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Current Microbiologic Aspects of Enteric Infections of Children*

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It is characteristic of many infectious diseases that they do not occur with the same frequency and severity in all countries of the world nor do their features always remain unchanged over a period of years. Enteric infections are no exception. There is little doubt that diarrheal disease has played a very significant role in morbidity and mortality of infants in the past and still contributes today to both in some parts of the world. These differences and changes are accounted for, in part at least, on the basis of changes in virulence of the etiologic agents and, probably to a much larger extent, by host factors, notably malnutrition and underlying diseases. It is the object of this presentation to discuss certain microbiologic aspects of enteric infection of infants and children, largely on the basis of experience in the United States.

Enteropathogenic, enterotoxic, and enteroinvasive Escherichia coli enteritis:

For many years the cause of enteritis of infants, so often fatal in the past, has remained a mystery, since the search for such pathogens as *Salmonella*, *Shigella*, *Vibrio*, etc., proved to be unrevealing. It was the German pediatrician Adam[1, 2] who first reported on the presence of certain biotypes of *Escherichia coli* in these infants and suggested that they may be etiologically related to the illness. Largely due to the pioneering work of F. Kauffmann[3] on the antigenic characterization of *Escherichia coli* and the studies by workers on both sides of the Atlantic[4-13] on the pre-

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sence of antigenically characterized strains associated with severe outbreaks of the disease in newborns and infants, enteropathogenic *E. coli* was considered to be an etiologic agent for enteritis of infants. These strains were identified by the presence of characteristic O and K antigens, the latter as the B variety. The evidence of the probable etiologic role rested on the following observations: (1) In epidemics the strain was usually found in most of the affected infants and often in large numbers. Such strains occurred with much lower frequency in healthy infants and adults. (2) Recognized enteric pathogens were not present. (3) In nursery epidemics the disease, notably that associated with *E. coli* O111, O55, and O127 was characterized by extraordinary contagiousness. (4) Chemotherapeutic agents, such as neomycin, proved to be effective both bacteriologically in eradicating the organism and clinically. Similarly, antibiotics were highly effective for prophylaxis. (5) A specific immune response to the particular serotype of *E. coli* could be documented in some 50 % of affected infants.[14] (6) In adult volunteers feeding of an enteropathogenic *E. coli* strain caused mild disease and a specific immune response in contrast to a "normal" strain. (7) Observation of infants exposed to such an enteropathogenic strain revealed in colonization and development of diarrhea. On the basis of these observations certain serotypes of *E. coli* were termed "enteropathogenic".[15]

There is little question that during the past quarter of the century the disease of infants associated with such serotypes has changed in character, the clinical manifestations today being very much milder than in the past. It is unknown whether changes in the microorganism, in the host, or in both, account for these differences. It is also noteworthy that certain enteropathogenic *E. coli* serotypes were found far more frequently in severe epidemics in nurseries, for example, *E. coli* O111:B4, than others, such as *E. coli* O26:B6, indicating differences in contagiousness. It was repeatedly pointed out that the antigenic structure of these serotypes of *E. coli* did not account for clinical manifestations, and the pathogenesis of enteropathogenic *E. coli* enteritis remained a mystery.

The question of enteropathogenicity of *E. coli* has been re-opened, largely through the recent developments in the field of cholera.[16-19] Recent studies have clarified the pathogenesis of Asiatic cholera and led to the discovery and characterization of the pathogenically important enterotoxin, the so-called choleragen. Even the mode of action of this toxic product, which causes fluid transfer into the lumen of the gut and associated diarrhea, has been largely identified. The toxin acts by stimulating adenyl cyclase resulting in an increase of cyclic AMP. Of particular interest is the observation that certain strains of *E. coli* produce a

