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PAHO ADVISORY COMMITTEE ON MEDICAL RESEARCH

Washington, D.C.
11-15 July 1977

THE DIARRHEA OF TRAVELERS

NEW DIRECTIONS IN RESEARCH

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NEW DIRECTIONS IN RESEARCH

Presented by

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Washington, D.C., USA

at the

SIXTEENTH MEETING OF THE
PAHO ADVISORY COMMITTEE ON MEDICAL RESEARCH

CONFERENCE PROGRAM

"THE DIARRHEA OF TRAVELERS
NEW DIRECTIONS IN RESEARCH"

Washington, D. C.
29-30 November, 1976

Sponsors: The World Bank, the Pan American Health Organization, the United Nations Development Programme, and Cornell University Medical College.*

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THE DIARRHEA OF TRAVELERS - NEW DIRECTIONS IN RESEARCH

Chairman: Dr. James A. Lee
Convener: Dr. B. H. Kean

MONDAY, 29 NOVEMBER 1976 — 9:00-9:30 A.M.

I. Introductory Remarks:

Dr. James A. Lee - Moderator
Dr. Hector R. Acuña
Mr. William T. Mashler
Mr. Somerset R. Waters

II. Epidemiology and Clinical Features — 9:30-10:30 A.M.

Dr. Sherwood L. Gorbach - Moderator
Dr. Karl A. Western - Rapporteur

Dr. Eugene J. Gangarosa
Dr. B. H. Kean
Dr. Leonardo Mata

Coffee and Refreshments — 10:30-11:00 A.M.

III. Etiology — 11:00 A.M.-3:00 P.M.

(Lunch 12:30-1:30 P.M.)

Dr. R. Bradley Sack - Moderator
Dr. Herbert L. Dupont - Rapporteur

Dr. B. Rowe - Escherichia coli - General Considerations - 10 min.
Dr. Gorbach - Escherichia coli - Toxigenic Strains - 10 min.
Dr. Neil R. Blacklow - Viral Pathogens - 10 min.

Dr. Samuel B. Formal
Dr. Richard L. Guerrant
Dr. Albert Z. Kapikian
Dr. Jorge Olarte
Dr. David A. Sack
Dr. Luiz R. Trabulsi

Coffee and Refreshments — 3:00-3:30 P.M.

IV. **Prophylaxis** 3:30-5:30 P.M.

Dr. Gangarosa - Moderator
Dr. Guerrant - Rapporteur

Dr. Dolores G. Evans - Surface Antigens - 10 min.
Dr. Stanley Falkow - Genetics of Toxigenic E. coli - 10 min.
Dr. Nathaniel F. Pierce - Antitoxin Immunity - 10 min.

Dr. Doyle J. Evans
Dr. Garth W. Jones
Dr. H. William Smith

Social Hour 6:00 P.M.

Dinner 7:30 P.M.

TUESDAY, 30 NOVEMBER 1976

V. Therapy 8:30-10:00 A.M.

Dr. Dupont - Moderator
Dr. Richard B. Hornick - Rapporteur

Dr. Gangarosa
Dr. Gorbach
Dr. Kean
Dr. John Nelson
Dr. R. Bradley Sack

Coffee and Refreshments 10:00-10:30 A.M.

VI. Future Directions

Dr. Kean - Moderator
Dr. Gorbach - Rapporteur

Dr. Dupont
Dr. Gangarosa
Dr. Hornick
Dr. R. Bradley Sack

VII. Adjournment 1:00 P.M.

Meeting Site: Pan American Health Organization Building
525 23rd Street, N. W.
Washington, D. C. 20037 (Room C)

Emergency Telephone: Should you wish to leave a number behind for emergency calls, the number of PAHO is 202-223-4700; their international Telex code: OFSANPAN.

CONFERENCE

THE DIARRHEA OF TRAVELERS - NEW DIRECTIONS IN RESEARCH

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THE DIARRHEA OF TRAVELERS --

NEW DIRECTIONS IN RESEARCH

SUMMARY OF INTRODUCTORY REMARKS

Introductory remarks made by representatives of the sponsoring institutions laid stress on the economic, political, and financial implications of travelers' diarrhea. Despite its publicised toll and the importance of bringing it under control, travelers' diarrhea has not attracted widespread interest in the world's biomedical community. And, the diarrheal diseases, of which this is one significant form, rank highest as an obvious and fundamental influence on human welfare and an important deterrent to economic development throughout the developing world. Travelers' diarrhea affects a large percentage of the one-quarter billion people who annually travel across the world's frontiers. Worldwide international tourism receipts amounted to U.S.$45 billion in 1975; thus, the impact of this disease is estimated to be very substantial.

Research into the diarrheal diseases of travelers can be expected to contribute greatly to a better understanding of indigenous diarrhea among the citizens of developing countries. Sickness, disability and death from the diarrheal diseases produce global statistics which are literally incomprehensible.

"Fear of sickness" is one of the major deterrents to underdeveloped countries receiving a larger share of the world's tourist dollars. By far the most common sickness suffered by tourists is diarrhea. At the rate at which international travel is growing, it was estimated that within ten years travelers crossing national frontiers will annually be spending U.S.$100 billion. How much of this enormous transfer will go to developing nations will depend in no small way on finding ways to protect the travelers from the shattering effects of diarrhea--hence, the urgent need for stepped-up research aimed at a better understanding and prevention/control of this important enteric disease.

SUMMARY OF SESSION: EPIDEMIOLOGY AND CLINICAL FEATURES

The session began by defining a traveler as a person who leaves his country or who travels to a different environment in his own country. The definition of diarrhea is a situation in which a person passes more than two or three times the number of bowel movements than are his custom, with the movements being liquid in consistency, and associated with one of the following symptoms: fever, abdominal cramps, nausea, vomiting, and chills. Recent studies have shown that approximately 75 per cent of cases of travelers' diarrhea are due to toxigenic Escherichia coli otherwise called TECosis. The TECosis syndrome has an incubation period of approximately 48 hours and most commonly occurs 9-12 days after arrival in a new environment. In studies in Kenya and in Mexico City, travelers' diarrhea was defined as three or more watery stools a day; two stools a day with other symptoms was also called travelers' diarrhea. One or two watery stools without other symptoms was called "loose motions," which may mean mild travelers' diarrhea.

