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with best wishes
to Dr. L. J. Mata
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SHIGELLOSIS:

A CONTINUING GLOBAL PROBLEM

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Chapter 3

Shigellosis in Central America

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ABSTRACT

Shigella infections are very common in Central America, except in Costa Rica and Panama where prevalence rates are low. Shigellosis is the most serious among all the specific diarrhoeas, due to its invasive character, systemic manifestations, severe nutritional impact, and tendency to become recurrent over prolonged periods.

All species of shigella are found in Central America; village studies reveal the occurrence for several serotypes in any single day. The commonest species are *S.flexneri* and *S.sonnei*. The Shiga bacillus is rare at the moment;but an extensive epidemic covered the whole Isthmus in 1969-71. The epidemic Shiga bacillus bear the multiple-drug resistance plasmid; more recently, some strains have been isolated containing the ampicillin plasmid as well.

The differences in mortality due to diarrhoea among the Central American nations, attest to the importance of environmental factors in determining shigella infections. The reductions or increases in diarrhoea mortality recorded in the last 15 years appear to reflect changes in the socio-economic situation in those nations.

INTRODUCTION

Shigella is a unique bacteria because it is virtually adapted to one host, namely man; primates and dogs are occasional victims of this invading organism. Because of limiting host-parasite relationship, *shigellae* depend on direct or indirect man-to-man contact to perpetuate themselves in nature. Thus, maintenance of infection in general population depends on effective faecal-oral transmission; that is, infection is related to personal hygiene and environmental sanitation.

Shigella has the capacity to invade the mucosal epithelial cells where they multiply, resulting in shedding of damaged cells and infectious bacilli. Its virulence varies considerably, a quality favouring infection with just a few bacilli. This property is very important for the survival of an agent known for its vulnerability in the environment. Although shigella is not completely adapted to the human host (it causes disease, often of severe and even fatal course), it induces many mild and occasionally asymptomatic infections, ensuring their maintenance in the community. It is then expected that shigella and shigellosis are very common in Central America and that their incidence reflects the degree of sanitation and socioeconomic development of the various countries involved.

Diarrhoeal disease in Central America.

Except for surveys and epidemiological studies conducted in Guatemala in the late 50's and in the 60's (1,2), and in Costa Rica and Panama in the 60's (3-5), practically no other comprehensive epidemiologic observations have been made in the area.

These observations revealed that the diarrhoeas are the commonest illnesses in the first year of life, and the second after respiratory infections in the second and third year of life (6). If the common colds and other "minor" respiratory infections are removed, the diarrhoeas stand out as the major source of morbidity in infancy and pre-school age. Since the methods of procedure and bacteriologic technique used in the various studies were different, no attempts are made to compare those data. It is reported, however, that diarrhoea morbidity tends to be greater in Guatemala and Honduras than in Panama and Costa Rica.

Such variability in morbidity, acting in conjunction with occurrence of varying severity of malnutrition, is reflected in the different rates of mortality due to diarrhoeal diseases in the Central American countries (Table 1). Guatemala, El Salvador and Nicaragua had the most serious problem around 1975 (7). It is possible that an improvement is occurring in Nicaragua in recent times. Since a significant proportion of all diarrhoea deaths occursamong infants, diarrhoea has the greatest influence on infant mortality, as was demonstrated for Costa Rica (8).

TABLE 1

MORTALITY ATTRIBUTABLE TO DIARRHOEAL DISEASES
(DEATHS PER 100,000), CENTRAL AMERICA

Country	Year	Age, years	
		1	1-4
Costa Rica	1968	1,778	105
	1977	361 (-8.8)*	25 (-8.4)
El Salvador	1969	1,276	205
	1974	1,276 (+12.5)	182 (-2.2)
Guatemala	1969	1,739	978
	1976	1,400 (-2.7)	511 (-6.7)
Honduras	1969	651	210
	1976	708 (+1.2)	161 (-3.3)
Nicaragua	1968	2,091	198
	1977	1,229 (-4.5)	104 (-5.2)
Panama	1968	482	112
	1974	306 (-6.0)	75 (-5.5)

* In parenthesis, percent change.

