MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

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ACUTE DIARRHEAL DISEASES AND FOOD POISONING

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INTRODUCTION

Acute diarrhea of sudden origin is a distressing complaint which occurs commonly and is one that often prompts the seeking of medical attention. Diarrheal syndromes have posed frustrations to physicians in that the etiology of the majority has remained elusive, relatively little has been known regarding pathogenesis and specific therapy has not been available or the results have been controversial. However, over the past several years, major progress has been made in each of these areas and a current review is timely.

DEFINITIONS

Before discussing pathogenetic mechanisms and specific considerations, definition of terms is appropriate. *Dysentery* is a clinicopathologic entity characterized by frequent bowel movements associated with pus and blood in the stools and usually accompanied with abdominal cramps and tenesmus. *Diarrhea* is the term used to describe frequent bowel movements not associated with pus or blood. *"Food poisoning"* is generally used to describe food-borne disease outbreaks and may be associated with dysentery, diarrhea or non-gastrointestinal symptoms, e.g., botulism. The term implies a mode of spread, not an etiology.

Diarrhea or dysentery due to food poisoning has been subdivided into two broad categories based upon pathogenesis (Table 1). In light of current knowledge, this categorization is less useful in that it is now clear that many enteric pathogens produce disease through the release of enterotoxins following multiplication within the intestine.

Enterotoxins are exotoxins which are synthesized within bacterial cells and elaborated into broth cultures. Most exotoxins are soluble in aqueous media, protein-polypeptides, antigenic and generally relatively heat-labile.

TABLE 1

COMPARISON OF INTOXICATION AND INFECTION TYPES OF GASTROENTERITIS

Category	*Intoxication**	*Infection‡*
Pathogenesis	Ingestion of preformed toxin	Multiplication of organism within gut
Incubation period	Brief (1-4 hours)	Longer (12-24 hours)
Duration of symptoms	Brief (hours)	Longer (days)
Vomiting	Severe	Usually not marked
Fever	Usually absent	Usually present
Convalescence	Rapid	More prolonged
Communicability	Non-infectious	Infectious

* As exemplified by staphylococcal enterotoxic gastroenteritis

‡ As exemplified by salmonella gastroenteritis

PREVALENCE

Even in developed countries such as the United States, acute diarrheal diseases and food poisoning represent major health problems, i.e., even with under-reporting in 1970 there were reported: 23,448 persons reported with food poisoning, 22,096 persons with salmonellosis excluding typhoid fever (346), 13,845 persons with shigellosis and 2,888 persons with amebiasis, i.e., over 60,000 persons reported.

The major etiologic categories of food poisoning for 1970 are listed in Figure 1.

PATHOGENIC MECHANISMS

The demonstration by Gangrosa et al. that the intestinal mucosa was intact in classical epidemic cholera provided the major stimulus to investigations of the pathogenesis of the cholera syndrome (1). Subsequently, Finkelstein and associates demonstrated that Vibrio comma grown in synthetic medium elaborates a "choleragen" which causes experimental cholera when administered by gavage to suckling rabbits, into isolated ileal loops in the rabbit, dog or cat, or when administered to volunteers (2,3). When exposed to enterotoxins, the loops of intestine which are ligated but remain in vivo become distended with fluid. This system has been used to demonstrate the presence of enterotoxins.

FIGURE 1

INDIVIDUALS INVOLVED IN FOODBORNE DISEASE OUTBREAKS (CONFIRMED AND UNCONFIRMED) BY CAUSATIVE ORGANISM, UNITED STATES, 1970

