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# STUDIES OF DIARRHEAL DISEASE IN CENTRAL AMERICA

## IX. *SHIGELLA* CARRIERS AMONG YOUNG CHILDREN OF A HEAVILY SEEDED GUATEMALAN CONVALESCENT HOME*

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The clinical course of acute diarrheal disease of early childhood in less developed countries is regularly much prolonged beyond the one or two days characteristic of more favored regions.[1] In two villages in rural Guatemala the average was 5.9 and 8.5 days.[2] Among 1,070 cases observed during five years, 13% exceeded 15 days duration and sometimes lasted for a month or two or even longer. If patients are able to spread infection for longer periods, then persons with inapparent infection, corresponding to the carrier state, may exhibit a parallel behavior. In developing regions the resistance of the host is ordinarily low grade, in both instances, by reason of a prevailing malnutrition and a succession of acute illnesses. The usual length of the carrier state under these circumstances is inexactly known, either for the healthy or the convalescent host. Observations in other areas, commonly with mild disease and for well nourished young adults, indicate a brief period.

Epidemiological evidence supports a spread by contact as the main mode of transmission.[3] The predominance of index cases among preschool children in family outbreaks, sometimes to the extent of 71%, suggests that carriers among older members of the family are an important source of infection. The restricted contacts of little children make it probable that infection is acquired within the family rather than through outside exposure.

For these reasons the community dosage of infection, otherwise stated as the number of foci of infection existing at a prescribed time, becomes a critical consideration. Collectively these foci comprise patients acutely ill, persons with the distinctive chronic diarrheal disease, and both healthy and convalescent carriers. An evaluation of the four elements is limited by the absence of a demonstrable microbial agent in most persons ill or exposed to acute diarrheal disease. Comprehensive investigations in rural and urban areas of Guatemala have demonstrated a total frequency of established bacterial pathogens (*Shigella*, enteropathogenic *Escherichia coli* and *Salmonella*) in 24% of clinical cases among children from birth to four years old, most of the agents (83%) being *Shigella*.[4] The prevalence of carriers in the general child population of the same age was high; for total bacterial pathogens, 11.7%, and for *Shigella*, 7.8%.

The similarities in epidemiological behavior of the undifferentiated diarrheas and those of specific origin suggest an infectious origin for most and a consequent general significance of carriers. With carrier observations restricted of necessity to diarrheas of specific nature, *Shigella* infections were selected for study. They are the largest single group. The direct objective was to identify kinds of foci of *Shigella* infection, to observe their relative frequency, and especially to measure the time each was potentially active in spread of infection. The present study was made in a convalescent home for young children in Guatemala City, Central America, having a closed population especially suited to the particular purpose.

### MATERIALS AND METHODS

*The convalescent home.* El Hogar de Niños Convalecientes de la Sociedad Protectora del Niño de Guatemala is an institution accommodating about 100 children aged two to six years. Patients are from rural villages and from the lower social strata of the city. All are convalescent from recent acute illness and with few exceptions are malnourished. The usual stay is long, ordinarily

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several months. The children are housed in three wards of about equal size, with additional facilities for isolation. Most of them are ambulant; there is free communication between wards, and they play and eat together. The incidence of acute diarrheal disease at the time of the study was 235 cases per 100 children per year, with shigellosis accounting for more than the usual proportion. Antibiotics and sulfonamides were not used in treatment of diarrheal disease.

*Bacteriological methods.* Rectal swabs were streaked directly on SS (shigella-salmonella) agar plates, at the bedside. Suspicious colonies, from six to 12 if so warranted, were transferred to TSI (triple sugar iron) agar. Presumptive isolates were transferred to urea (Christensen), citrate (Simmons) and semi-solid agar. Cultures surviving these screening tests were identified by slide agglutination, using group- and type-specific commercial serums, and by further physiologic tests.[5]

*Definitions and assumptions.* To recognize a pattern of foci of infection more readily, the following interpretations were made. Acute diarrheal disease was defined as a clinical illness associated with three or more liquid or semiliquid stools within a 24-hour period.