similar, heat-labile enterotoxin, accounting for acute diarrheal disease of adults and children. Indeed, in a recent study it was shown by Rudoy and Nelson[20] that enterotoxin-producing strains of *E. coli* occur with higher frequency in children with diarrhea than in control subjects, although even the latter may be colonized with such strains. In addition, certain strains of *E. coli* produce a second, unrelated, heat-stable enterotoxin. A recent report[19] indicates that strains producing this toxin alone may cause diarrhea in adults. Its role in diarrheal disease of infants and children requires further elucidation. Yet another mechanism whereby *E. coli* may produce diarrheal disease has recently come to light. Some strains have invasive properties, penetrating the epitheilum of the intestinal wall or, experimentally, the conjunctiva of the guinea pig. Such strains are referred to as enteroinvasive. Thus, it is clear that there exist at the present time a number of candidates as etiologic agents of diarrheal disease, namely, enterotoxic and/or enteroinvasive strains of *E. coli*. It appears that these strains are quite unrelated to the serologically identified enteropathogenic strains mentioned above. So far as this writer[21] is concerned, it is important to learn whether the enteropathogenic strains, which were responsible for serious illness of the newborn and infants, were pathogenic by one of the above mechanisms or whether the pathogenicity was due to an as yet undefined mode of action. Should strains have been preserved from the above mentioned epidemics their enterotoxic and/or enteroinvasive properties should be determined. It must be kept in mind that virulence factors may be lost on culture in the laboratory. It appears that the particular age-related virulence of the serologically characterized strains of *E. coli* associated with the epidemics in the past and the extraordinary contagiousness among infants is not explained exclusively on the basis of enterotoxin production or enteroinvasive characteristics demonstrated by the newly developed techniques. Therefore, the final chapter on *E. coli* enteritis of infants and children remains to be written in the future. In view of the changed characteristics, as seen in the U.S.A. at this time, it is not unreasonable to suggest re-consideration regarding isolation, chemoprophylaxis and chemotherapy of enteropathogenic serotypes. Should virulence and contagiousness assume previous orders of magnitude, reconsideration of this approach will be necessary.

Salmonellosis:

Salmonellosis is the collective term used to include all infections of man and animals caused by the numerous members of the genus *Salmonella*. One of these members, *Salmonella typhi*, is the only species res-

ponsible for typhoid fever. A few other members may cause a clinical picture resembling typhoid fever, namely, paratyphoid fever. Essentially all other 1,400 members of this genus may cause disease, although ten members account for approximately 65 - 70 % of human infections.

Typhoid and paratyphoid fever have been largely controlled in certain parts of the world and present no longer a major public health problem. Thus, in the U.S.A., fewer than 400 cases have been reported during 1975. Nonetheless, it is important to keep in mind that occasional epidemics have occurred in countries with good hygiene, including Switzerland, Great Britain, and Germany. In contrast to typhoid fever, *Salmonella* gastroenteritis and food poisoning is still a common disease even in countries in which typhoid fever has been essentially eliminated. Thus, in the United States, it is estimated that there occur some two million cases of *Salmonella* infection a year in man. Most of them are self-limited and mild in nature and thus do not come to the attention of physicians. Even when physicians are consulted, the specific diagnosis is usually not made because appropriate laboratory examinations are not carried out. In addition, all positive findings of salmonellae in specimens from such patients are not reported to Health Departments and thus are not included in national statistics. On the basis of some 20,000 strains being submitted to the Center for Disease Control and on the justified assumption that only 1 % of infections are represented by these isolates, the above mentioned figure of two million cases seems entirely justified.

Our own studies[22] have indicated that subclinical and/or mild infection is frequently present in older siblings of children or infants with more severe *Salmonella* gastroenteritis requiring medical attention. Evidence for this conclusion is provided by the documentation of a significant and specific immune response to the causative agent in these siblings. Particularly in the absence of positive fecal cultures the demonstration of a specific antibody response is singularly helpful in the study of family epidemics, the diagnosis of mild and subclinical infection, and the prevalence of salmonellosis.

While it is obvious that systemic *Salmonella* infections, including typhoid fever, osteomyelitis, meningitis, and others, require antibiotic therapy, it has become evident that antibiotics neither are effective clinically nor bacteriologically in localized *Salmonella* gastroenteritis. In fact, it has been shown that the carrier state is prolonged following antibiotic therapy as compared to symptomatically treated or even untreated patients. Very recent observations[23-25] suggest that therapy with trimethoprim-sulfamethoxazole may shorten the carrier state in contrast

to antibiotics. Additional studies are indicated to determine the effectiveness of this regimen in various age groups and to ascertain the safety of this treatment in relation to effectiveness, notably in carriers.

