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Travelers' Diarrhea in Panamanian Tourists in Mexico

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To determine whether residents of developing countries are unlikely to acquire travelers' diarrhea, 64 Panamanians of widely divergent socioeconomic strata were studied during a 15-day tour through Mexico. Twenty-three (36%) tourists experienced 27 episodes of travelers' diarrhea that were caused by seven different pathogens. The most commonly identified etiologic agents were rotavirus (26%), Norwalk virus (15%), and *Campylobacter fetus* (11%), whereas enterotoxigenic *Escherichia coli* was not frequently associated with travelers' diarrhea. Acquisition of travelers' diarrhea was correlated directly with high socioeconomic status. Varying levels of immunity to enteropathogens that are endemic in Panama may explain the different isolation rates of pathogens.

The widely held assumption that travelers from developing countries are less likely to develop travelers' diarrhea than travelers from developed countries because of lifelong exposure to indigenous pathogenic enteric organisms has never been directly validated [1–3]. Therefore, we used a protocol similar to those used in previous investigations of travelers' diarrhea [4–7] to follow 64 Panamanians during their 4,000-km, 15-day, five-city bus tour through Mexico in March 1978.

Materials and Methods

Study population. After approval of the protocol by the human experimentation committees at all cosponsoring institutions, we contacted a local travel agent in Panama City who provided us with the names of 64 Panamanians, ranging in age from 10 to 74 years (mean, 35 years), who were planning a tour through Mexico. All 64 persons volunteered to participate in our study. Of the 64 subjects, 25 had previously traveled outside of Panama, 31 were of low-income strata (mean annual income, <$2,000), and 81% were female.

Study design. During a visit to each subject's home before the trip, the following epidemiologic and demographic data were obtained: previous international travel and episodes of travelers' diarrhea, family size, living conditions, highest level of education, and occupation. We obtained fresh samples of stool and blood from all subjects within 10 days of their departure. Surveillance for travelers' diarrhea (passage within a 24-hr period of three or more liquid stools with cramps, vomiting, fever, or prostration) was conducted at least three times a day while the subjects were in Mexico and daily for the first five days upon their return to Panama. To be considered a second episode of travelers' diarrhea in the same individual, at least two asymptomatic days had to follow termination of the initial episode before the recurrence of symptoms. The clinical features of duration, temperature elevation, and symptoms were recorded upon detection of travelers' diarrhea. Stool specimens were collected from each subject within 12 hr of the onset of diarrhea. Subjects were cared

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for by one of us (R.W.R.) during each episode. To maximize compliance we supplied and directly administered all prescribed treatments at no cost to the subjects. Only one subject received antibiotic therapy for travelers' diarrhea: a 26-year-old man with severe dysentery. During the final day of the tour in Mexico, we collected a stool sample from all 64 subjects (designated the concluding trip sample). A questionnaire completed during the return trip to Panama was used to identify preferences in food and water consumption that could be associated with the acquisition of travelers' diarrhea. A second blood sample was obtained from all subjects 15 days after their return to Panama (concluding trip sample).

Although traveling as a group, study subjects had widely varying opportunities for exposure to pathogens causing travelers' diarrhea. Subjects dined twice daily at restaurants of their own choice and pursued widely divergent activities in each of the five cities visited by the tour.

We constructed a composite socioeconomic index (Hollingshead index) [8] based on occupation and education to determine the relationship among the group's widely divergent socioeconomic status, their likelihood of acquiring travelers' diarrhea, and their immune status before the trip (based on titers before the trip of antibodies to various pathogens causing travelers' diarrhea). This index is based on a linear-regression model in which the education level is graded one to six and the occupation level is graded one to seven. To determine the index value of a single subject, the education variable is multiplied by five and the occupation variable is multiplied by six. The sum of these variables equals the socioeconomic score. The lowest value is 11 and the highest value is 72.

Linear-regression and χ^2 techniques were used in data analysis [9].

Laboratory tests. Bacteriology. Pretrip and concluding trip stool samples were processed directly in the Gorgas Memorial Laboratory, Panama City, Panama. Pretrip stool samples were inoculated directly onto primary isolation media. Samples taken at the conclusion of the trip were maintained for 24 hr in Stewart's transport medium before being plated onto primary isolation medium in the Panama laboratory.

