by a congested halo of hyperplastic lymphoid tissue.[5] Later, extensive edema, congestion and ulceration became evident (Figure 2). The advanced colonic lesion showed varying degrees of coagulation necrosis of the mucosa, extending sometimes to the submucosa. Toxic megacolon was noted in five percent of autopsy cases, and in these, the inflammatory process involved the muscularis mucosae with varying degrees of destruction of the plexus. Fibrin thrombi were present in veins and arterioles of the submucosa and lamina propria in almost all cases with severe colonic involvement. The most frequent complications were thromboembolism, cortical necrosis and toxic megacolon. Disseminated intravascular coagulation was discovered in 24 percent of the cases (Figure 3), with lesions in kidneys, adrenals, pancreas and liver.[5] Proctoscopic examination revealed an inflamed mucosa persisting after disappearance of dysentery.

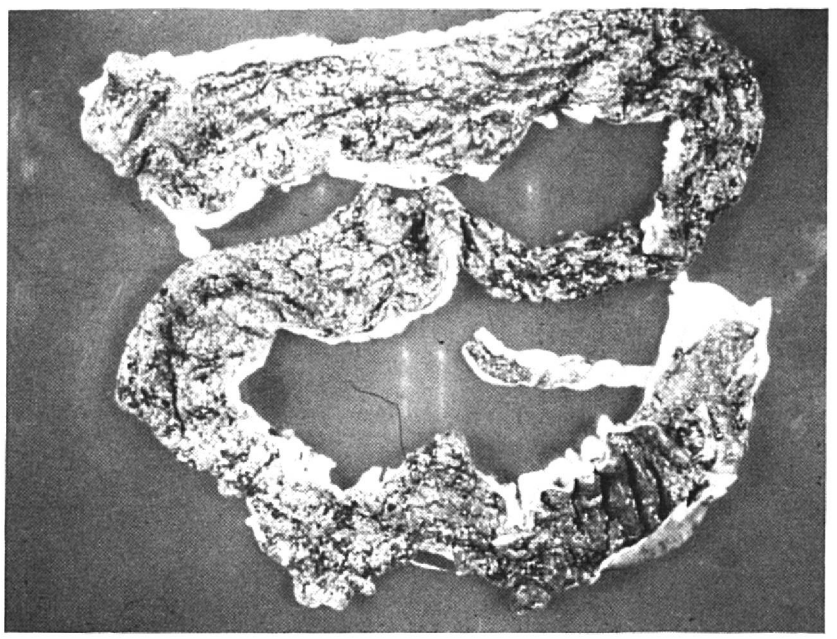

Figure 2—Terminal small intestine, appendix, and colon showing extensive confluent hemorrhagic necrosis and ulcerations. Note that no sector of the mucosa remains intact.[5]

The pathogenesis of the disease has been explained on the basis of the capacity of virulent organisms to penetrate and replicate in the intestinal mucosa.[10, 14] However, the finding of an enterotoxin of *S. dysenteriae* 1 presents a new complication to the understanding of the pathogenesis.[15, 16] The role of the toxin deserves serious scrutiny, particularly for its possible implications in disease prevention.

Mortality

The case fatality rate for untreated village patients was 8.4 percent and ten to 15 percent for severe hospitalized cases.[11] These figures were for the first epidemic year and resulted in part from inadequate knowledge of disease causation, use of inappropriate antibiotics, and administration of emetin and other antiamebic drugs. Shortly after the etiology was established and the medical community accepted the new concept, the case fatality rate decreased to one percent in treatment centers.[11, 21] At

this point, 5,600 deaths had been recorded. Sex differences were not evident by age group; mortality was greater among children under five (estimated 630 per 100,000) and adults over 44 years of age (estimated 359 per 100,000).[26] No deaths were recorded in breast fed infants under six months. The profile of death rates for dysentery in Guatemala in the '60's, (Figure 4) reveals a distinct increase during the epidemic season.[26] Although diarrhea mortality was much in excess of expectation in many communities (as illustrated in Figure 5), the crude mortality rate for the whole of Guatemala did not increase remarkably as a result of the epidemic. However, the fact that this disease attacked persons of all ages, resulting in significant mortalities for adolescents, adults and elderly people cannot be neglected, although an assessment of the impact on these age groups was not made.