Studies are being conducted with Peace Corps volunteers going to Kenya for two years. The first year involved 39 volunteers who experienced an attack rate of about 60 per cent over a five-week period. The disease was very similar to that described in Mexico City, but was relatively shorter in duration. Some believed that the definition of diarrhea should fulfill the physicists' definition of a liquid; that is, that it takes the shape of the container. Additional objective criteria need to be developed if we are to compare research studies in a meaningful fashion.

It was reported that the frequency of recovering an etiologic agent was directly related to the severity of diarrhea. In students in Mexico with 10 or more unformed stools an etiologic agent was recovered 84 per cent of the time versus 34 per cent recovery in milder diarrhea. The chance of recovering the etiologic agent is a cogent reason for research workers to distinguish grades of diarrhea, but focus specifically on a symptom complex primarily caused by toxigenic E. coli was felt to be too restrictive. Giardiasis is often manifested not so much by loose stools but by steatorrhea, malabsorption and weight loss.

EPIDEMIOLOGY AND CLINICAL FEATURES (CONTINUED)

The risk of acquiring travelers' diarrhea is related to who you are, where you go, and what you do. A Latin American who travels to another Latin American country is at a low risk. Similarly, a North American who visits the United Kingdom apparently is relatively safe. But the North American who visits a Latin American country seems to be at high risk of developing diarrheal disease.

In almost any population there is a background level of diarrheal illness from two to five per cent, due to a variety of causes. In a 1969-1970 study, American travelers who visited the British Isles and Scandinavia, exclusively, for an average stay of twenty days had diarrheal attack rates of only 4.2 per cent and 5.6 per cent, but there is a significantly higher level of diarrhea in North Americans traveling to Southern Europe. Several studies corroborate the earlier work which showed that North Americans experience even higher levels of illness when they visit Latin American countries, particularly Mexico. The attack rate, for example, ranges from thirty per cent in one first study, to fifty per cent in subsequent studies.

North American travelers in Europe who spent their time with relatives had the expected background levels of diarrhea of about 3.5 per cent. As their activities increased, diarrheal rates also increased. Students seemed to have the highest attact rate. Research groups who are focussing their efforts on studying North American students abroad have capitalized on this observation.

There is a significantly increased risk of diarrhea disease if one consumes raw vegetables, salads, or any raw foods. In a more recent study conducted in Mexico, there was a very significant association of illness with the consumption of salads containing raw vegetables. A 1970 study assessed different prophylactic and preventive measures in North Americans who traveled to an international congress in Mexico City. These who took no precaution at all, had an attack rate of fifty-five per cent. But those who took prophylactic medication only, drank bottled liquids only, or who avoided salads had a similar attack rate.

EPIDEMIOLOGY AND CLINICAL FEATURES (CONTINUED)

In a small group, persons who drank no water, persons who drank only commercially bottled water, or persons who drank purified water had about the same attack rate. What is most interesting is that those who frequently drank tap water had an attack rate about half that of those who avoided tap water. In summary, it does not seem that there is much we can do to advise the traveler to avoid diarrheal illness.

Some recent information was presented at the PAHO/WHO International Seminar on Typhoid Fever in Mexico City. During 1972-1973 an extraordinarily high weekly attack rate of typhoid fever occurred in the metropolitan Mexico City. This outbreak is memorable because of the large number of cases, conservatively estimated to be in excess of 100,000, the duration of the epidemic, and its spread over such a large geographic area. Historically most typhoid outbreaks have occurred in a limited fashion, e.g., a week, and at a particular place, e.g., a restaurant. Evidence was presented that this outbreak may have been due to a commercial product. During the epidemic period there was a selective higher risk of persons in the age group of five to twenty-four. If contact transmission were important in this disease, one would expect to find the highest attact rate in age groups one to four.

Examining the food-specific attack rate shows an association between illness and the consumption of bottled beverages. The attack rate was 30.8 per cent for those who consumed bottled beverages as compared to 7.1 per cent of those who did not consume bottled beverages. One product, Cidral, had a statistical association with the illness. Public health officials have been cautioning travelers to avoid drinking water because of the supposed risk of diarrheal diseases. Actually, the use of bottled beverages may possibly increase the risk of typhoid fever and travelers' diarrhea.

EPIDEMIOLOGY AND CLINICAL FEATURES (CONTINUED)

Two studies of British troops were reported from South Arabia and the United Arab Emirates. Twenty to twenty-five per cent of soldiers experienced a diarrheal episode within the first ten days of arrival.

There are no differences between travelers' diarrhea and the diarrhea seen in Guatemalan children, either in terms of symptomatology of causative agents. E. coli and viruses are spread to breast-fed children at three to six months of age. They initially acquire the agents that are already endemic in the community. Eventually the pediatric community becomes immune to endemic strains, but remain susceptible to imported strains. The attack rate is difficult to standardize in community studies. An attack rate in Guatemalan villages of about one hundred to three hundred per hundred child-years has been established, e.g., one to three attacks per child per year. Diarrhea was defined as an episode that began after at least two weeks of no gastrointestinal symptoms in that particular child. With less stringent criteria, the rate of diarrhea goes up dramatically. It is better to express morbidity in terms of the days, weeks or months the children are ill. By this measurement, a child will have diarrhea as much as forty per cent of the time. The diarrhea experience usually begins with episodes that are indistinguishable from those described here as travelers' diarrhea. Whatever we learn from travelers; diarrhea will have immense application to the understanding, prevention and control of diarrhea in the developing nations.

The paucity of data with respect to acquired immunity to the agents involved in travelers' diarrhea was noted. There is evidence that Bengalis have titers of antibody that neutralizes E. coli toxin in their serum, indicating possible exposure to this agent. The situation, however, is confused by the presence of cholera in the community.

EPIDEMIOLOGY AND CLINICAL FEATURES (CONTINUED)

The best evidence of naturally acquired immunity to enteric infection is still the studies of cholera in Bangladesh where a distinct relationship exists between age and the acquisition of serum antibodies directed against the somatic antigen of Vibrio cholera, and serum titer can be correlated with protection. Persons who have had cholera appear to be relatively resistant to a second attack of cholera for a period of one to two years. Further studies are needed to determine exactly how long such protection lasts.