Shortly after collection stool specimens obtained during the trip from subjects with travelers' diarrhea were inoculated into Stewart's and Cary-Blair transport media. Previous work has demonstrated that enteric bacterial pathogens, including enterotoxigenic *Escherichia coli* (ETEC), salmonellae, and *Campylobacter fetus*, but not shigellae, are likely to be successfully maintained for two weeks in refrigerated Cary-Blair medium [10]. These stool specimens from subjects with travelers' diarrhea were also directly plated onto MacConkey's agar to increase the likelihood of recovering shigellae. After overnight incubation five colonies that did not ferment lactose and that were of different colony types, if present, were removed from each MacConkey's agar plate and placed onto nutrient agar for transport back to Panama and subsequent testing for shigellae.

In Panama all stools and swabs that had been maintained at 5 C on Stewart's or Cary-Blair media or on nutrient agar were first streaked onto MacConkey's, salmonella-shigella, and thiosulfate-citrate-bile salts agar plates and inoculated overnight onto selinite F broth and alkaline peptone broth for subsequent streaking onto a second MacConkey's, salmonella-shigella, and thiosulfate-citrate-bile salts agar plate. Suspicious colonies were placed onto triple sugar iron agar and, when indicated, analyzed with the API system (Analytab Products, Plainview, N.Y.).

From each original MacConkey's plate five lactose-positive colonies typical of *E. coli* and a pool of 10 other typical *E. coli* colonies were selected and stored on nutrient agar. All *E. coli*-appearing isolates were tested in duplicate for production of heat-labile (LT) [11] and heat-stable enterotoxins [12]. Titers of antibody to LT were determined in duplicate [13]. A disk diffusion method [14] was used to determine the sensitivity of all bacterial enteropathogens to ampicillin, bacitracin, colistin, erythromycin, gentamicin, kanamycin, neomycin, penicillin, tetracycline, and triple sulfonamide.

To isolate *C. fetus*, fecal samples (from before the trip) or swabs (from episodes of travelers' diarrhea or concluding trip stool samples) were plated onto medium consisting of brucella agar base and 10% sheep erythrocytes with vancomycin (10 mg/liter), polymixin B (2.5 international units/ml), and trimethoprim (5 mg/liter). Plates were incubated at 43 C in an atmosphere of 5% O_2, 10% CO_2, and 85% H_2 and were examined at 24 and 48 hr. Gray, nonhemolytic and comma-shaped colonies were further characterized with oxidase and catalase tests. Oxidase- and catalase-positive orga-

nisms were characterized by using differential growth rates in NaCl solutions, production of H_2S in Kligler's medium with lead acetate paper, and sensitivity to nalidixic acid [15, 16].

Parasitology. Stool specimens were emulsified in 10% formalin and in 5% polyvinyl alcohol. Formalin-preserved stools were stained with iron hematoxylin. Both types of specimens were examined by direct light microscopy. Only when trophozoites (*Giardia lamblia* or *Entamoeba histolytica*) or intracellular red blood cells (*E. histolytica*) were seen was a subject's illness ascribed to that particular parasite.

Virology. Stools for virus examination were frozen on dry ice immediately after collection and were later stored at −70 C for subsequent detection of rotavirus antigen using an enzyme-linked immunosorbent assay [17]. Titers of antibody to human rotavirus were determined by using a CF assay with Nebraska calf diarrhea virus and O agent as substitute antigens [18]. Antibodies to Norwalk virus were determined by using a solid-phase microtiter radioimmunoassay [19]. A positive serologic diagnosis was defined as a fourfold or greater increase in antibody titer between pretrip and concluding trip serum samples.

Results

Twenty-three (36%) of the 64 subjects had at least one episode of travelers' diarrhea, and four persons had two episodes.

