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SYMPOSIUM ON SHIGA DYSENTERY

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Approximately 200 scientists attended the III Central American Congress of Microbiology in Guatemala City, July 26-30, 1971. To take advantage of this event, the Institute of Nutrition of Central America and Panama and the Department of Research Development and Coordination, Pan American Health Organization, organized a Symposium on Shiga Dysentery with the participation of about 60 scientists at which 30 papers were delivered. Almost everyone who has contributed to the study and understanding of Shiga dysentery was present in the meeting, thus creating a unique opportunity for the exchange of knowledge and ideas about this important nosologic entity.

A summary of the symposium follows.

Historical Aspects

The first reference to the existence of acute dysentery associated with high mortality can be traced to Biblical times. The Shiga bacillus (*Shigella dysenteriae* type 1) and its associated disease were first recognized by Drs. Shiga and Krüse at the turn of this century. Whenever this bacterium has been isolated, it has almost invariably been found in severe and geographically widespread epidemics. The Shiga bacillus type 1 was one of the commonest serotypes throughout Europe before World War I, but endemic cases and outbreaks decreased with time and by World War II it was scarcely recognized in the Old World. Few outbreaks and only occasional isolations have been reported in the United States. Very little is known of its presence in Africa.

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Limited laboratory resources and lack of epidemiologic surveillance are responsible for the almost complete lack of information about the history of Shiga dysentery in Central America, although a large outbreak in El Salvador, with approximately 3,000 deaths, was recognized in 1915. Reports from Mexico and Guatemala based on limited studies indicate that the Shiga bacillus was endemic in Middle America before 1968, although it appeared to be a rather uncommon organism. South American bacteriologists have noted the apparent absence of the Shiga bacillus in their countries.

At the end of 1968 and the beginning of 1969, a series of severe outbreaks was recognized in Guatemala in the region bordering on Mexico. Within a few months the whole country was affected and the epidemic had spread to several neighboring nations.

Clinical Characteristics

Physicians unaccustomed to this type of shigellosis were surprised by the severity and violence of the disease. It begins with cramps and watery stools. Within a few hours or days evacuations consist of blood, mucus, and pus, with virtual absence of other matter. Fever is common. Tenesmus and rectal pain, vomiting, and prostration are also frequent. The patient feels wretched, has severe intestinal pain and discomfort, and shows signs of toxemia. Rectal prolapse may be seen, but neurologic manifestations are rare.

The disease may run a very rapid course and death ensues within a few days, and lethality in untreated cases may be as high as 15 per cent. If no treatment is given, disease is usually protracted, running a course of weeks or even months with recurrent diarrhea occasionally resembling that seen in malabsorption. In such cases there is flatulence, abdominal distension, and emaciation, and many are associated with malnutrition.
**Pathology**

Only limited pathologic investigations were carried out in Central America during the 1968-69 epidemic. The commonest descriptions were of predominating lesions in the rectum, sigmoid, and terminal ileum. In 95 per cent of cases the colonic mucosa was extensively ulcerated from the ileocecal valve to the pectineal line. In a few the terminal ileum was also involved. The appendix was affected whenever the colonic mucosa was damaged.

Toxic megacolon was found in approximately 5 per cent of cases, probably due to ischemic necrosis of ganglia of the myenteric plexus secondary to multiple fibrin thrombi, or due to the direct action of exotoxin on the plexus. The histology shows the classical picture described in Manson-Bahr's treatise. In some cases scarring that left areas of inflamed mucosa was found. The severity of the colonic lesion was responsible for the toxic state. The magnitude of the intestinal lesion and the appearance of toxic megacolon may be attributable to the virulence of the organism, but the underlying malnutrition may also have played a role.

Generalized intravascular coagulation syndrome was frequently encountered. The more affected tissues were—in order of importance—kidney, pancreas, spleen, adrenals, and liver. The etiology of intravascular coagulation in shigellosis has not been elucidated but might be explained as resulting from septicemia or the exotoxin. This syndrome was thought to be responsible for death in 25 per cent of the patients.

**Mortality**

Mortality was very high in Guatemala, El Salvador, Honduras, and Nicaragua. Characteristically, it affected patients in all age groups, a good indication of the population's almost universal susceptibility to the disease. The rates were high among children under one year and adults over 45.