It was reported that U.S. students appear to develop immunity after being in Mexico a year or longer. Whereas the attact rate for diarrhea is forty per cent per month for the first semester, after the first semester it is twenty per cent per month, in contrast to eleven per cent per month for the Mexican students.

Circulating antitoxic antibodies to E. coli were discussed. The lowest titers are seen in a group of students from the United States. The highest base line titers are found in Mexican students. American students who have spent more than a year living in Mexico had serum titers that are intermediate between the recently arrived American students and the local Mexican.

Reinfection, that is another spell of travelers' diarrhea in the same group of travelers,was discussed. In one study six hundred non-immune soldiers were transferred from the U.K. into the Arabian Gulf and put in a camp housing some three thousand immune troups who had been there for two years. The new arrivals had a twenty-five per cent attack rate of diarrhea within the first ten days of arrival. Most of this was due to a toxigenic E. coli; a few, however, had shigellosis. In about a fortnight's time, the travelers (non-immunes) had a second burst of diarrhea of epidemic proportion, this time due

EPIDEMIOLOGY AND CLINICAL FEATURES (CONTINUED)

to many different shigella serotypes. But the garrison troops, the immunes, simultaneously experienced this outburst of shigellosis.

Reference was made to the high incidence of travelers' diarrhea, thirty-five to forty per cent, among the 1200 scientists who attended the International Congress of Tropical Medicine at Tehran. Fifty per cent of those who came from the United Kingdom, Germany, and the United States developed diarrhea, compared to twelve per cent of those that came from Japan, France, Brazil and Portugal. Of the large group of Iranians only two per cent were ill during that period, suggesting that immunity does exist. Also commented on was the problem of using a vaccine to produce immunity to cholera in which long term persistent immunity is required. With travelers, however, it is necessary to produce immunity for a relatively short time, several weeks to a few months. Vaccines that have been unsatisfactory in cholera may be useful on a short-term basis in travelers' diarrhea.

SUMMARY OF SESSION: ETIOLOGY

There was general agreement that travelers' diarrhea is caused by a multiplicity of etiologic agents, the most frequently isolated being toxigenic Escherichia coli. A person going to a distinct geographic area is at risk to all enteric infections found locally. However, even with careful laboratory procedures, the causes of such diarrhea currently can be detected in only seventy-five per cent of cases.

An understanding of the relationship between E. coli and enteric infections, began with studies of pediatric diarrhea in the 1920's. Since that time serotyping of the organism has been possible through examination of somatic, flagellar and capsular antigens. In the 1940's an association of certain O groups with outbreaks of infantile enteritis was noted. While it has been generally accepted that certain serotypes of E. coli are responsible for infantile diarrhea, the situation in adults is just now being examined. In an outbreak of travelers' diarrhea among six hundred British soldiers transported non-stop from the United Kingdom to South Arabia several years ago, a single serotype of E. coli was identified. At that time there was no information concerning pathogenic mechanisms by the enteric agents.

About the same period workers in Japan and the United States demonstrated that E. coli isolated from humans with diarrhea were either enterotoxigenic or capable of invading the intestinal mucosa like shigella organisms. A series of studies beginning in the veterinary field and in cholera research led to the elucidation of both the heat-labile and heat-stable enterotoxins of E. coli and of the plasmid control of these agents. The standard tests for determining heat-labile toxin are the Y-1 adrenal cell, Chinese hamster ovary cell, and the ligated rabbit loop model. The stable toxin, for the moment, is best detected through the suckling mouse assay.

ETIOLOGY (CONTINUED)

Several studies have sought a connection between classical infantile enteropathogenic serotypes and the LT and ST-producing strains and have failed to find a consistent relationship. However, it has been the observation of several workers that the ability of E. coli to produce enterotoxin is not random and that certain serotypes tend to be more frequently implicated. Invasiveness is more clearly serogroup related. Sophisticated serotype analysis should be applied to future studies to assess the relationship between serogroup and pathogenicity.

That plasmids provide the genetic information for the pathogenic potential of a microbe, but that the carrier organism is of extreme importance was reaffirmed. Two workers were unable to make a virulent organism when the requisite plasmids were put into an E. coli K12.

The major problem with determining toxigenicity of E. coli isolates is their detection in the laboratory. Heat-labile toxin (LT) assays are reasonably successful, and a number of laboratories are using the Y-1 adrenal cell or the CHO tissue culture system. The major difficulty is the detection of heat stable toxin (ST). At the present time, the only reproducible assay is the suckling mouse test. The relationship between positivity in this model and pathogenicity for humans remains unresolved. Another problem relates to the small sample of E. coli examined from the large number present in a stool specimen. Five to ten isolates are picked for study, and this is a crude sample of the total population of 108 organisms per gm. It has not been established that the pathogen will invariably dominate in numerical supremacy over other fecal bacteria during the acute episode. We are in need of a reproducible test to identify toxigenic strains within the large population of E. coli that are present in a fecal specimen.

ETIOLOGY (CONTINUED)

Within the past five years, certain viruses have been implicated in the pathogenesis of acute non-bacterial gastroenteritis. One group is the reovirus-like agents which has been termed rotavirus, duovirus, orbivirus-like and infantile gastroenteritis virus by different investigators. The agent is responsible for both sporadic and epidemic outbreaks of gastroenteritis in infants and young children throughout the world. Studies conducted in England and the United States have shown that approximately fifty per cent of all children hospitalized with gastroenteritis are infected with the reovirus-like agent; it is identified in approximately ninety per cent of infants and young children during the peak winter months; the incidence falls to twenty per cent during the summer months. There are neutralizing, complement fixing and immunofluorescent stainable antibodies to these viruses. It has been shown recently that subclinical infection occurs in adult relatives of infected babies. Adult infection may on occasion be accompanied by diarrhea. The agent can be propagated in gnotobiotic piglets and newborn, colostrum-deprived, rhesus monkeys.

The second of the two recently recognized viral agents in diarrhea is the parvovirus-like agent. These are samll (27nm in size), and have been shown recently to cause three well-described outbreaks of gastroenteritis. The viruses isolated in Norwalk, Ohio, Hawaii, and Montgomery County (Maryland) appear distinctive in that clinical immunity to one of the agents does not appear to confirm protection to other agent (based on volunteer cross-challenge experiments).