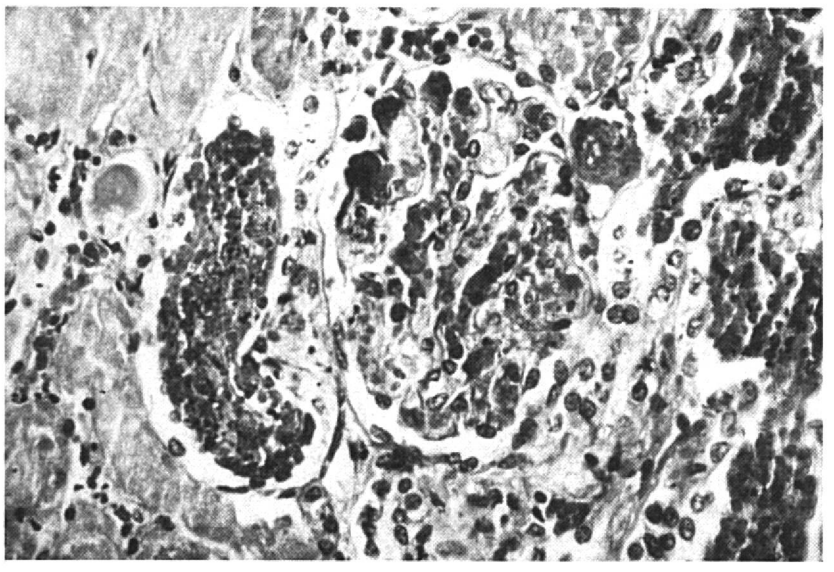

Figure 3—Section of kidney showing fibrin thrombi in afferent and interlobular arterioles. Hematoxylin-eosin, 250 x.[5]

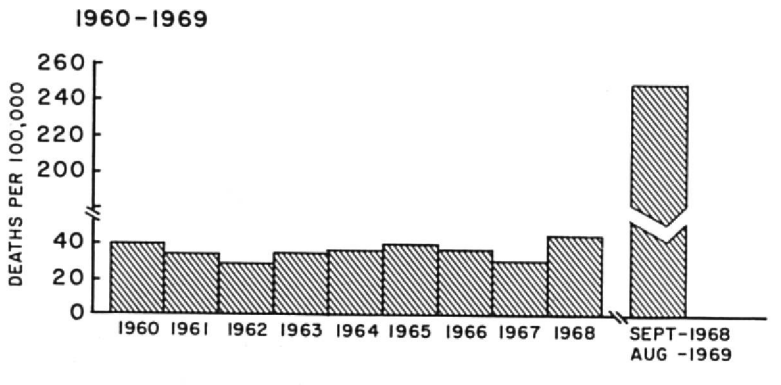

Figure 4—Mortality rates for dysentery, Guatemala 1960-69. Note a five-fold increase during the first epidemic year.[26]

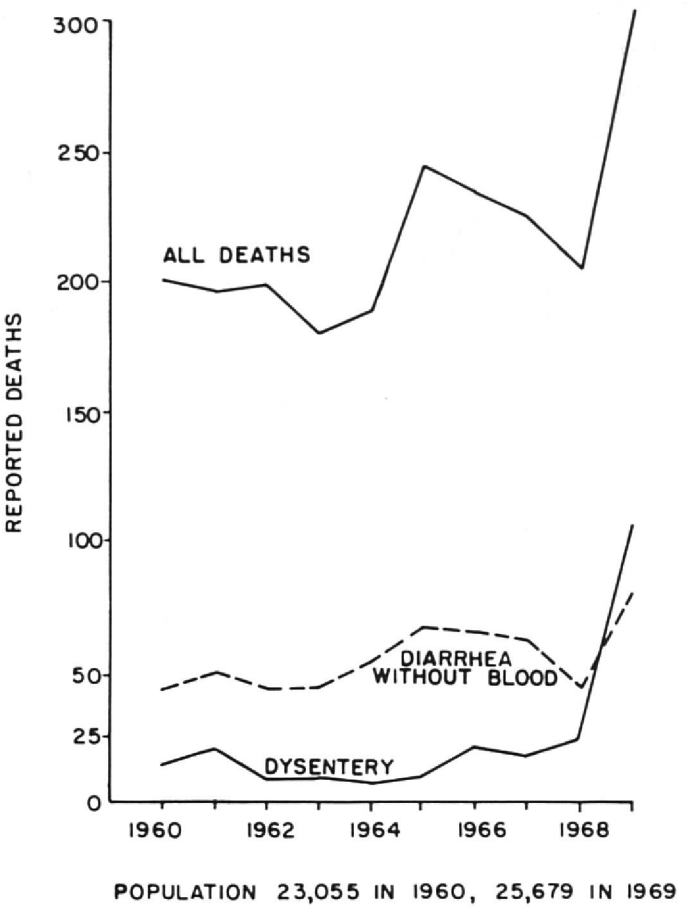

Figure 5—Mortality by all causes, diarrhea, and dysentery in the Municipality of Gualán, Guatemala, 1960-69. Note the increase in deaths by dysentery and the corresponding peak in total mortality during 1968-69. The excess in total deaths during 1965-66 was due to other factors.