Chronic recurrent diarrheal disease was an illness exceeding 15 days duration, occasionally with diarrhea continuing unabated but characteristically with intermittent exacerbations and remissions and sometimes periods of clinical absence of the sign, but for no longer than two weeks. A case was termed undifferentiated diarrheal disease if *Shigella* was absent from daily rectal-swab cultures made during clinical manifestations; and termed clinical shigellosis if it was present. A carrier was a child who harbored a *Shigella* in the absence of discernible clinical disease, either with infection inapparent throughout its course (healthy carrier) or as a feature of incubation period, convalescence or post-convalescence (incubatory or convalescent carrier). As a general term, shigellosis was expressive of *Shigella* infection, to include both patients and carriers.

In both carrier and clinical states, periods of variable length occasionally intervened between bacteriological demonstrations of *Shigella* when daily cultures were made. (If the same sertoype was isolated within a week the situation was recognized as a relapse and within two weeks as a recurrence, in both instances constituting a single episode.) When the interval was longer than two weeks, the event was characterized as a reinfection, and recorded as a new case or a new carrier according to circumstance. These distinctions are arbitrary, because any of the three prescribed situations of relapse, recurrence or reinfection may be no more than a technical failure to demonstrate the agent, or any one may be a reinfection.

If a new serotype succeeded the original one, or was added to it, this was clearly a reinfection, and a new case or new carrier. A multiple infection was considered to occur when one or more additional serotypes were superimposed upon an existing infection, either case or carrier. Double or triple infections were those where more than one serotype invaded concurrently. Each serotype invasion has been recognized as an independent episode in the tabulations which follow, although combinations are described separately.

## RESULTS

Initial examination of the 110 children resident in El Hogar in June, 1964 showed 32.7% infected with *Shigella*. Extensive surveys of general rural populations of preschool children had given a prevalence of 7.8%, about one-fourth that frequency.[4]

Twenty patients were drawn from those likely to remain for at least two months. All had been admitted from other hospitals after illnesses that had averaged 51 days, with a range of five to 180 days. They had been resident in El Hogar for appreciable periods, from 19 to 213 days with an average of 88 days. With few exceptions they were examined clinically each day in the course of the study for the presence or absence of illness, and bacteriologically for *Shigella*. When observations began, six of the 20 children had clinical diarrheal disease, one with *Sh. flexneri 1*, one with *Sh. sonnei* and four with no demonstrable *Shigella*. Of the 14 without diarrheal disease, three were carriers of *Sh. flexneri 3*, one of *Sh. sonnei*, and the remainder were free of the infectious agent. For the group as a whole, 30% had shigellosis; for all residents of El Hogar the ratio was 32.7%. Ten patients had second degree malnutrition (25–40% below standard weight for age);[6] seven had first degree (15–24% below standard), one had third degree (more than 40% below standard), and two were within normal

TABLE 1

Shigella *cases and carriers among 20 children resident in a convalescent home; daily serial examinations, clinically and bacteriologically, 8 to 20 weeks, Guatemala, 1964*

| | Shigellosis | | |
|---|---|---|---|
| | Healthy carriers | Chronic recurrent diarrheal disease | Acute diarrheal disease |
| Number of persons | 8 | 3 | 1 |
| Days observed, total | 492 | 335 | 57 |
| Average, days | 62 | 112 | 57 |
| Days of infectiousness | | | |
| Maximum | 48 | 136 | 28 |
| Minimum | 1 | 51 | — |
| Average | 17 | 107 | 28 |
| Relapse | | | |
| Number of persons | 5 | 3 | 0 |
| Number of relapses | 22* | 0 | 0 |
| Recurrence | | | |
| Number of persons | 1 | 3 | 0 |
| Number of recurrences | 1 | 10 | 0 |
| Reinfection | | | |
| Homologous serotype, persons | 2 | 0 | 0 |
| Heterologous serotype, persons | 1 | 1 | 0 |
| Undifferentiated (non-*Shigella*) diarrhea | | | |
| Number of persons | 6 | 0 | 1 |
| Number of cases | 8 | 0 | 1 |

* Includes 2 instances where the relapse was from carrier to clinical case.

limits for children of the area. The distribution was that of the population of the institution. Well nourished children were usually not admitted nor were the acutely malnourished (kwashiorkor). The sample was judged representative.