Although viruses have been frequently hypothesized as a cause of travelers' diarrhea, there are virtually no studies of their incidence in this disease. The study of gastroenterologists visiting Mexico City two years ago involved examination of diarrheal stools by electron

ETIOLOGY (CONTINUED)

microscopy of only thirteen of the one hundred and seven participants in the study; the results were negative. Two of the fifty-one ill participants had an antibody response indicative of infection with the agent. Studies of diarrhea in twenty-seven U.S. marines in South Korea, uncovered reovirus-like agents in two men. The parvovirus-like agent has not been looked for in outbreaks of travelers' diarrhea by either serological techniques or by electron microscopy. Clearly, however, this needs to be done.

Of forty Peace Corps volunteers traveling to Kenya, three developed four-fold titer rises to reovirus-like agents. This further suggests that these agents may occasionally be responsible for acute diarrhea among traveling adults. Volunteers experimentally infected with reovirus-like agents were discussed. Since most individuals had pre-existing antibody against the agent, it was difficult to find seronegative subjects for challenge experiments. Two-thirds of the volunteers with no antibody developed a serologic response to infection; half excreted a reovirus-like agent, and one-third developed clinical illness which included fever, diarrhea, and vomiting.

Investigations with a group of thirty-nine Peace Corps volunteers during their first five weeks in Kenya were cited. Twenty-seven of the thirty-nine volunteers developed diarrhea, and there were multiple episodes in eleven. Enterotoxigenic E. coli were isolated from seventeen of the twenty-seven volunteers with diarrhea and from one of the twelve volunteers without illness. Many serotypes, some previously not associated with pathogenicity, were involved and strains producing heat-labile and/or heat-stable enterotoxin were also identified. These studies demonstrated that toxigenic E. coli were the major agents of travelers' diarrhea in a continent were studies previously had not been performed.

ETIOLOGY (CONTINUED)

Other research has demonstrated the importance of heat labile toxin producing E. coli in acute diarrheal disease in the United States, Mexico and Brazil and evidence was presented that the strains were responsible for between fifty and seventy per cent of illness. Studies performed during 1965 and 1967 demonstrated that shigella and salmonella frequently were implicated in diarrheal disease among a group of 155 Americans staying in Mexican hotels. These agents were recovered in twenty-five per cent of the individuals. In each of the more recent studies a small number of strains of E. coli which elaborate only the heat-stable enterotoxin have been isolated from humans with diarrhea. Studies performed at the University of Maryland demonstrated that only ST strains were capable of producing illness in volunteers.

In Mexico among student populations, food was implicated epidemiologically as the vehicle for transmission of toxigenic E. coli and shigellosis.

In a survey of food from a variety of sources including restaurants, the school cafeteria and street vendors coliforms, Shigella sp and Salmonella sp were isolated. Contaminated foodstuff was also incriminated during the outbreak in South Arabia. Examination of foods obtained from supermarkets by the FDA disclosed that eight per cent of those randomly studied contained toxigenic E. coli with the same serotypes incriminated as in diarrhea. These studies support the notion that food serves as a major source of infection.

A major obstacle to future research in this area is the difficulty with various laboratory assays. As more data are accumulated, it has become clear that enterotoxigenic strains of E. coli show host specificity. Strains pathogenic in pigs, for example, do not cause disease in rabbits or man. More work is needed to determine the

ETIOLOGY (CONTINUED)

significance of this species specificity and to characterize the elements which make strains virulent for man. The other issue deals with the presence of mixed infections. In approximately twelve to twenty-five per cent of cases of travelers' diarrhea,multiple pathogens are found. It is difficult to ascribe etiologic significance to the various isolates in such instances.

SUMMARY OF SESSION: PROPHYLAXIS

Three major areas of attack were outlined for prevention of diarrhea of travelers: (1) the epidemiologic approach aimed at preventing transmission of the causative agents; (2) full utilization or enhancement of nonspecific host resistance factors which are normally present, such as gastric acidity, intestinal motility and normal bowel flora; and (3) the development of vaccines to boost specific immune processes such as systemic or local antibodies against toxins or adhesive bacterial proteins or pili, or to enhance specific competing receptor substances.

(1) Epidemiologic prevention: The number of pathogenic organisms ingested is a major determinant of whether or not a patient will actually become infected. Some traditional concepts regarding the dangers of ingesting such foods as fresh salads have been confirmed in recent studies. However, other widely-held views such as the safety of commercially bottled beverages are now being soundly refuted. Not only has bottled water been incriminated in the spread of Vibrio cholerae in Portugal but there is recent evidence to suggest that the large outbreak of antibiotic-resistant typhoid fever in Mexico was also transmitted by a bottled beverage. It appears that noncarbonated bottled drinks are more suspect than carbonated ones, possibly because of the lower pH of carbonated drinks which would render them hostile to many microorganisms. Evidence was also presented on the high coliform counts,and thus the potential risk,of such popular food in Mexico as tortillas and certain types of beverages. It is clear that the regulation of commercial food and drink products is lacking or non-existent in many parts of the world. There is a great need for more information in order to devise means to prevent the diarrhea of travelers.

(2) Nonspecific Host Resistance: Gastric acidity is a substantial barrier to enteric infections; neutralization of this barrier with antacids can greatly reduce the infecting dose of several pathogens. The frequency and severity of various enteric infections appears to be increased among achlorhydric patients.

PROPHYLAXIS (CONTINUED)

Normal intestinal motility provides an additional host defense against enteric infections. Data from experimental animals and from patient experience show that inhibition of normal intestinal motility by opiates or by antimotility drugs such as the combination of diphenoxylate hydrochloride with atrophine (Lomotil) may prolong or enhance the severity of certain enteric infections. While there is debate about the effect that inhibition of normal intestinal motility has upon intestinal absorption, some have demonstrated the striking impairment of the distribution of a barium bolus in the small bowel after use of methantheline bromide. Whereas over ninety per cent of a radio-labelled bolus was normally absorbed in less than ten minutes, less than seventy per cent was absorbed over one-half hour following methantheline administration. Thus, it appears that normal intestinal motility may play a role not only in ridding the infected host of an invasive pathogen, but also in absorption of fluid and electrolytes. There is a great need for data from controlled clinical trials among travelers to determine the efficacy of the antimotility drugs widely used by travelers who acquire, or even worry about acquiring, a diarrheal illness.