Epidemiology of shigellosis.

A general description of the epidemiologic behaviour of shigellosis will be made. *Shiga dysentery* will be discussed later. Prevalence studies emphasizing standard and consistent methods in Guatemala showed shigella carrier rates ranging from 5 to 25 (4,9). Curiously enough, shigella prevalence is lesser in Costa Rica and even less in Panama(Table 2) (5,9,10). There is a seasonality for shigella carriers with low rates at the end and the beginning of each year (the "cold" dry season throughout most of the highlands of Central America), and high prevalence rates from May through September, the wet and humid season (9).

While this applies generally to relatively large communities, or to a region or a nation, a different behaviour can be observed in smaller communities or villages studied prospectively. Thus, the introduction of new serotypes or new virulent strains may lead to outbreaks lasting for several months, until enough persons become infected and immune, to diminish or arrest spread of infection (6).

TABLE 2

PREVALENCE OF *SHIGELLA* CARRIERS IN THE CENTRAL AMERICAN COUNTRIES

Country	Population Studied	Number 4 individuals	*Shigella* prevalence and range
Guatemala	7 rural villages, 1956, 1958	7,223	6% (0.5-9.4)
Panama	30+ rural localities, 1966	10,000+	1% (0-13%)

The "seeding of communities" occurs through introduction of new strains from large urban and market centres by adults and older children, who then disseminate infection in their own families (6). The diversity of serotypes found in point-prevalence studies of rural communities attests to the active dissemination of virulent serotypes and strains at any one time (Table 3). For instance, three of six villages studied in 1956 had, on one particular day, 7 different serotypes. Survey was conducted on about 700 children under 5 years (11).

However, since shigella often becomes chronic especially in malnourished individuals (see below), the possibility that healthy and convalescent carriers maintain infection in the community is plausible. In fact, this may explain the "reappearance" of the Shiga bacillus in Central America, as will be discussed later.

Prevalence of shigella is also influenced by age, since most breast-fed infants are quite resistant to shigella infection (12), and they become shedders particularly after the first birthday. But there is a cohort effect in the manner that the various shigella serotypes invade growing children in a community, as clearly shown in the Cauque study (Figure 1) (6).

It is generally accepted that severity varies according to shigella species (17). But this may not be the case among children with nutrition deficits, except perhaps for *S. flexneri*, which often tended to induce a more severe type of diarrhoea, and for the Shiga bacillus, for its unusually high virulence (14).

TABLE 3

SHIGELLA SEROTYPES FOUND IN POINT-PREVALENCE SURVEYS, MARCH-APRIL 1956

Shigella Serotype	Locality					
	Masagua	La Fragua	Sn. Miguel Petapa	Sn. Bartolome M.A.	Sta. Cruz Balanya	Pueblo Nuevo Vinas
A1			1			
2		2	8		1	1
3						1
B1a					2	
1b						10
2a			2			
2b	1	3				2
3			1	2	3	1
4a	1	1			1	
5	2	1	1			
6			3		20	5
C5		1				
7					2	
D		4	3	4	3	7
Total serotypes	3	6	7	2	7	7

Shiga dysentery.

In 1969, a regional epidemic of Shiga bacillus dysentery got underway, first in the border between Mexico and Guatemala, and then spreading into many regions of Mexico, and into most of Guatemala, Belize, El Salvador, Honduras, and Nicaragua (15,16). Eventually, Costa Rica was hit, (Figure 2) but the wave did not extend into Panama (17).

In total, more than half a million cases of dysentery must have occurred from 1969 to 1971 in Central America, and not less than 20,000 deaths were recorded (15-19). The case fatality rate was as high as 10-15% in some villages, when the correct form of treatment was still unknown.