Thirteen children were observed for the next eight weeks, five for ten weeks and two for 21 weeks. Eight children remained consistently negative for *Shigella*, while 12 at one time or another harbored the infectious agent. Eight of them were healthy carriers, three were patients with chronic recurrent clinical shigellosis, and one was an acute case (Table 1).

With a single exception, all of the 12 children with shigellosis were malnourished, four having first degree malnutrition, and seven having second degree. Of children with no *Shigella* one was within normal limits, three had first degree malnutrition, three had a second degree state, and one child was more than 40% deficient.

During the observations, both groups of children, those with and without shigellosis, experienced clinical undifferentiated diarrheal disease, so that counting all cases (clinical shigellosis and undifferentiated), the two groups of children had an equivalent incidence of acute diarrheal disease. Numerically this was slightly in excess of the prevailing frequency for the institution, 235 cases per 100 children per year, but the study populations were too small to establish reliable differences.

*Healthy* Shigella *carriers*. The observed time a *Shigella* was present does not always measure the full length of the carrier state. Some children were demonstrated carriers at first examination with no knowledge of how long the condition had existed. In other instances the child was discharged while still a carrier, with persistence thereafter unknown. Actual duration was determinable in better than half of instances. A plus sign after a stated duration indicates an observed duration with an added unknown time.

Carriers usually had a single serotype throughout the observed course. In eight of 46 children (the original 20 and 26 others to be noted later), two serotypes were present concurrently at some time during the infection. The ordinary behavior was that one type persisted for an appreciable time, and appeared mainly responsible for the existing inapparent infection, while the other was transitory, superimposed for a day or two and then diappearing. In one instance, however, a superimposed second infection continued active, together with the original infection, for five weeks.

Two children had a multiple infection with more than two serotypes, in both instances short lived. In one child an original carrier state with *Sh. flexneri 2* persisted for eight weeks; *Sh. flexneri 3* and *Sh. flexneri 4* ultimately were added, after which the total carrier condition cleared promptly, and remained so through the twentieth week. In the other instance, a double infection of *Sh. flexneri 3* and *Sh. flexneri 4* was present on initial examination. By the next week, *Sh. flexneri 3* had disappeared but *Sh. flexneri 1* and *Sh. sonnei* were added to give a coexistent triple infection. Only *Sh. flexneri 4* was still present when observations ended in the tenth week. Four serotypes had been present

during that time and yet there had been no clinically recognizable diarrhea.

Reinfection of a previous carrier with a different serotype was uncommon; two instances were noted, both transitory. Reinfection with the same type after the prescribed interval of two weeks was noted once. By contrast, reappearance of the same organism after brief absence, corresponding to relapse or recurrence, was a characteristic feature of chronic recurrent clinical shigellosis, noted on numerous occasions, and usually marked by return of acute diarrhea.

A transition from an established healthy carrier state to active diarrheal disease occurred twice, once after 13 days as a carrier and again after 15 days. This is not within the usual concept of shigellosis, where initial host resistance usually determines a firm response as case, carrier or no reaction. The carrier periods were too long to fall within any usual concept of incubatory carrier; seven-day maximum and usually three or four days. With the carrier state interpreted as fundamentally an inapparent infection, the precipitating factor responsible for the change has epidemiological interest, in relation to disease incidence and to disease origin. These two cases were not the chronic recurrent shigellosis to be described, where alternating carrier and clinical states were a characteristic feature. The disease that followed the carrier state was wholly ordinary acute diarrheal disease. A brief clinical attack of moderate severity ended with no convalescent carrier state in one instance, and of four days duration in the other, and long freedom from infection thereafter. The following case report is cited:

*Case 1.* On initial examination, a boy aged four years, second degree malnutrition, had an undifferentiated clinical diarrhea which lasted two days. No *Shigella* was demonstrated by daily cultures then nor immediately thereafter. Three days after the attack ended, the child became a healthy *Sh. flexneri* carrier, and doubly so, for both types *1* and *4* were identified. *Sh. flexneri 1* was present for a single day, but *Sh. flexneri 4* persisted for 13 days, at the end of which time the carrier state relapsed into clinical diarrhea of 10 days duration with *Sh. flexneri 4* present throughout the illness. Following a four day convalescent carrier state, the infectious agent disappeared and the subsequent 33 days were uneventful.

*Chronic relapsing and recurrent bacillary dysentery.* Although brief periods of freedom from *Shigella* were noted, the outstanding characteristic of this syndrome was a low-grade infection with indefinite, minor symptoms, *Shigella* continuously present, and punctuated irregularly by exacerbations to acute active diarrhea. These acute episodes showed much clinical variation. Occasionally they were severe, with blood and mucus in the stools; more often they were of moderate severity; and rather regularly the intensity of signs and symptoms varied greatly within a particular attack. They were of longer average duration than ordinary acute diarrheal disease.

*Case 2.* A girl aged two years five months, second degree malnutrition, when first seen had severe diarrheal disease with blood and mucus in the stools and *Sh. sonnei* present. The attack lasted for three days. After two days with no diarrhea but *Sh. sonnei* still present, a new invasion by *Sh. flexneri 4* was demonstrated with a return of acute diarrhea. The disease continued active for five days, with *Sh. sonnei* and *Sh. flexneri 4* associated. Thereafter and in the absence of definite symptoms but occasional loose stools, *Sh. flexneri 4* persisted for five days and *Sh. sonnei* continuously until the 28th day when a third acute diarrheal event developed. For the first six days only *Sh. sonnei* was recognized but then again was joined by *Sh. flexneri 4* for a further seven days of diarrhea. As symptoms subsided *Sh. flexneri 4* disappeared promptly from cultures but *Sh. sonnei* continued present for the next five weeks, after which the infection relapsed for the fourth time into a two-week clinical attack. After freedom from symptoms for a week, a fifth *Sh. sonnei* episode intervened, of two weeks known duration. The patient was lost to observation with diarrheal disease still active. *Sh. sonnei* had persisted for 136+ days; *Sh. flexneri 4* was present for a total of 20 days.

A second similar case with *Sh. flexneri 3* infection was first seen in the carrier phase, had three brief clinical recurrences, and the infectious agent was present in 51 of 64 daily cultures. A third patient with initial *Sh. flexneri 1* clinical disease acquired an added *Sh. sonnei* on the third day of illness. *Sh. flexneri 1* disappeared after 27 days, with *Sh. sonnei* continuing as did clinical diarrhea. During 135 days of observation *Sh. sonnei* accounted for 107+ days of active diar-

TABLE 2

*Shigellosis, cases and carriers, by period of infectiousness, children aged 2 to 6 years, Convalescent Home, Guatemala, 1964*

| *Shigella* | Shigellosis, all forms* | | Period of infectiousness, weeks | | | | |
|---|---|---|---|---|---|---|---|
| | No. of infections | % of total | One or less | 2–4 | 5–9 | 10–14 | 15–20 |
| *Sh. dysenteriae 2* | 2 | 4 | 2 | 0 | 0 | 0 | 0 |
| *Sh. flexneri 1* | 5 | 9 | 2 | 1 | 1 | 1 | 0 |
| *Sh. flexneri 2* | 5 | 9 | 2 | 1 | 1 | 1 | 0 |
| *Sh. flexneri 3* | 19 | 34 | 12 | 4 | 1 | 2 | 0 |
| *Sh. flexneri 4* | 7 | 12 | 4 | 2 | 0 | 1 | 0 |
| *Sh. sonnei* | 18 | 32 | 6 | 3 | 3 | 4 | 2 |
| Total | 56 | 100 | 28 | 11 | 6 | 9 | 2 |

* Cases and carriers; multiple coexistent or serially occurring infections are listed individually; 46 children.

rhea and 28 days of carrier state. The patient was lost to observation with diarrhea still present.