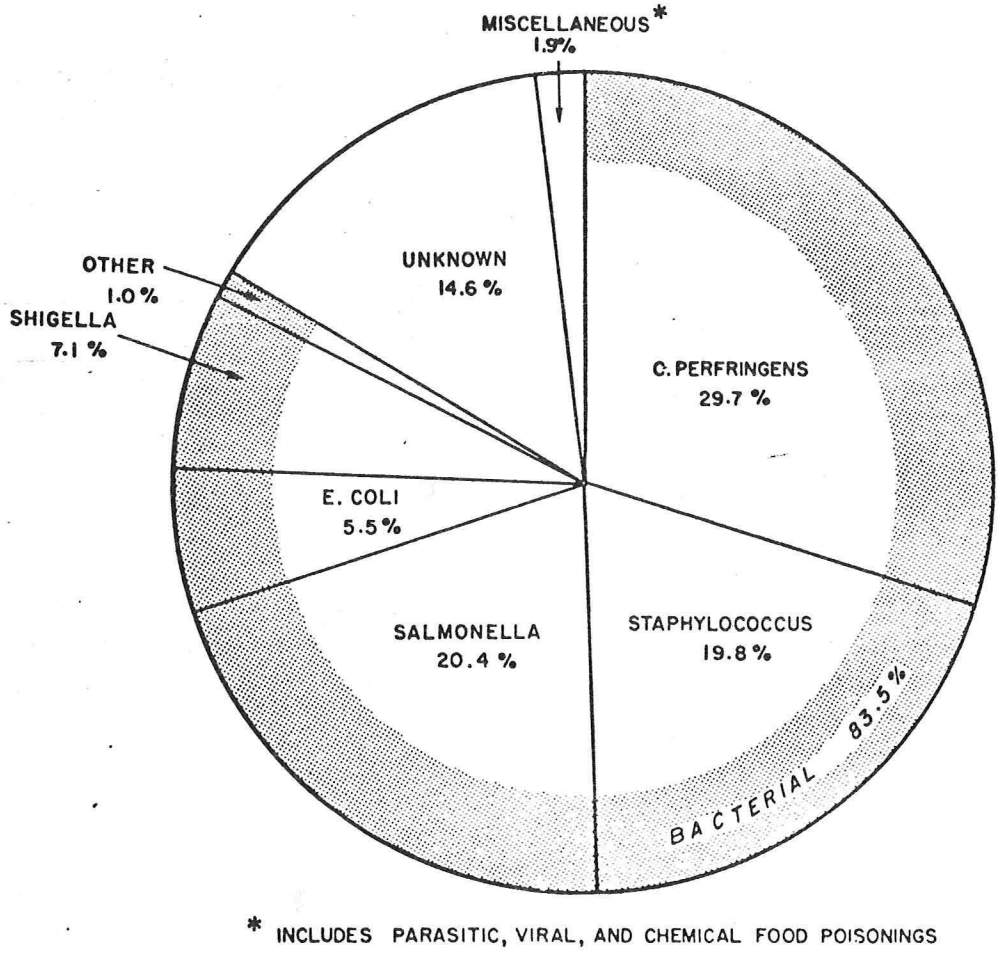


Figure 1 is a pie diagram illustrating the relative percents of individuals involved in the major etiologic categories of food poisoning for 1970. A total of 23,448 individuals developed food poisoning during 1970, compared to 28,563 during the previous year. Over 80% of individuals experienced food poisoning of bacterial etiology. *Clostridium perfringens* food poisoning affected nearly 30% of all patients, followed by salmonellosis (20.4%), staphylococcal gastroenteritis (11.8%), shigella (7.1%), and *Escherichia coli* (5.5%). The remaining bacterial etiologies (*Bacillus cereus*, *Clostridium botulinum*, enterococcus, and *Vibrio parahemolyticus*) affected less than 1% of all patients. Parasitic, chemical, and viral food poisoning involved only 1.9% of all patients. Food poisoning of unknown etiology caused 14.6% of cases.

In contrast, a major feature in the pathogenesis of bacillary dysentery involves the formation of ulcerative lesions of the intestinal tract. These lesions have been thought to be the result of absorption of toxic products of shigella. However, Formal, LaBrec, Schneider and associates demonstrated dysentery bacilli in the lamina propria of the ileum, cecum and colon of experimentally infected guinea pigs with the epithelium of the mucosa overlying these regions intact (4). Subsequent studies suggest that organisms penetrate epithelial cells and reach the lamina propria via this means. At this stage the epithelial barrier remains intact. Here the organisms multiply further, and many elaborate toxic products resulting in death of the epithelium and ulcer formation (5). Because primates are the only hosts that are naturally susceptible to shigellosis, other experimental measures which correlate with the ability of bacilli to invade the intestinal epithelial cells of monkeys and starved-opiated guinea pigs have been sought. The ability of strains of shigellae to invade (a) HeLa cell monolayers and to produce (b) keratoconjunctivitis in the guinea pig (Sereny Test) correlates well with the ability to invade intestinal epithelial cells (5,6).

Dupont and associates have demonstrated that these laboratory tests of pathogenicity correlated well with the clinical responses in volunteers (Table 2) (7).