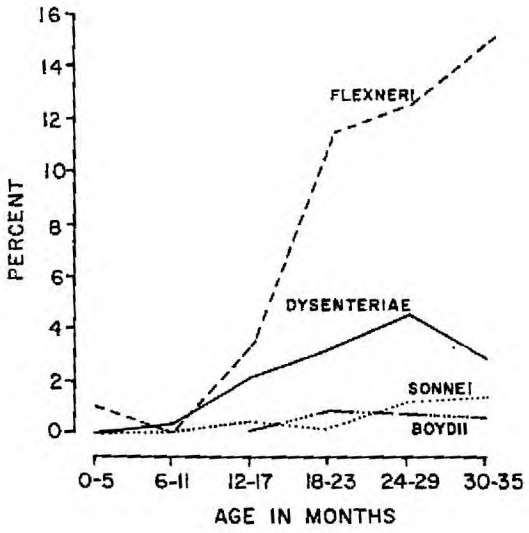

Fig. 1

The dysentery was mistakenly diagnosed as amebiasis with a "complicating virus" (?), because sulfonamide, tetracycline and chloramphenicol, usually successful in treating bacillary dysentery, were fruitless in this outbreak. On the other hand, poor laboratory technique failed to isolate *shigellae* and, concomitantly, inflammatory mucosal cells were misdiagnosed as amoeba trophozoites (15).

Studies in several hundred strains of *S.dysenteriae* type 1 showed that most were resistant to the three antimicrobials above mentioned, plus streptomycin, a characteristic frequently mediated by a transmissible plasmid (Table 4) (15,16,20). Practically all strains of the Shiga bacillus isolated during the epidemic were invasive in the guinea pig's conjunctiva, and possessed several cytotoxins (20). It is hard at this point, however, to fully understand the high virulence and marked pathogenicity of the epidemic strains of *S.dysenteriae* 1.

The Shiga bacillus had been recovered from ill persons and asymptomatic carriers before the epidemic (9,11). Those strains, however, did not possess the multiple-drug resistance plasmid. Like other *shigellae*, the Shiga bacillus elicits a serological response demonstrable by reacting "O" polysaccharide against IgM antibodies from the patients (21,22). The reaction is quite serotype-specific for the Shiga bacillus and other serotypes, and a titre of 1:20 by the passive haemagglutination test is considered significant (21). Extensive testing of sera from a statistical sample of more than 5000 families (in over 180 communities) in Central America, and assuming a titre of at least 1:40 as positive, revealed the presence of *S.dysenteriae* type 1 antibodies throughout the isthmus (Figure 3) (23,24).

Fig. 2

TABLE 4

CHARACTERISTICS OF STRAINS OF *S.DYSENTERIAE* TYPE 1, 1969-71
CENTRAL AMERICAN EPIDEMIC

Characteristics	Number tested	% with characteristics
Resistance to tetracycline, chloramphenicol, streptomycin and sulfathiazol	180	99.4
Sensitivity to ampicillin nalidixi acid, trimethoprim-sulfa	205	100
Invasiveness of guinea pig's conjunctiva	20	100