Treatment and Prevention

The severe systemic manifestations and necrosis of the intestinal mucosa, as well as the elevated case fatality, demand prompt antimicrobial therapy in appropriate dosage to arrest bacterial metabolism. A good clinical correlation with the *in vitro* results of drug sensitivity has been observed. Complete failure was obtained when sulfonamides, chloramphenicol or tetracyclines were instituted.[11, 21] Several Central American workers confirmed the effectiveness of ampicillin, nalidixic acid, collistin, nitrofurantoin and trimethoprim-sulphamethoxazole.[8, 24, 28, 30] The last combination of drugs provides the most effective results, but considering cost and effectiveness, nalidixic acid becomes the drug of choice.[24, 28] In remote rural areas fortuitous circumstances forced the use of large doses of penicillin which proved adequate in approximately two-thirds of cases, a finding in agreement with the *in vitro* tests. [11, 21] Treatment with antibiotics resulted, by itself, in relief of pain and fever, reduction of the number of bowel discharges, and disappearance of blood from the stools within 24 to 72 hours. Patients could

be discharged after one week of antimicrobial therapy. The clinical response to the antibiotic correlated with a partial or total restitution of the colonic microflora which in these patients became profoundly altered.[22] Although hydration is important, particularly in small children, it did not appear as the key aspect in the management of Shiga dysentery.

Adequate vaccines from mutants or hybrids of *flexneri* organisms have been successfully applied to the control of shigellosis in Yugoslavia.[25] However, the effort of several investigators to develop an oral vaccine for Shiga dysentery has not been encouraging.[9, 18] Presently, the only possible avenue for prevention of Shiga dysentery is improvement of personal and environmental hygiene and increase in the availability of water.[12] If proof is finally given that the Shiga bacillus enterotoxin plays a role in the pathogenesis of the disease, then vaccination with a toxoid presents a sound possibility.

Epidemiology

In 1898 the medical literature recorded for the first time the existence of the Shiga bacillus, which caused extensive epidemics in the Far East and Europe.[32] A high mortality was characteristic of outbreaks in Japan in the first decade of this century. A very large epidemic with 3,000 deaths was recorded as early as 1915 in El Salvador.[31]

A change in the relative frequency of *Shigella* serotypes in Europe has been recorded. The Shiga bacillus dominated until 1924, followed by a substitution by *flexneri* serotypes after World War I and another substitution by the *sonnei* group after World War II.[17] While the Shiga bacillus had essentially disappeared from Europe, sporadic isolations in the Middle and Far East and in Central America demonstrated its endemic behavior. Considering the difficulty in isolating the organism, the prevalence of cases and carriers has likely been underestimated. Reports of isolations from Mexico, Guatemala, El Salvador and Honduras confirmed the existence of indigenous endemic foci.[2, 23, 24, 27, 35] Examination of a large collection of serum specimens revealed the existence of individuals with evidence of recent infection with the Shiga bacillus before the regional epidemic occurred in Central America.[23, 26] The prevalence of persons with significant titers was greater in Guatemala, El Salvador and Honduras (see Table 3), countries that later were more affected.

Table 3

PREVALENCE OF HEMAGGLUTINATING ANTIBODIES TO THE SHIGA BACILLUS, 189 RURAL AREAS OF CENTRAL AMERICA, 1965-1967

Country	Number of persons examined	Positive*	
		Number	%
Guatemala	3052	56	1.8
El Salvador	1137	11	1.0
Honduras	1227	5	.4
Nicaragua	1397	12	.9
Costa Rica	2475	6	.2
Panama	2061	13	.6
Total	11346	103	.9

*Titer of 1:40 or greater by the indirect micro-hemagglutination test

The reasons for the exacerbation of the endemic focus and for the rapid and widespread dissemination of the epidemic strain are unknown.[12, 20] The organism has the episome of the multiple resistance to antibiotics. Attempts to link the presence of the episome with an increase in virulence have been unsuccessful; the as yet unrecognized factor (or factors) could well be transferred concomitantly. The development of the epidemic was undoubtedly related to host and environmental characteristics. Poor personal hygiene, malnutrition and crowding, deficient environmental sanitation, scarcity of water, increase in communications stimulated by internal commerce and the Common Market, large migrations from highlands to lowlands for the harvesting of cash crops and a war between two of the countries undoubtedly were contributory factors. A severe drought in 1969 followed by intense rains apparently favored the establishment of common sources of contamination at the community level.[11, 12, 20, 24]