TABLE 2

PATHOGENICITY OF ENTERIC ORGANISMS

Organism	*GP eye invasion*	*HeLa cell invasion*	*GP intestine invasion*	*Rabbit ileal loop*	*Cholera syndrome in volunteers*	*Shigellosis in volunteers*
E. coli (strains 4608, 1624)	+	+	+	0	0	+
E. coli (strains B2C, B7A)	0	0	0	+	+	0
E. coli 0148 K?H 28	0	0	0	+	-	-
Shigella	+	+	+	0	0	+
E. coli	0	0	0	0	0	0

To date, differences between *E. coli* strains have not correlated with serogrouping.

Correlations between clinical features and laboratory findings can now be developed (Table 3) (8).

TABLE 3

CLINICAL CORRELATIONS OF ENTEROPATHOGENICITY

Organism	*Diarrhea/ Dysentery*	*Abdominal Pain*	*Vomiting*	*Incubation Period (Hrs)*	*Mucosal Penetration*	*Entero-toxin*	*Extraintestinal Manifestations*
Shigellae	+/+	+	±	24-72	+	+*	Seizures; meningismus
Escherichia coli	+/0	±	0	24-72	0	+	Minimal
	0/+	+	0	24-72	+	0(?)	Variable
Vibrio cholerae	+/0	0	±	24-72	0	+	Hypokalemic nephropathy
Salmonellae	+/±	±	±	12-36	+	0(?)	Fever; bacteremia
Clostridium perfringens	+/0	++	±	8-15	0	+†	Minimal
	0/+‡	++	+	18-48	±	0(?)	Shock
Staphylococci	+/0†	±	++	4-8	0	+†	Minimal
	0/+§	+	±	Indeterminate	±	+(?)	Shock

* ? only *S. dysenteriae 1*

† Preformed toxin ingestion

‡ Necrotizing jejunitis (enteritis necroticans) may be clinically similar to dysentery

§ May occur when enterocolitis is produced by proliferating enterotoxin-producing organisms

Enterotoxins

The characteristics of bacterial enterotoxins are listed in Table 4 (8).

The ability of cholera toxin to inhibit ion transport in an epithelial membrane was first demonstrated in the isolated frog skin (9,10). Most recently Moore, Bieberdorf, Morawski, Finkelstein and Fordtran reported studies in which both ion transport rates and electrical potential difference (PD) were determined simultaneously in the normal and choleragen-treated dog ileum in vivo (11). The results indicate that, during cholera, HCO_3 is actively secreted (i.e., against both an electrical and a concentration gradient); Cl is also actively secreted, against a modest electrochemical gradient. Electrogenic pumping of one or both of these anions is probably responsible for an observed PD change of approximately 13 mv (lumen negative). Na secretion can be accounted for entirely by passive ion movement. K secretion can be partly explained by passive diffusion secondary to the negative intraluminal PD; however, its concentration in the secreted fluid is two to three times higher than expected on the basis of passive forces, suggesting a component of active K secretion. The PD response of the choleragen-treated ileum is normal in response to glucose, but there was no PD response to saline-free mannitol perfusion. This suggests that the normal differential permeability of the ileum to anions and cations may be altered by choleragen, although other explanations of this finding are also possible.

The possibility that cholera toxin might produce hypersecretion via an intermediary such as 3'-5'-adenosine monophosphate (cyclic AMP) was inferred from comparisons to the effect of drugs known to alter tissue levels of cyclic AMP (12,13). Theophylline, which inhibits the breakdown of cyclic AMP, causes the same type of rapid increase in anion secretion and short-circuit current as the direct administration of cyclic AMP. Cholera toxin produces a similar increase but only after a lag as long as an hour. Toxin pretreatment also blunts the response to subsequently administered theophylline, thus giving one more line of evidence that a common pathway is involved.

The outstanding hypersecretory effects of cholera toxin account for the focus of this discussion although staphylococcal enterotoxin B also causes chloride hypersecretion in vitro (14) and it seems probable that other toxins will be shown to share this property. A role of cyclic AMP like that identified in studies using cholera toxin has not been confirmed regarding other toxins with the exception of one report that frog erythrocyte adenyl cyclase was activated by a *C. perfringens* extract of undetermined enterotoxicity (15).