The role of normal bowel flora as a major host defense mechanism is probably the most often overlooked. The protective role of normal flora against the invasion of the gastrointestinal tract by "outside" pathogens has been well documented in experimental animals and in humans. The infecting dose of Salmonella typhimurium in mice is reduced over 100,000 fold by the administration of one dose of streptomycin. This reduced resistance correlated well with a reduction in normal colonic flora and in their antibacterial acidic products. Normal resistance was restored with the return of normal enteric flora, especially Bacteroides, several days after antibiotics were discontinued. Furthermore, Swedish tourists who took the prophylactic antimicrobial, oxyquinolin, acquired

PROPHYLAXIS (CONTINUED)

significantly more salmonella infections than those who took no antimicrobial prophylaxis. As with antimotility drugs, there is a great need to determine and carefully weight the potential risk: benefit ratio of antibiotics as well.

(3) Specific immune processes: Regarding specific humoral immunity to E. coli, there are now at least five different "virulence" factors which offer potential targets for specific protective immunity. The first is the heat-labile enterotoxin, which is logically and pathogenically analogous to cholera toxin; its role in the pathogenesis of travelers' diarrhea is now well documented. The heat-stable enterotoxin produced by E. coli does not appear to be antigenic by available tests; its role in contributing to human disease, particularly "Turista" in Mexico, is becoming increasingly apparent. A third type of E. coli toxin, a cytotoxin similar to that produced by shigella, was introduced at this conference. If analogies to the Shigella (Shiga) toxin hold, this may provide another antigenic target for antitoxic immunity to this type of E. coli. A fourth mechanism of E. coli pathogensis involves the ability of certain strains of E. coli to invade the colonic mucosa in a manner akin to shigella. There may be potential for immunity to this invasive process either by non-specific phagocytic or other host resistance processes or, possibly, by a specific humoral immunity to a portion of those organisms that is responsible for their invasiveness. Finally, analogous to the K-88 antigens in strains of E. coli first described in piglets, additional information was provided about the "colonization factors" identified among E. coli isolates from humans. These surface proteins are antigenic; antibodies against this antigen might prevent attachment of the E. coli in the upper small bowel where colonization of strains that are also toxigenic appears to be critical for the production of human disease.

PROPHYLAXIS (CONTINUED)

The genetics of toxigenic E. coli was explained. Now that the plasmids responsible for LT, ST and K-88 surface antigen production have been cloned, and methods for genetic manipulation, including transposition of these genes to other plasmids have been developed, studies can now be done with amplification of enterotoxin production. In vitro studies of enterotoxin biosynthesis and its control are now possible. Attenuated strains are already being engineered such as an E. coli that produces "toxoid" (antigenically potent but biologically inactive toxin). There is great potential in this work for the development of toxoid or colonization vaccines.

The role of serum and locally secreted intestinal IgA antitoxic immunity was reviewed. The initial parenteral cholera toxoid trial in humans offered only modest (forty per cent) protection lasting approximately three months against clinical cholera. However, studies suggest that an orally-administered booster exposure to antigen, following parenteral primary immunization, may offer protection for a longer period.

The outlook for greater and longer-lasting protection when local antitoxic immunity is combined with immunity to other factors such as the colonization factor or with the use of live toxoid-producing vaccines is substantially brighter. The potential importance of antibodies in mature human breast milk after intestinal exposure to other E. coli antigens was emphasized.

In contrast to the Crater Lake outbreak where only thirty-six per cent of cases developed serum antitoxic antibody, over ninety per cent of U. S. students in Mexico who acquired diarrhea due to LT-producing E. coli responded with a rise in antibody.

PROPHYLAXIS (CONTINUED)

Returning to the enteropathogenic organism's ability to colonize the upper small bowel, it was reported that (a) bacterial attachment is mediated by adhesive substances on the bacterial surface reacting with carbohydrate, sterol or phospholipid receptors on the animal cell surface and (b) motile bacteria may respond chemotatically to materials released from the tissue and such may increase or decrease the association of bacterium with the animal cell.

A tantalizing nonspecific host resistance factor was introduced from the Veterinary experience with E. coli diarrhea among weaned pigs. A reduction of food intake to one-third the ad lib consumption offered substantial protection against experimental E. coli diarrhea. From this observation it seems reasonable that large amounts of food ingested by gluttonous travelers might neutralize gastric acidity, dilute local antibody or offer additional nutrients to organisms in the upper gastrointestinal tract, thereby reducing the infecting dose of the pathogen required to cause disease.

Regarding the role of antimicrobial agents in turista, studies done several years ago revealed that a non absorbable sulfonamide effectively reduced the attact rate of diarrhea over a two- to three-week period from thirty-five per cent to approximately seven per cent. However, substantial concern was raised about the potential risk of antibiotic resistance developing as a consequence of prophylactic use.

In summary here there are opportunities for substantial advances in all three areas of preventive attack on diarrhea of travelers. Better quality control of food and drink products sold to the traveling public would undoubtedly reduce the risk of developing enteric infections.

PROPHYLAXIS (CONTINUED)

The nonspecific host factors such as gastric acidity, intestinal motility, and normal bowel flora emphasize the risk of drugs that alter these factors, but also offer potential agents for enhancement of the attack against enteric pathogens. Finally, there are immunoligical and bio-chemical avenues for attack at specific virulence factors or receptor sites. It is clear that a multi-disciplinary approach toward the prevention of travelers' diarrhea is needed, not only from the standpoint of the travelers' health, but also to better control diarrheal diseases in the developing countries.

SUMMARY OF SESSION: THERAPY

This session covered the important therapeutic aspects of travelers' diarrhea. Since there is no available vaccine or widely-accepted chemotherapeutic agent for preventing this disease, complex proper therapeutic measures are necessary to abort the infection in patients, to prevent complications and to inhibit the spread of the etiologic agents. The therapeutic approaches available at present include appropriate fluid replacements, antimicrobial drugs and those medications that are aimed at the symptomatic relief of the diarrheal syndrome. The aim of this session also was to define the current state of knowledge in these general areas and to identify segments that need additional investigation.