*Children with no Shigellosis.* Eight of the 20 children were without demonstrable *Shigella* during observation. Three had no diarrheal disease, three had chronic recurrent diarrheal disease, and the remaining two patients had ordinary acute diarrheal disease, each with two brief episodes during eight weeks. The three cases of chronic recurrent diarrheal disease were acquired during the study period. The attacks lasted respectively for 46+ days, 42 days and 44 days. Chronic recurrent diarrhea of non-*Shigella* origin as here observed could not be differentiated clinically from that with *Shigella* present.

In summary, among 20 children resident in this highly seeded convalescent home, 12 showed *Shigella* at some time during observations which ranged from eight to 21 weeks, in most instances the shorter period. Eight did not have shigellosis, although they had an equivalent incidence of diarrheal disease. Among children harboring *Shigella*, the infectious agent was excreted in 75 of 154 person-weeks of experience, in 27 weeks by persons clinically ill with acute diarrheal disease, and in 48 weeks by carriers, all forms.

*Period of communicability in Shigellosis.* The clinical studies just described differentiated four kinds of excretors of *Shigella* bacilli. To amplify information on the length of time infectiousness persisted, a further group of 26 children from the same population was studied as they developed shigellosis, including both clinical cases and healthy carriers in essentially the same proportion as in the first series. Bacteriological examinations were by the same technics, but once weekly instead of daily, and clinical reactions were not followed in detail. Observations extended usually for 10 weeks, in some instances 20 weeks, and for one only five weeks. Table 2 presents duration of shigellosis for the 46 persons by weeks.

Although three of the four *Shigella* groups were identified including four serotypes of *Sh. flexneri*, material differences in their realtive frequency became evident. Two agents accounted for two-thirds of all infections, *Sh. flexneri 3* and *Sh. sonnei*. Four other serotypes were collectively responsible for the remainder. Except for *Sh. flexneri 3* and *Sh. sonnei*, the period of communicability of infected persons, as judged by presence of the infectious agent, was more often than not of short duration. For *Sh. sonnei*, long communicability was especially characteristic.

In about one-half of all instances, infectiousness was brief, sometimes a single day or less than one week. For another one-fourth, duration was two to four weeks. Six of nine infections lasting for 10 to 14 weeks were related to either *Sh. flexneri 3* or *Sh. sonnei*. The two of 15 to 20 weeks duration or more were due to *Sh. sonnei*.

## DISCUSSION

The duration of infectiousness of shigellosis, taken as a measure of the capacity to spread infection, was longer among children of this heavily seeded convalescent home than ordinarily recorded. Such a result is consistent with the protracted clinical course of the disease in this study and in this region generally. It was also true for healthy carriers. Although many invasions were brief, even casual, the number of long periods is impressive, and sufficient to suggest that the healthy carrier along with chronic recurrent shigellosis has been underrated as a focus of infection in shigellosis. The findings on convalescent carriers after ordinary acute shigellosis are too few for an opinion, although what was observed is in accord with the usual view that the convalescent carrier state is often absent, and if present, persists for a few days only, uncommonly

beyond two weeks. The extent to which the present findings apply to children of a general population, living under the usual conditions of a less developed country, is still to be determined.