Outbreaks in villages or urban centers were explosive, with the index case usually an adult, and large population sectors were compromised within a few weeks or months. Many outbreaks occurred along the main highways and waterways, the attack rate varying from six to 34 percent.[11] Person-to-person transmission was crucial but some point-epidemics suggested a common vehicle, perhaps water, milk or another food. The velocity with which the epidemic spread throughout Central America is illustrated in Figure 6. Within six months the total Republic of Guatemala was involved;[26] four months were required to cover El Salvador.[30] The epidemic spread to Honduras, taking approximately one year to cover the country. Nicaragua was seeded in three

months; the epidemic extended to the northern part of Costa Rica where it remained localized without further spread to the south. Cases were exported to the United States[6, 7] and to the highlands of Costa Rica; indigenous or autochthonous cases were notified in these countries but no serious outbreaks actually developed. Epidemics occurred in Mexico.[29]

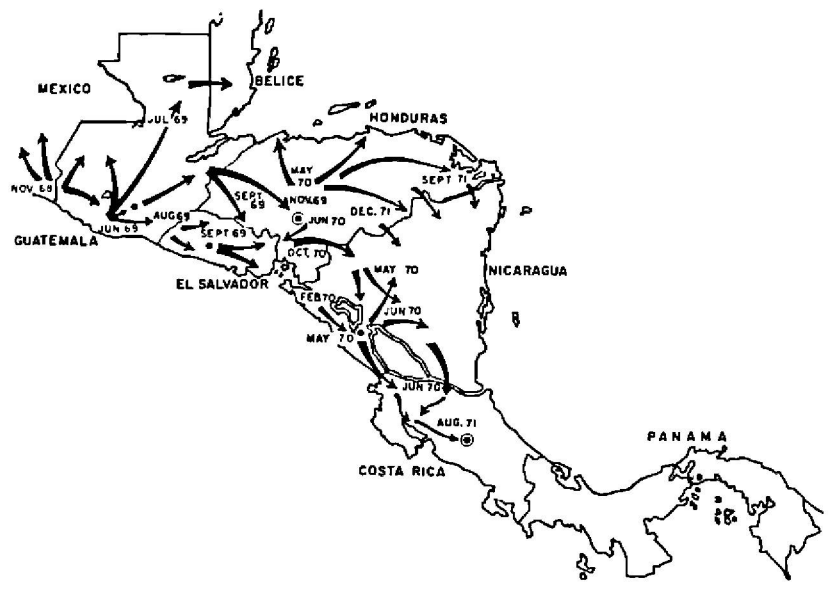

Figure 6—Evolution of the first epidemic wave of Shiga dysentery in Central America.

The attack rate and case fatality rate decreased as the epidemic progressed. This was due, in part, to better knowledge of the etiology and better treatment. Another possibility is a host-parasite adaptation, classically recognized for other diseases.

Isolated outbreaks were recorded in Guatemala in 1972 three to four years after the initiation of the regional epidemic. Some of these outbreaks represented a second or third blow to the community. When this was the case, the persons involved were mainly young children. However, primary outbreaks were still recorded last year, attacking persons of all ages. Overall, the incidence of *Shigella dysenteriae* 1 cases has decreased to a minimum in Guatemala, and similar reports are available from the rest of Central America.

Surveillance of shigellosis in 1969 and 1970, the epidemic years, revealed a preponderance of *Shigella dysenteriae* 1 isolations, with the remaining indigenous serotypes displaced to a secondary position. Prospective *Shigella* surveys in two lowland and one highland villages of Guatemala during the past year indicated reversion to the pre-epidemic situation, that is, an increase of the *flexneri* and *sonnei* groups, with little or no isolations of the Shiga bacillus (unpublished observations).

Comments

The evolution of a vast regional epidemic of Shiga dysentery involving seven countries of Middle America is a warning that old diseases could reappear with particular violence. The epidemic resulted in hundreds of thousands of cases and thousands of deaths in a few years. A considerable part of the high mortality recorded in the first epidemic year was due to misdiagnosis, failure in providing effective antibiotics, and the indiscriminate administration of amebicides, particularly emetin. The impact of the epidemic on the economy and development of the countries that were most affected cannot be assessed accurately but cannot be neglected. Presently, outbreaks are rare, while multiple endemic foci remain throughout the Isthmus as evidenced by the continuous reporting of sporadic cases.

Progress has been made by medical and health workers in ability to differentiate between bacillary and amebic dysentery, and in proper diagnosis and treatment of the disease. Systems of surveillance and case recording have been instituted in El Salvador and Costa Rica. Adequate conditions for control and prevention are operative in the United States and Costa Rica, which probably account for the limited spread of the disease within and outside these two countries. The epidemic organism has not been reported beyond the limits of the original boundaries observed in 1971.

This unfortunate epidemic event provides a good example of how easily a classical disease can be misdiagnosed, of how much need there is for good diagnostic laboratories and surveillance systems in developing countries, and above all, of the necessity to improve environmental conditions if prevention is to be accomplished.

Acknowledgement

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For summary of general discussion of this paper, see pages 58 to 59.