1. Fluid Therapy for Severe Diarrheal Disease

In patients with cholera the replacement of lost body fluids is responsible for the present low mortality rate. This disease, induced by an enterotoxin operative in the upper small bowel, activates the secretion of protein-free, isotonic fluid in large volumes of liquid stools. Death results from hypovolemic shock. Parenteral infusion of isotonic electrolyte solutions is lifesaving, but this route presents major logistic problems because of the need for large numbers of bottles of IV fluids in areas of the world where manufacture, storage, and transportation problems are monumental.

The evolution of oral replacement fluid therapy sprang from the need to solve these practical problems. Oral replacement fluid containing approximately 90 meq. sodium, 80 meq. chloride, 30 meq. bicarbonate, 20 meq. potassium and 2 per cent glucose, is the currently acceptable formulation. This solution has been very effective in adult patients with cholera and appears to be equally effective in other forms of diarrhea such as that of travelers. The degree of dehydration that occurs in travelers' diarrhea is minimal in most cases compared to that of the cholera patients. Only an occasional patient with travelers' diarrhea appears to lose large volumes of fluid. Appropriate replacement

THERAPY (CONTINUED)

of electrolytes even with minimal fluid loss should be beneficial. No controlled studies have yet been done in adult travelers to determine the efficacy of this means of treatment. If such studies are done, they should be designed to determine the effect oral fluid therapy would have on the associated symptoms of the syndrome such as malaise, headache, and vomiting. Do dehydration of electrolyte shifts contribute to the development of these symptoms?

The risk of dehydration in the elderly, who are frequent travelers, needs to be emphasized. Dehydration can lead to postural hupotension. Those persons with significant atherosclerosis may sustain coronary or cerebral artery occlusions as a result of a drop in blood pressure. Thus, the need for oral replacement fluid should be communicated to the public. Faced with an upset gastrointestinal tract, a patient may want to limit oral fluids to stem the nausea,which in the presence of continuing diarrhea with liquid stools, could be disastrous. An education program is needed to stress the importance of oral fluids in turista.

Very few adults have difficulty with oral replacement of fluids. The taste is salty but various flavorings have made the solutions more palatable. A few adults with carbohydrate intolerance may experience increase diarrheal stools. The ingestion of water in addition to the electrolyte solution will allow the kidney to better regulate the electrolyte balances.

Children, especially infants, have not been adequately tested for their tolerance to these electrolyte solutions. Previous formulations tended to have excess sodium and lead to hypertonic dehydration. There is evidence that this complication may have been triggered by the eight per cent glucose in these solutions rather than the sodium content. Several studies to evaluate the efficacy of the oral fluid replacement formula in children under two years of age are underway.

THERAPY (CONTINUED)

Currently in the USA there is a commercial supplier of an appropriate electrolyte glucose powder. It is prepared in foil packets and the contents are put in eight ounces of water to obtain the proper solution. One need not purchase such a product as the ingredients are readily available for inexpensive home manufacture: one-half teaspoonful of salt, one-half teaspoonful of sodium bicarbonate, one-fourth teaspoonful of potassium chloride, and four tablespoonsful of table sugar. This is stirred into a liter of water.

The formula as given above is effective in those diarrheas caused by toxigenic enteric pathogens causing disease in the upper small bowel. Whether it will be equally effective in those diarrheal states caused by invasive pathogens that may disturb the absorptive capacity of the small and large bowel and which cause a loss of protein in addition to the electrolytes requires additional study. Some animal experiments indicate the absorption of glucose may be impaired in the invasive forms of diarrhea.

II. Antimicrobial Therapy for Travelers' Diarrhea

As with other forms of infectious diseases, it is necessary to specify the etiological agent of the diarrhea state in order to intelligently apply antibiotic treatment. Few experts disagree about the effectiveness of certain antibiotics in the treatment of shigellosis. There is disagreement, however, about which form of shigellosis requires antibacterial therapy. Those persons with small bowel involvement only, i.e., those with liquid stools, without pus or mucus,rarely require treatment as the disease is usually "over" by the time the laboratory reports the presence of shigella in the stool. Those patients with classic dysentery, i.e., small volume stools containing blood and mucus, will benefit from treatment. The disease course is shortened and the

THERAPY (CONTINUED)

organism is rapidly eliminated from the stool. Shigella vary in their susceptibility to antibiotics. Most Shigella sonnei strains are resistant to ampicillin. In some parts of the United States Shigella flexneri strains remain sensitive to ampicillin. Shigella dysenteriae infections and other resistant strains will check response to nalidixic acid or oxolinic acid or to trimethoprim-sulfamethoxazole (TMP-SMZ).

The use of antimicrobial drugs to treat salmonella infections in otherwise healthy persons has failed to yield conclusive results. These is evidence that oral antibiotics prolong the excretion of salmonella in the stool. It has been the practice to treat patients at the extremes of the age scale infected with salmonella. The clinical impression is that these patients have less disease than if not treated with antibiotics. When antibiotics are used in salmonella gastro-enteritis, they should be used only for a few days, three to five, then stopped.

Currently, efforts are being made to evaluate various antibiotics for their efficacy in diarrhea caused by E. coli which produce ST and LT. Earlier studies of treating turista in American students in Mexico with sulfathalidine, neomycin or tetracycline showed no benefit. However, these drugs, did reduce significantly the incidence of travelers' diarrhea when used prophylactically. Discrepancies may be explained in part by the nature of the infection. In most affected persons, the duration of the disease is less than forty-eight hours. Organisms may not persist in the small bowel longer than this period and thus would be difficult to eradicate by antibiotics since the chain of events causing the diarrhea has already been initiated without continued presence of the organism being necessary. The life span of intestinal epithelial cells is about two days and conceivably as they are sloughed into the lumen, so are the attached E. coli or their exotoxin, which are washed distally by the fluid secretion. This explanation, however, does not fit with

THERAPY (CONTINUED)

the more prolonged diarrhea seen in cholera patients (organisms persist for four days in upper small bowel) where the mechanism of diarrhea production is the same as E. coli. Of interest is the efficacy of antibiotics in shortening the duration of cholera induced diarrhea and in the rapid elimination of the vibrios from the stool. The results of "ongoing" double blind studies designed to determine the role of antibiotics in treatment of E. coli diarrhea of travelers are eagerly awaited.