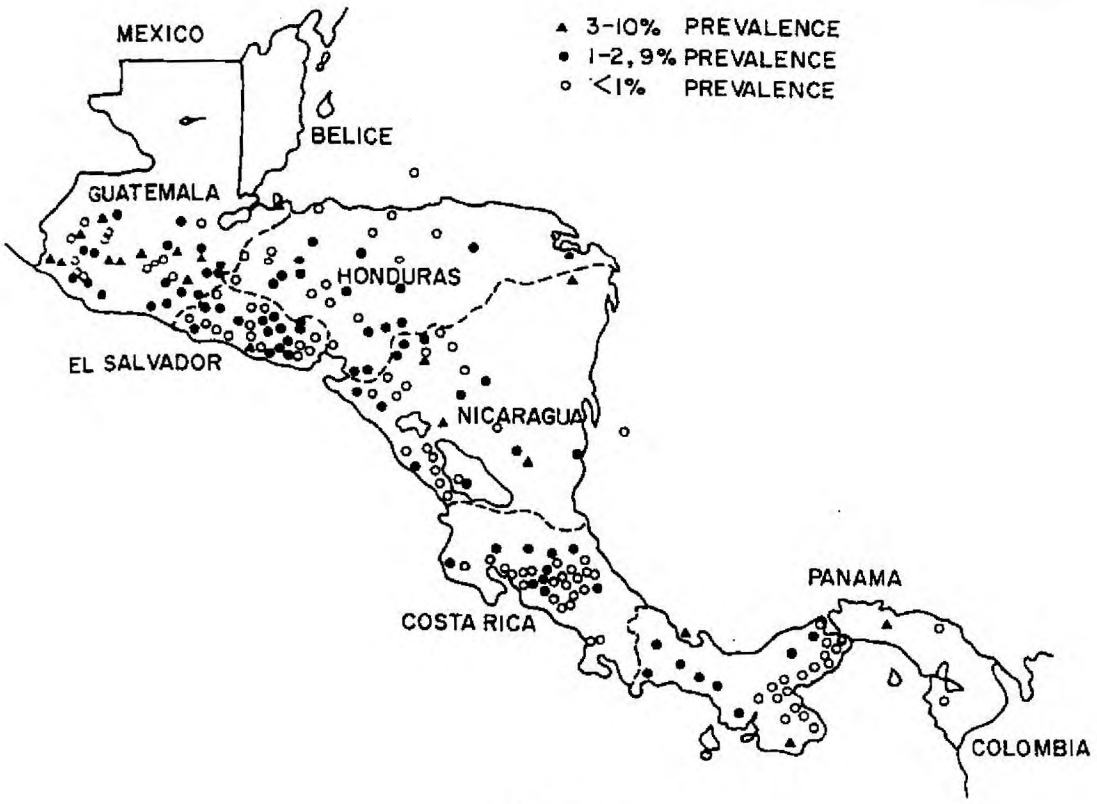

Fig. 3

It is evident that the Shiga bacillus is endemic in the regions and that it is generally not diagnosed, either because it is difficult to isolate in regular media (we prefer tergitol 7 agar with tryphenil-tetrazolium chloride (15)), or because serotyping generally is not done. The reasons for the apparent exacerbation of the organism and for the explosive dissemination in Central America in 1969-71 remain unclear, although several explanations may clarify at least part of the phenomenon (15,16,19).

The epidemic subsided after 1972, although outbreaks in villages and outbursts of cases in hospitals have been noted thereafter; it was abated in Costa Rica where only a few hundred cases and few deaths were reported. Part of the reason for the arrest of the epidemic, especially in Nicaragua and Costa Rica, can be partly attributed to rapid application of the new knowledge of treating severe cases with appropriate antimicrobials. In fact, Costa Rica, a country in transition that enjoys a higher level of hygiene and sanitation than the rest of Central America, benefitted from aggressive campaigns to strengthen mechanisms aiming at diminishing transmission. The epidemic did not progress south of the Central Plateau, and did not reach Panama or South America (17,19,24).

Surveillance systems are in operation in Guatemala and in Costa Rica. In a small outbreak in an Indian Guatuso family, several strains of *S.dysenteriae* 1 resistant to ampicillin were isolated, another complication in the already complex situation of the epidemic Shiga bacillus (25).