To illustrate the ineffectiveness of antibiotic therapy in the control of a localized *Salmonella* infection, attention is called to a very unusual patient with *Salmonella* bacteriuria complicating lymphosarcoma.[26] This patient was treated with ampicillin for 19 weeks, tetracycline for one week, and chloramphenicol for more than four months, and yet the pathogen *(S. typhimurium)* was not eradicated from the involved kidney.

Infection in patients with impaired resistance may differ strikingly from the disease seen in otherwise healthy subjects. This is well illustrated by our observation[27] documenting that *Salmonella typhimurium* and other *Salmenolla* types invade the blood stream far more frequently in the former than in the latter group. Therefore, when *Salmonella* gastroenteritis develops in such subjects, chemotherapy may well be indicated to prevent complications of the localized enteric disease.

Shigellosis:

Shigellosis is a bacterial disease of the large intestine, often, but by no means always, associated with bloody diarrhea and systemic features. Most of the cases seen in Western New York are mild in nature and usually do not require hospitalization or even medical attention. So far as the pathogenesis of shigellosis is concerned, it is now clear that invasion of the mucous membrane plays a significant role rather than the production of enterotoxin. The distribution of the four *Shigella* species shows striking differences. In the United States, *Shigella sonnei* is encountered far more frequently than the other species, namely, *Shigella flexneri*, *S. boydii*, and *S. dysenteriae (Shiga)*. In contrast, in Japan and other parts of the world, *S. flexneri* is more prevalent than *S. sonnei*. The reasons for these differences are by no means clear, since both species exist in these countries. It is of interest to note that the originally described Shiga bacillus is hardly ever seen in the United States. However, attention is called to the recent Shiga bacillus epidemic that took place in Central America and resulted in a large number of deaths. Because of the mild nature of shigellosis as seen in the U.S.A. at the present time, it is not surprising to note that many cases are not diagnosed and included in health statistics. Our own studies[28,29] have clearly shown that the documentation of the immune response to the etiologic agent supplements bacteriologic diagnosis and makes recognition of culturally negative cases and subclinical infections possible. Study by health departments of a few cases of shigellosis may also lead to the recognition of otherwise

overlooked cases, as shown by the investigation of an outbreak of *S. flexneri* dysentery among American Indians.[30] Only very rarely is the infection transferred during delivery from mother to child.[31] Whereas in otherwise healthy individuals the infection remains localized to the gastrointestinal tract and adjacent tissues, blood stream invasion may be observed in subjects with reduced resistance, as described recently.[32] Documentation of the immune response of patients with opportunistic infections aids in the clarification of the role of suspected pathogens, particularly when exclusion of contamination is needed and only a single specimen is available for bacteriologic analysis.[33, 34]

A number of antimicrobial agents are effective in the treatment and prevention of shigellosis, provided that the strain is susceptible to the particular drug. Since antibiotic-resistant strains have been encountered, it is desirable to determine the antibiogram, particularly when confronted with outbreaks of the disease. It is noteworthy that antibiotic resistance may be due to the acquisition of R factors, namely, plasmids consisting of genetic material which code, through one or another mechanism, for changes in the bacterial cell that result in resistance. Since such R factors may be acquired from various species of gram-negative, enteric bacteria, it follows that unnecessary antibiotic therapy should be avoided, lest antibiotic-resistant bacteria become predominant in the intestine and thus provide plasmids for transmission to potential pathogens.

Other pathogens:

Needless to say, other microorganisms cause enteric infection, such as staphylococci, clostridia, *Yersinia enterocolitica*, and possibly other members of the family *Enterobacteriaceae*. In addition, recent studies[35-37] have led to the recognition of viral agents as causes of enteritis of infants, children and adults, and it is particularly in this area that additional investigations are needed before a complete understanding of the causes and pathogenesis of infectious enteritis is accomplished.

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