III. Symptomatic Treatment of Travelers' Diarrhea

There are four mechanisms by which antidiarrhea drugs may interfere with the pathogensis of diarrhea: (a) alter intestinal motility, (b) absorb toxins or bacteria present in the lumen of the gastrointestinal tract, (c) influence the milieu of the gut fluid so as to inhibit growth of enteric pathogens, and (d) block secretion of fluid in the small bowel. Each of these mechanisms will be explored in greater detail in order to put their present relevance in the symptomatic treatment of diarrhea into perspective.

First, antimotility drugs--examples of this class of agents include paragoric, opium, anticholinergic drugs, and combinations such as Lomotil. These drugs are dangerous in infants. Their effectiveness in lessening motility in adults has been counterproductive in shigellosis, salmonellosis and possibly TECosis. For relief of severe cramps, Lomotil is of benefit but should only be used infrequently and not prolonged beyond two or three doses. It is difficult for most travelers and many physicians to accept the fact that antiperistaltic drugs may be counterproductive. Therefore, it is important to continue investigations of the effects of these drugs in patients with well characterized diarrheal conditions.

THERAPY (CONTINUED)

The second group are those medications that could absorb toxins in the intestinal lumen prior to their attachment to receptor sites on the epithelial cell membranes. In experimental animals it is possible to bind cholera or E. coli toxin to gangliosides therefore preventing them from reaching gangliosides in the cell membrane. This approach has not been tested in man. The popular over-the-counter medicines containing kaolin, pectin, bismuth, etc. are compounded for the purposes of absorbing and detoxifying toxins. In recent studies conducted in Central America these agents failed to alter the diarrhea syndrome in tested children. One compound, Pepto Bismol, did have an effect but as will be discussed later it was not due to the bismuth. In summary, there is very little evidence at present to justify strong recommendations for the general utilization of these drugs in the control of travelers' diarrhea.

Included in the third group of agents which may change the intestinal milieu so as to inhibit enteric pathogens are lactulose, Lactobacillus acidophilus and yogurt. Lactulose is non-absorbable or metabolized in the upper small intestine. However, this disaccharide will promote acidification of the lower intestinal contents because of degradation by the intestinal flora. While this may be effective in salmonella or shigella infections, it is not useful in treating TECosis where the disease is primarily proximal small intestine. In addition, a large dose of lactulose will cause diarrhea. The use of lactobacilli or yogurt to combat diarrhea has not been widely accepted. These organisms are not normal inhabitants of the upper small intestine and do not seem to be important in the nonspecific defenses established by bacterial interference phenomena.

THERAPY (CONTINUED)

The fourth group of drugs included in this discussion offer exciting prospects for future use. As additional studies demonstrate the mechanisms involved in fluid secretion, efforts have been made to interfere with one of the many steps involved. Studies in rabbits suggested that prostaglandins may play a role in the production of fluid by salmonella, shigella and perhaps cholera in experimental models. By employing a potent prostaglandin, indamethacin, prophylactically, most of the fluid produced by salmonella and cholera and about half of that induced by shigella infection could be inhibited. After further animal studies, similar inhibitors may be investigated in man. Salicylates are inhibitors of prostaglandins but in addition have been shown to have a direct absorptive effect on intestinal epithelial cells. Thus, the beneficial effects noted with Pepto Bismol in the amelioration of diarrhea in children may be due to the subsalicylate contained in the product. These results need to be expanded and confirmed.

Finally, future studies in animals will be directed at "turning off" the secretory stimulus in the epithelial cells. Currently, various binding nucleotides are being studied to determine if they can not only block the action of enterotoxins but also not actuate the adenyl cyclase in intestinal epithelial cells. The results of these studies may be significant factors in directing the development of future antidiarrheal drugs.

SUMMARY OF SESSION: FUTURE DIRECTIONS

The final session of this conference dealt with proposals for future directions in research of the diarrhea of travelers. The chairman of this session placed the following charge before the participants: "I want your dreams and then I want your practical solutions."

EPIDEMIOLOGICAL RESEARCH

Strong emphasis was placed on the need for further studies of the epidemiology of travelers' diarrhea. It was suggested that the potential for immediate, short-term benefit, in terms of prevention, would come from such studies since more basic research on vaccine development is several years in the distance.

At the present time, we need more information concerning the vehicles of transmission and the protracted survival of pathogens in sites outside the body. The bottled beverage industry has been implicated in recent outbreaks and may be an important source of contamination. The food industry in many developing countries does not operate under adequate regulations of quality control that can assure pure products. Of a special concern are the ready-to-consume foods including ice cream and packaged products. Increased emphasis in this area would yield immediate benefits. Several speakers indicated that additional studies of the epidemiology of travelers' diarrhea are required from many parts of the world. Currently, our main information is from Mexico, and it would be important to confirm the observations concerning epidemiologic patterms and etiologic agents in other countries. To be included in such studies would be the attack rate among travelers, the severity of disease, the propensity for recurrent episodes in the same journey, and the effect of an acute episode on intestinal physiology with regard to chronic diarrhea and malabsorption.

While investigating the epidemiology of travelers' diarrhea in a specific country, there should be studies of the patterns of diarrhea in the local community. Since the microorganisms responsible for the diarrhea of travelers are acquired from the local environment, it is likely than many of the permanent inhabitants suffer from similar attacks of diarrhea, although less frequently. The main focus should be pediatric diarrhea, since the attack rate and severity of diarrheal disease is most pronounced in this age group. In a sense, the traveler, with his naive immunologic system, is epidemiologically more akin to the young child within the country who has not yet been exposed to environmental pathogens.

ETIOLOGICAL AGENTS OF TRAVELERS' DIARRHEA

There was general agreement that an important priority is to increase the sensitivity of our diagnostic tests for identifying the pathogens of travelers' diarrhea. Approximately one-third of such cases remained undiagnosed since a specific microorganixm cannot be identified by available methods. There are also cases in which multiple pathogens are identified either by culture or by serology, and it becomes difficult to incriminate a specific agent in these instances.

With regard to toxigenic E. coli, we need more information on the type of toxin (heat-labile or heat stable) that is elaborated by pathogens causing diarrheal disease in travelers. Careful testing should be done on such isolates in order to gain complete information on the pathogenesis and epidemiologic patterns. More extensive study of the surface antigens would be extremely important. Such antigens as K may determine host specificity so that strains causing disease in animals can be differentiated from those infecting man. Besides toxigenic E. coli, there should be an increased awareness of other pathogenic enteric bacteria.