In Guatemala, 10,000 deaths were attributed to Shiga dysentery in 1969. During the second and third waves of the epidemic, mortality tended
to predominate in the younger age groups, indicating a change in the age distribution of susceptibles.

Mortality rates were higher in the lowlands than the highlands and much greater in rural than in urban areas. Rates were higher in Guatemala, where the epidemic first struck. Mortality tended to be lower in the other countries, a possible indication of better medical knowledge of the disease and its therapy.

Epidemiology

As noted, the Shiga bacillus was endemic in Middle America. By means of a serologic procedure (passive hemagglutination) that permits the investigation of specific antibodies to the Shiga bacillus, it has been retrospectively possible to examine a large, representative collection of sera from Central America. Specific Shiga bacillus antibodies are produced in two-thirds of the cases within 10 days of onset of the dysentery. They decline with time, and one year later are virtually gone. The sera examined were collected from a random sample taken in 1965-67, and represent all ethnic groups, geographic areas, and socioeconomic strata of the isthmus. Analysis of the serum bank showed that many villages had serologic evidence of the presence of the Shiga bacillus. In some other localities the rate of antibody titers was so high as to suggest the occurrence of outbreaks. Not less than 1 per cent of the total population examined (approximately 12,000 persons) showed evidence of recent infection with the bacillus.

The strain responsible for the Central American epidemic had the multiple drug-resistance factor not present in the preepidemic strains. Although it may be postulated that the epidemic strain might have been introduced from another geographic region, it is more likely that the organism originated from endemic foci. The reasons for the strain's acquisition of the drug-resistance factor, with its enhanced virulence, and its apparently increased communicability are unknown.

Outbreaks occur after introduction into the community of an index case, very often a man returning from an infected area. Additional cases,
usually within the family, follow. The community is seeded and an explosive outbreak ensues, often furthered by serious contamination of the water supply at the same time there is effective person-to-person transmission. Many outbreaks are of the point-epidemic type. Additional outbreaks may occur later in the same community.

Hundreds of villages were affected simultaneously or one after the other in the 1968-69 epidemic in an explosive way not recorded before in the area. The same applied to the affected countries, since the outbreak covered all Guatemala within six months and all El Salvador in four more months. The outbreak followed the main lines of communication, principally highways and rivers. In Honduras the epidemic took a year to move from the west to the east, which may be attributed to the greater isolation of the villages and poorer communications in that country.

Within a year the epidemic extended as far south as Nicaragua. Because the medical community was better prepared as a consequence of the experience in Guatemala and El Salvador, the epidemic caused fewer deaths in Nicaragua. A few outbreaks were reported in the northern part of Costa Rica, but the epidemic did not reach that country's central highlands in any significant manner, nor did it extend to Panama.

The presence of exacerbated foci of Shiga dysentery in Central America, in times when international travel is common, creates a potential danger of spread to other areas. Systematic surveillance in the United States has revealed the unusual occurrence of Shiga dysentery, consisting at first of imported cases or their contacts but more recently of indigenous cases whose origin is unknown. The high level of hygiene and environmental sanitation in the United States makes a serious epidemic unlikely, but protracted seeding is possible and there is some danger for the poor.

**Etiologic Considerations.**

No isolations of the Shiga bacillus were made by official or private laboratories in Guatemala for nine months after the 1968-69 epidemic started. An incorrect diagnosis of amebiasis took firm root because
appropriate laboratory procedures to isolate \textit{Shigella} were lacking and macrophages and other inflammatory cells in stools or trophozoites of \textit{Entamoeba histolytica} were found in a few cases. Both factors led to an equivocal designation of the epidemic as amebic dysentery. Most physicians and health authorities accepted this notion and so patients were inappropriately treated for at least 10 months.

The use of Tergitol 7 with triphenyl tetrazolium chloride (T7T) permitted isolation of the Shiga bacillus from approximately half of severe cases. Investigation of hemagglutinating antibodies resulted in confirmation of the outbreak's nature which, with the isolation of the organism, served to change the prevailing misconception. Using T7T agar, Shiga bacillus concentrations of $10^5$ to $10^8$ per g or ml of feces were found. Profound alterations of the fecal microflora were also demonstrated. The changes were: (a) a very marked diminution of the anaerobic component--sometimes to undetectable levels--from the usual counts of $10^{11}$ per gram; (b) diminution of coliforms; and (c) absence of the predominant component of the flora (bifidobacteria, bacteroides). There is no explanation for the alterations described but it may be postulated that the inflamed mucosa does not permit the normal proliferation of the indigenous microflora. These changes revert to normal within 48 hours of the start of antimicrobial therapy.