Clinical results. Illness began on the third day of the trip, peaked between Tasco and Acapulco on March 11 and 14, and tapered off shortly after the group's return to Panama (figure 1). The onset of illness occurred three to 17 days after arrival in Mexico, with the median onset at 10 days after arrival. The median duration of illness was 38 hr (range, 2–91 hr). The median number of loose stools passed by subjects with travelers' diarrhea during the peak 24 hr of their illness was eight (range, three to 34 stools). Abdominal cramps, malaise, nausea, and anorexia occurred frequently (table 1). Temperature elevation to >38 C was documented in 83% of the cases. No specific clinical symptomatology characterized the illness caused by a particular pathogen of travelers' diarrhea, although subjects with diarrhea due to Norwalk virus passed fewer stools (mean number, five) per peak 24-hr period of illness than did patients with diarrhea due to rotavirus (mean number, eight). Six (60%) of the 10 episodes of travelers' diarrhea in which a pathogen was not identified were very mild (three loose stools with mild prostration and no fever), a result which suggests a possible noninfectious etiology.

Epidemiologic results. We could not identify the transmission mechanisms of those pathogens causing travelers' diarrhea. In two of the eight family groups (accounting for 20 [31%] of the 64 subjects) in the tour, the temporal clustering of their illness suggested a common-source transmission. A man and his wife developed rotavirus diarrhea concurrently, and two middle-aged sisters simultaneously developed Norwalk virus–induced diarrhea. The campylobacter enteritis that occurred in two teen-aged sisters was separated by an

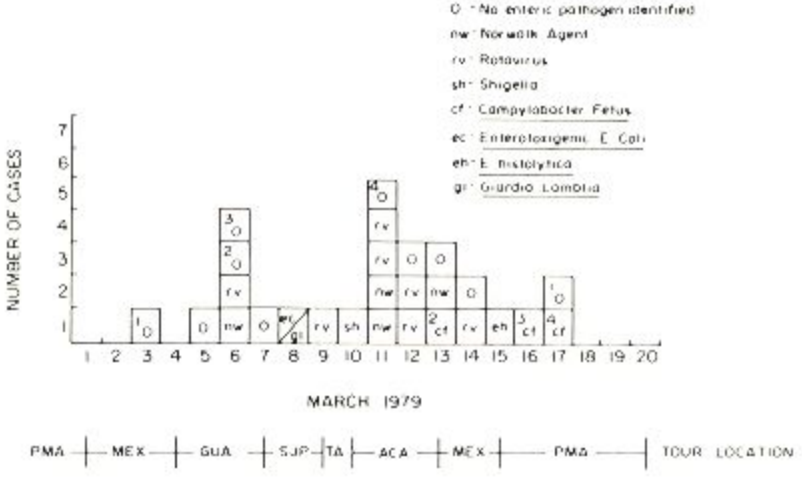

Figure 1. Cases of travelers' diarrhea in a group of 64 Panamanian tourists in Mexico in 1979, by etiologic agent and date plus place of onset. Four subjects (numbered) experienced more than one episode of disease. PMA = Panama; MEX = Mexico City; GUA = Guatemala; TA = Tasco; SJP = San Jose Purua; ACA = Acapulco.

Table 1. Frequency of symptoms of travelers' diarrhea in ill persons among a group of 64 Panamanian tourists in Mexico.

Symptom	Percentage of episodes with symptoms (n = 27)
Diarrhea*	
3–4	40
5–8	40
9–31	20
Abdominal cramps	83
Fever	83
Nausea	67
Anorexia	67
Headache	60
Myalgia	50
Vomiting	30

* Stools per day.

interval of three days. Precautionary measures to prevent travelers' diarrhea did not decrease the likelihood of acquisition (tables 2 and 3). Socioeconomic status was significantly associated with the probability of acquiring travelers' diarrhea (r = 0.282, P = 0.024), as subjects with the highest socioeconomic status were most likely to acquire travelers' diarrhea.