The role of viruses in travelers' diarrhea has not been adequately studied. The parvovirus-like agents should be further investigated since they are notorious for producing large-scale outbreaks of diarrheal disease among children and adults. Diagnostic tests for this virus are still in early stages of development. The reo-like virus has been well-studied in children, but there are few longitudinal investigations to assess its natural history, and relatively little information concerning its importance in diarrhea of travelers. There are also Corona viruses which cause disease in animals, and they have been recently described in human infections. We need techniques to search for this agent, as well as other viruses which may be relevant to the etiology of travelers' diarrhea.

PATHOGENESIS

The pathogenesis of microbial agents causing diarrheal disease was targeted as an area requiring further research. Good progress is being made on the heat-labile toxin of E. coli. There is relatively scanty information concerning the heat-stable toxin, both in terms of its chemical structure and its mechanism of action. It was suggested that a third type of E. coli pathogen, distinct from toxin-producers or invasive strains, may be the causative agent in some cases of diarrhea. Finally, there is need to study other enteric bacteria for toxin-producing potential.

Several participants directed attention to another mechanism of pathogenesis, namely, colonization of the gastrointestinal tract. The ability to colonize and adhere to the intestinal mucosa is a prerequisite for all diarrhea-producing microorganisms, and this aspect should be an area of active investigation. Some E. coli strains possess a K antigen on their surface which allows them to multiply in the small intestine. The receptors on the epithelium surface for these antigens have not been identified. Recent studies have suggested that intestinal immunity to such colonization factors may be important in the prevention of diarrheal disease. For this reason, the key to vaccine development may lie in a better understanding of colonization and adherence factors.

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but their presence in the gut lumen may reduce adhesion in much the same way as the antibody.

A major priority for future research is a better definition of intestinal immune mechanisms. Immunological events in the gut are not necessarily reflected by serum antibody since the two systems may, in certain critical areas, behave independently. Further research is required to learn how intestinal immunity develops, how specific such immunity is in its memory for prior exposure, and how long and at what level of effectiveness intestinal immunity persists. It was emphasized that in

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order to study pathogens causing diarrheal disease in man, it is necessary to study patients or human volunteers, since intestinal microbial pathogens are species specific. Longitudinal field study of diarrhea should be undertaken in order to investigate development of immunity. It was also emphasized that the volunteer studies have provided important information with regard to diarrheal disease, and that such studies should be supported in the future. Veterinary bacteriologists in the group emphasized that important data can be obtained from studying animal pathogens in the native animal species. They warned against the tendency to study human pathogens in animal models because of intraspecies differences.

GENETICS AND MOLECULAR BIOLOGY

Several participants stressed the necessity to gain further information concerning the molecular mechanisms by which microorganisms cause disease. With regard to toxigenic E. coli , it is apparent that genetic mechanisms control pathogenicity, both in terms of toxin production and colonization factors. Such research needs to be extended to other microbial pathogens associated with travelers' diarrhea. An understanding of genetic mechanisms of pathogenicity could potentially yield "vaccine strains." For example, it might be possible to engineer, by genetic manipulations, an E. coli strain that produces a natural toxoid having the capability of inducing immunity but not causing disease. Such a toxoid, for example, might be a sub-unit of the natural toxin which is capable of binding with appropriate receptors, but lacks the capability of initiating the series of events leading to intestinal fluid production. An alternative approach is an E. coli strain capable of colonizing the bowel but lacking the ability to produce enterotoxin. In this instance, antibodies might be developed against the colonization factor, which in turn would prevent virulent strains in nature from adhering to the mucosal surface and initiating diarrhea. Besides providing

GENETICS AND MOLECULAR BIOLOGY (CONTINUED)

potential vaccine strains, molecular biology can assist in purification of toxins or other virulent factors. E. coli strains can now be produced in the laboratory which make many copies of toxin, hence, vastly increasing the concentration of toxin produced from a culture. The increase yield facilitates the purification of toxin and other virulence factors.

PREVENTION OF TRAVELERS' DIARRHEA

It was generally agreed that two strategies should be applied to the problem of prevention: a short-term approach which utilizes the lessons of epidemiology and a long-term approach which involves a vaccine that brings together information from the fields of immunology, pathogenesis, and molecular biology.

All participants agreed that the problem of travelers' diarrhea is a reflection of the general level of sanitation in the community. Improvements in the food and beverage industry would bring great benefits to both the traveler and the community at large. Direct action programs in the developing countries, as well as dissemination of information to travelers regarding safety of foods and beverages, should be supported. In order to encourage tourism, it will be necessary to institute control measures in hotels and restaurants frequented by foreign visitors. However, it was emphasized that this should be part of an overall program of sanitary control in these countries. On the horizon is the possibility of prevention by development of appropriate vaccines. Significant progress is being made with E. coli, salmonella and shigella vaccines, but the long-range development must be tied to attaining basic information concerning the immunology of the gut. These points were made in the other sessions, and were given stronger emphasis during the discussion of vaccine development.

TREATMENT OF TRAVELERS' DIARRHEA

The over-riding concern in considering therapy of the diarrhea of travelers is the risk: benefit ratio. Most participants believe that antimicrobial therapy might potentially reduce the symptoms of diarrhea although this is not yet proven. However, the risk of widespread usage of these drugs impose certain hazards. To be considered are the risk to the individual traveler from side effects of the drugs, and, in addition, the risk to the population at large that might attend the widespread use of antibiotics, i.e., selection of antibiotic-resistant pathogens, not only among E. coli, but a broad range of pathogens in the community.

Besides the use of antibiotics, however, there are other approaches to the symptomatic treatment of travelers' diarrhea. Further research is required to assess the role of antispasmodics and antimotility drugs. It was reported that bismuth preparations might be effective in travelers' diarrhea. Another potential for future research is the use of agents that interfere with binding of toxins, or that prevent the activation of adenyl cyclase. In the latter category, there has been some promise with salicylates and guanine nucleotides. It was agreed by the participants that studies of pharmacological agents to relieve the symptoms of diarrhea should be actively encouraged.

The conference was concluded with a request from the Chairman for specific proposals from the participants for research projects which they would like to conduct during the next five years.