Genetic manipulations were made with *S.dysenteriae* 1 strains isolated in this family outbreak (25), in extensive outbreaks in Bangladesh (26), and Mexico (27,28). The results, in Table 5, indicate a distinct homogeneity of the ampicillin plasmid in strains of these organisms recovered in those distant places (24,30). In fact, the nature and biology of the multiple-resistant plasmid also showed to be identical for a variety of strains of different *Enterobactericeae* recovered from different materials, diseases and patients, as this ampicillin plasmid was also found identical to that found in the ampicillin-resistant strains of *Salmonella typhi* of the extensive outbreak in Mexico (31), as well as in many other regions of the body (32). It is evident that the plasmids associated with virulence, being transmitted throughout the world, are the same according to the relatively crude techniques used in molecular biology; but it may be possible that once more sophisticated techniques and molecular epidemiology develop, plasmids of different situations or geographical regions may turn out to be different.

Clinical aspects of shigellosis.

Shigellosis is usually a serious disease, characterized by cramps, multiple bowel movements of watery diarrhoea first, and later multiple small evacuations of mucous and blood and pus; vomiting, prostration, anorexia and fever may also occur, and the severity varies with the species of shigella, with the serotype, and according to the current strain circulating in the community. The Shiga variety is the most serious, as illustrated by the high

TABLE 5

IDENTITY OF Ap^r PLASMIDS OF *ENTEROBACTERIACEAE**

Bacillus carrying Ap^r plasmid	Mol. wt. (daltonx10^6)	N° copies in *E.coli* K-12	Polymerase 1 requirement
S.dysenteriae 1 (Mexico)	5.5	39	+
S.dysenteriae 1 (Costa Rica)	5.5	31	+
S.dysenteriae 1 (Bangladesh)	5.5	30	+
S. panama	5.5	35	+
C. freundii	5.5	35	+

* After Crosa, Olarte, Mata, Luttropp and Penaranda.

attack rate and severity of symptoms recorded at any one time. Leukemoid reactions were described in Central America (33) and in Bangladesh (34). *S.dysenteriae* 1 can be associated with "toxicosis", toxic megacolon, involving the entire organ and even parts of the adjacent small bowel mucosa. The lesion is of coagulation necrosis of the mucosa and sometimes of the submucosa. When there is toxic megacolon, the inflammatory process compromises the *muscularis mocosae*, with varying degrees of destruction of the plexus. Thrombi were found in veins and arteriols of the submucosa and *lamina propria* in all cases of fatal colonic involvement. The common complication was thromboembolism, cortical necrosis and toxic megacolon (35). Intravascular coagulation was found in one quarter of all fatalities autopsied, with lesions in kidneys, adrenals, pancreas and liver.

Nutritional implications.

It was evident from our observations in Guatemala, that shigellosis can easily develop in the well-nourished host, making him very ill and eventually, rendering him weak and postrated, as noted in Guatemalan adults who had naturally recovered from the disease. The pathogenic actions that favour or accentuate malnutrition are obscure, but they are related to cell invasion, tissue destruction, increased fluid and electrolyte secretion, and the presence of enterotoxin in tissues (36,37).

The clinical demonstration that shigellosis has an adverse effect on nutritional status has derived from clinical and field studies. Hospitalized children recovered from malnutrition, easily go into negative nitrogen loss of considerable magnitude during the course of shigellosis (38). More recently, evidence indicates that shigellosis is a protein-losing enteropathy of relative importance (39). In the field, shigellosis is definitely associated with weight loss of long duration, if treatment with oral fluids and required antimicrobial drugs are not instituted (6). Weight deficit and height arrest can persist for weeks and months, and shigellosis can induce prolong wasting (chronic malnutrition), or it can precipitate severe protein-calorie malnutrition, particularly when it occurs coincidental with measles or other diseases (6,38).

Shigellosis, if not treated with drugs, tendsto persist in about one fifth to one quarter of the cases, as chronic recurrent diarrhoea. A study conducted when evidence suggested that antibiotics were not needed, and when effective oral rehydration had not become available, revealed that, all too often, shigella infections become chronic with recurrent symptoms. The significance of chronic shigellosis for the host nutrition has not been elucidated, although knowing the damage inflicted to the mucosa and the accompanying nutrient loss, it is expected to be important.

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