The Shiga bacillus showed resistance to tetracyclines, chloramphenicol, streptomycin, and sulfa drugs. All strains were sensitive to nalidixic acid, ampicillin, trimetoprim-sulfametoxazole, and other agents. All strains tested in the conjunctiva of the guinea-pig were invasive and virulent, and all tested have produced an exotoxin that behaves similarly to cholera toxin when tested in the ligated intestinal loop of the rabbit. The existence of \textit{Shigella} enterotoxins was not recognized before and their presence helps explain the toxic manifestations and other pathogenic aspects of shigellosis, especially Shiga dysentery.

\textbf{Treatment}

Dehydration is not the main feature in Shiga dysentery. Prostration, pain, exhaustion, and toxemia are more important. These symptoms are
hypothetically related to the extensive intestinal lesions that result from multiplication of the *Shigellae*, from endotoxin release after organisms are destroyed, or from the liberation of enterotoxin. All these phenomena improve greatly within two to three days when the proper drug, nalidixic acid, for example, is given in adequate dosages. When dehydration is present, particularly in small children, fluids must be given by mouth and if necessary by vein. Six to 12 hours after food withdrawal, feeding must begin. Often, relief of symptoms and prompt recovery is observed only with antimicrobial and nutritional therapy.

Thousands of cases were effectively treated in Nicaragua with nalidixic acid, in Guatemala with ampicillin, and in El Salvador with trimetoprim-sulfamethoxazole.

**Preventive Measures**

The mechanisms of Shiga dysentery's transmission have not been completely elucidated but the disease can be prevented by general measures including improvement of personal hygiene, boiling of water, special treatment of foods, and isolation of the ill. These measures proved effective in Costa Rica. Treatment is intended to curtail further spread of the disease and eliminate potential carriers.

Several *Shigella* vaccines for serotypes of the *flexneri* group have been developed in the United States. These hybrids or mutants are given by mouth in very high doses and exert a protective effect, as demonstrated in extensive field trials in Yugoslavia. Efforts have been made to develop similar vaccines for Shiga dysentery, but at the moment the vaccine remains in the developmental stage and there is no definitive proof that it can be safely used in children. The production of an avirulent strain of Shiga bacillus is looked upon with excitement in view of its potential use during outbreaks like the one observed in Central America.

**Recommendations**

The following recommendations were drawn up at the Symposium on Shiga Dysentery:
(1) Shiga dysentery will remain a problem in Central America for years. Thus, the most urgent need is for better surveillance so as to rapidly identify problem areas and guide control efforts. It is important that each laboratory-confirmed isolate be investigated to determine how it was transmitted and where it came from. Laboratory capabilities must be expanded throughout Central America and Mexico. Existing laboratories should be strengthened so that they can isolate and identify the Shiga organism. New laboratories should be established to insure adequate surveillance. Each country should have its own central reference laboratory with special capabilities for verification of laboratory isolations of S. dysenteriae and other pathogens. Intensive training and refresher courses should be emphasized. As the disease enters its endemic phase, serosurveys will be very helpful in the surveillance effort.

(2) There is clearly a need for a central reference laboratory for the entire region. This laboratory should be the center for referral of laboratory problems and training. Representative strains from different countries obtained at different times should be studied, lyophilized, and stored for future studies and reference purposes. The INCAP laboratory has unofficially served this role. It was recommended that this laboratory be officially designated as the Central Shiga Dysentery Reference Laboratory and that its capabilities be expanded to provide regular laboratory training and diagnostic services.

(3) Laboratory directors and epidemiologists from each of the Central American countries should meet at least yearly to exchange views on current problems and surveillance trends. The first meeting should be at INCAP in the early summer of 1972.

(4) Special surveillance efforts should be supported. For example, there is now a need for periodic serosurveys on the fringes of the epidemic area to elucidate its expansion. The central reference laboratory referred to in (2) above should be given funds to support such studies and provide overall technical guidance.
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