Microbiologic results. One or more of the seven enteric pathogens that we identified were detected in 14 (61%) of the 23 subjects with travelers' diarrhea and in 17 (63%) of 27 episodes of travelers' diarrhea (table 4). ETEC was isolated from the samples of three subjects before the trip. Rotavirus and Norwalk virus were the pathogens most frequently associated with travelers' diarrhea (table 5); they accounted for 26% and 15%, respectively, of all cases. The only ill subject from whom ETEC was isolated was also the only subject with a mixed infection; *G. lamblia* was concurrently identified in her stool sample. None of the 64 subjects had a fourfold increase in antibody titer to *E. coli* LT between the pretrip and concluding trip serum samples. Age and pretrip titers of antibody to LT did show a significant negative correlation (r = −0.273, P = 0.042); the youngest subjects had the highest pretrip titers of antibody to LT. However, pretrip antibody titers to LT, Norwalk virus, or rotavirus did not vary with socioeconomic status. All enterotoxigenic isolates were resistant to bacitracin, erythromycin, and penicillin.

Discussion

The high attack rate and relatively mild clinical picture we observed suggest that individuals from developing tropical areas may develop travelers' diarrhea. Our observations are in contrast to those of previous investigators who claimed that travelers' diarrhea was uncommon among travelers originating from developing tropical countries [1–3]. This discordance may be explained partially by the design and execution of these earlier studies—small numbers of cases, low completion rates of the questionnaire surveys, and a biased ascertainment of poorly defined cases [1–3]. A further explanation may derive from the fact that our study, like previous investigations of travelers' diarrhea [1–7], was descriptive in nature. Controlled investigations with high ascertainment of tourists from the developed and developing world traveling on the same trip would be helpful.

The multiple etiologic agents and their relative frequencies detected in our study also differ from those described in previous studies, despite our use of isolation techniques very similar to those used in previous studies in which ETEC was successfully isolated [1–7]. The percentage of episodes of travelers' diarrhea in which we were able to identify an etiologic agent was, however, similar to the rates in these studies. Our findings may be partially explained by our traveling with the group, plating in the field, and using techniques for isolating *C. fetus*. *C. fetus* has been recently recognized as an important pathogen of travelers' diarrhea [20]. Cases of travelers' diarrhea in which *C. fetus* was isolated occurred towards the end of the trip. Our storage methods may not have allowed

Table 2. Association between food consumption and acquisition of travelers' diarrhea in a group of 64 Panamanian tourists in Mexico.

Food consumed	Percentage of subgroup consuming food	
	Ill (n = 23)	Well (n = 41)
Vendor food	43	39
Salads with raw vegetables	70	80
Other raw vegetables	67	78
Unpeeled fruits	47	50

NOTE. None of the differences in consumption of a given food was statistically significant at the P = 0.05 level.

Table 3. Association between water consumption and acquisition of travelers' diarrhea in a group of 64 Panamanian tourists in Mexico.

Type of water consumed, health status	Frequency of consumption		
	Often	Seldom	Never
Only commercially bottled water			
Ill	63	30	7
Well	54	35	11
Tap water			
Ill	7	10	83
Well	6	24	70
Hotel water			
Ill	47	27	27
Well	39	33	28
Water-containing beverages			
Ill	37	57	7
Well	50	39	11
Beverages with ice			
Ill	57	40	3
Well	70	28	3

NOTE. None of the differences in consumption of a given type of liquid was statistically significant at the $P = 0.05$ level.

us to successfully recover any *Campylobacter* organisms that may have caused travelers' diarrhea early in the trip. Subjects in this study, unlike those in other studies carried out in Mexico, also traveled more extensively throughout Mexico and may have had broader exposure to enteropathogens. In addition to these and other methodologic differences, which we have attempted to minimize, between this study and previous studies of travelers' diarrhea, a difference in susceptibility to enteric pathogens in our cohort when compared with previously studied cohorts may also be important.