The usual statement on carrier duration in shigellosis is in general terms; that it is short,[7] of a few days duration or a few weeks,[8] with little distinction between healthy and convalescent carriers. Many observations are from individuals exposed under favorable conditions of environmental sanitation and nutrition,[9] or from military practice.[10] Few studies have been made among children in regions where acute diarrheal disease is highly endemic, more severe, with a high mortality, and where malnutrition is prevalent.[11]

Many surveys of carrier prevalence have been made in general populations of such areas, with demonstration of a high order of frequency, for example 5.2% and 11% in the western and southern United States respectively,[12,13] and 7.5% in Guatemala.[14] Few studies have been made of incidence, the frequency with which carriers develop in association with cases, or repeated occurrence in the individual child over an appreciable time. More importantly, the tendency has been to view all carriers as of equal significance. The situation resembles that once existing in hemolytic streptococcal disease.

Clinical studies of scarlet fever showed that the longer carrier states were among convalescents, compared with healthy carriers. Certain convalescents, essentially healthy and yet with low grade chronic infection of the nose marked by external excoriations and crusting lesions of the anterior nasal mucosa, were singled out as particularly active in spread of the disease. From these observations came the concept of the "dangerous nasal carrier" as extraordinarily important as a focus of infection.[15]

In the present study, those patients with a chronic recurring clinical shigellosis maintained the infectious agent for long periods of time, sometimes five months. The two *Shigellas* principally involved, *Sh. flexneri 3* and *Sh. sonnei*, accounted for two-thirds of all recognized infections in the El Hogar population. Chronic recurrent shigellosis is seemingly identified as the prototype of the dangerous nasal carrier in streptococcal disease. In both diseases, the dangerous carrier is not strictly a carrier but a patient with low grade infectious disease. The longer duration of inapparent infection, the recognized carrier state, offers the further suggestion of a degree of biologic activity relatively common, beyond limits of identification by present clinical methods, and yet corresponding to actual disease.

Nutritional state appears to have the same capacity to effect adversely inapparent infection, the carrier state, as has been proven for manifest disease.[16] The periods of infectiousness recorded in this study were indeed longer than stated, since either the beginning or the end of infection was indeterminable for close to a half.

The group of eight children with no *Shigella* during this long period of daily observations has an interest all its own. These children had as much diarrheal disease as did those where shigellosis was a component of the total, in number of episodes and of days of disability. They had both typical acute diarrheal disease and the chronic recurrent form, and in essentially the same proportions so far as the small numbers permit judgment. It is almost past credibility that these children were not invaded by *Shigella* at some time during the study, considering the environmental conditions. The critical question is why they did not experience an established *Shigella* infection, either inapparent as a carrier or manifest as diarrheal disease.

Extensive evidence supports a depleted nutritional state as favoring higher attack rates for acute diarrheal disease. Malnutrition in this study was of a high order, equally frequent and of comparable severity in the two groups, and they had equal and high attack rates for diarrheal disease, all forms. The clinical course was long, compared with conditions in industrialized countries, and so was the *Shigella* carrier state when present. Malnutrition by itself did not determine why shigellosis characterized one group and not the other; there were no essential differences. Possible explanations relate to such host characteristics as dietary influence or the nature of the intestinal microbiota. A previously acquired immunity is not the likely reason; the children were too young and the prevailing groups and serotypes of *Shigella* too many. The process may be allied to that responsible for the transition from carrier to case, observed twice.

## SUMMARY

In a closed institution for children aged two to six years, convalescent from malnutrition and

infectious disease, *Shigella* was present in 32.7% of the population. Acute diarrheal disease occurred at a rate of 235 cases per hundred children per year, the incidence being the same for children with and without *Shigella*.

Children with chronic recurrent shigellosis, typically persisting for weeks or even months, were revealed as a dangerous source of *Shigella* infection. The data, though limited, indicate that the convalescent carrier state after ordinary acute diarrheal disease was brief, a matter of a few days. The healthy carrier state, under conditions of the study, was longer, 48 days in one instance, with an average of 17 days.

Chronic undifferentiated diarrheal disease, no *Shigella* present, was clinically indistinguishable from chronic recurring shigellosis and similarly for acute diarrheal disease. That a carrier state of undetermined nature also exists in undifferentiated diarrheal disease can be inferred from an epidemiological similarity.

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