The rarity of ETEC as a causal agent in our study contrasts with its frequent occurrence in other recent studies of travelers' diarrhea in North American travelers to Mexico [4, 5] but is consistent with the findings of the only other study of similar design to the present investigation. This similar study demonstrated a 35% incidence of travelers' diarrhea in Latin American students at a school near Mexico City [21]. This study and our study also demonstrated a relatively milder clinical spectrum of illness than the one characterizing travelers' diarrhea in North American travelers to Mexico [5]. Studies of travelers' diarrhea involving North Americans have repeatedly shown ETEC to be the most prominent etiologic agent [4, 5]. In contrast, ETEC has consistently been shown to be an infrequent enteropathogen in North America [22]. In our study involving subjects from a country in which ETEC is an endemic cause of diarrhea, these organisms, while colonizing the intestines of three subjects before they left for Mexico, caused travelers' diarrhea in only one of the subjects in our study. Parenthetically, a second case of ETEC-mediated travelers' diarrhea occurred in the only North American on the tour. This individual was also the only person who had a fourfold increase in titer of antibody to LT between pretrip and concluding trip serum samples.

Pretrip titers of antibody to LT correlated inversely with age; young subjects had significantly higher antibody titers. This correlation suggests that ETEC, endemic in Panama, is most likely to infect children, giving them a temporary increase in titer of antibody to LT. These childhood infections seem to confer some long-lived immunity to LT-mediated diarrhea. The decline in titer of antibody to LT with age likely reflects the decrease in titer over the time since primary infection and not a decline in immunity to infection. The significant correlation of attack rate of travelers' diarrhea and Hollingshead index suggests that the higher socioeconomic levels of the Panamanian class

Table 4. Laboratory findings in stool samples from a group of 64 Panamanian tourists in Mexico.

Agent	Pretrip in Panama	Mexico	
		Travelers' diarrhea	Concluding trip
Enterotoxigenic *Escherichia coli*•	3	1†	0
Shigella	0	1	0
Campylobacter jejuni	0	3	0
Rotavirus	0	6	1
Giardia lamblia	0	1†	0
Entamoeba histolytica	0	1	1
No pathogen	61	10	62
Total	64	22‡	64

• All isolates produced only heat-labile enterotoxin. The serotypes of the isolates were O64:H?, O159:H46, and O140:H?.

† Isolated from the same individual.

‡ Not including one case of rotavirus diarrhea and four cases of Norwalk virus diarrhea that were diagnosed serologically.

Table 5. Antibody responses to antigens of three agents of travelers' diarrhea in a group of 64 Panamanian tourists in Mexico.

Antigen	Antibody response
*Escherichia coli**	0/64†
Rotavirus	6/64 (9)‡
Norwalk virus	7/64 (11)§

NOTE. Data are no. with fourfold or greater increase in antibody titer between pretrip and concluding trip samples/ total no. of paired sera tested (%).

* Heat-labile enterotoxin.

† Not including a North American traveling with the group but not participating in the study who had a fourfold increase in titer of antibody to heat-labile enterotoxin.

‡ Five of the six had travelers' diarrhea.

§ Four of the seven had travelers' diarrhea.

structure may have been less effectively exposed to enteric agents indigenous in their country, and they thus are more likely to develop travelers' diarrhea when effectively exposed during foreign travel. The high titers of antibody to *E. coli* LT in children, the correlation of attack rate for travelers' diarrhea with increasing socioeconomic status, and the rather different susceptibility and immunologic response to ETEC-induced travelers' diarrhea in the one tour subject who did not originate from Panama, viewed together, suggest that the minor role played by ETEC in our study may be due to preexisting immunity to ETEC in many of the members of the Panamanian contingent.

We were surprised by the 41% incidence of travelers' diarrhea attributable to either rotavirus or Norwalk virus. Both of these enteropathogens are important causes of endemic enteric disease in Panama [23]. It is possible that previous exposure to rotavirus and Norwalk virus does not confer as long-lasting an immunity as previous exposure to ETEC, or, alternatively, the strains of these enteric viruses endemic in Panama may not confer immunity to those present in Mexico.

We have previously demonstrated that travelers originating from the developing world are unlikely to acquire travelers' diarrhea during travel to the United States [24]. We have now demonstrated that subjects from developing countries traveling to other developing countries may also acquire travelers' diarrhea with the same frequency as travelers from the developed world. Our observations, involving one group, although it was a group with members of widely heterogeneous backgrounds and experiences while in Mexico, must be validated. However, our study does suggest that travelers' diarrhea, thought to be a scourge of only travelers from the developed world, may be a much greater problem than has been previously surmised.

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