TABLE 4

CHARACTERISTICS OF BACTERIAL ENTEROTOXINS

Parent Organism	*Estimated Molecular Weight*	*Optimum pH for Toxicity*	*Inactivated at 60°C*	*Inactivated by Protease*	*Tropism*	*Cytoxic*	*"Permeability Factor"*	*Intestinal Fluid Accumulation*
V. cholerae	60,000 (10,000-100,000)	8	+	+	Gastrointestinal; ? capillary	0	+	++
E. coli	> 10,000 ("non-dialyzable")	7-8‡	+	?	Gastrointestinal	?	0	+
C. perfringens	> 10,000 ("non-dialyzable")	6-9	+	+	Gastrointestinal; ? capillary§	?§	±§	+
S. dysenteriae-1	60,000	8	+	?+	Gastrointestinal; ? central nervous system*	+	0	+
Staphylococci (enterotoxin B)	35,000	7-8‡	0	+	Central nervous system; gastro-intestinal	+	0	+

† Inactivated by pronase (*Streptomyces griseus* derivative) but not inactivated by trypsin

‡ Active at this pH - optimum for enteric challenge not stated

§ Erythema without induration in response to intradermal inoculation

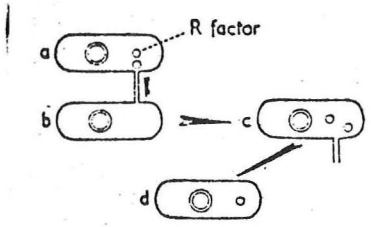
* Enterotoxin may be identical or closely related to neurotoxin

R FACTORS AND BACTERIAL DRUG RESISTANCE

The basis by which a bacterium becomes resistant to a given antibiotic has been assumed to result from a mutation in the chromosome of that cell. Such an event occurs spontaneously at frequencies of approximately 1 in 10^8 cell divisions. The mutation is perpetuated at the replication of the involved cell, the drug resistant phenotype being expressed by the daughter bacteria. Since different (families of) antibiotics, e.g., tetracyclines, chloramphenicol, affect bacteria by different mechanisms, a mutation to resistance to a given antibiotic does not affect the susceptibility of that cell to other antibiotics; resistance to multiple antibiotics develops as a consequence of separate mutations and is a rare event. Thus, resistance to two antibiotics occurs at a frequency of 1 in approximately 10^{16} cell divisions; that to three antibiotics, at a frequency of 1 in approximately 10^{24} cell divisions.

Observations made during epidemic shigellosis in Japan (1959) that not only were the responsible microorganisms resistant to four major antibiotics but also that the resistance was transferable to bacteria of different species were the stimuli for most of the research of the past decade on this problem. The early work in this area was summarized in 1963 by Watanabe (16). The mechanism of transfer of resistance involved conjugation which consists of the transfer of genetic material by physical contact between individual bacterial cells by means of a cytoplasmic bridge or "pilus" (Figure 2).

FIGURE 2



At present it is uncertain whether genetic material actually passes through the pilus or whether the pilus merely acts as a "grappling hook" allowing the formation of a cytoplasmic bridge elsewhere in the cell. In R factor type of conjugation, a cytoplasmic episome (resistance determinant) which is responsible for multiple drug resistance replicates itself within the cytoplasm and the resistance transfer factor (RTF) also replicates and induces the formation of a pilus which allows transfer of an R factor to a previously sensitive female type cell. This makes the recipient cell resistant and also induces the formation of a pilus in this cell, rendering it a male. The interbacterial transfer and expression of the R factor is complete within minutes in in vitro cultures, and 90% of sensitive bacteria are "infected" by R factors within 2 to 4 hours after the introduction of a few bacteria bearing the R factor (R^+ bacteria). There has been some confusion in the literature concerning terminology, but it seems to be resolved that the episome, which is responsible for the transmission of drug resistance between bacteria, is termed an R factor. It is composed of DNA autonomous of chromsomal DNA. The R factor seems to be composed of two entities, the resistance determinants and the resistance transfer factor (RTF) such that the R factor without the RTF can produce resistance but it cannot be transferred to other cells; the R factor without the resistance determinants can be

transferred but exhibits no ability to cause resistance (17). There is evidence that the resistance determinants for the various antibiotics can themselves be transferred independently (10).

At the time of Watanabe's review there had accumulated a number of suggestions in the literature that a defect in permeability to the antibiotics was a prime mechanism of expression of resistance. The reasoning was as follows: chloramphenicol, for instance, inhibited protein synthesis in a sensitive strain but not a resistant strain of *E. coli*. However, chloramphenicol was equally effective in inhibiting protein synthesis in lysates of both strains. It was thus suggested (18) that in the resistant strain there was a permeability barrier which did not permit the chloramphenicol to reach the protein synthesizing apparatus. However, the demonstration by Okamoto and Suzuki (19) that cell-free systems could inactivate antibiotics if suitable cofactors were added obviated the need for a permeability defect explanation in R factor-mediated resistance since inactivation of the chloramphenicol adequately explained the above observations. Chloramphenicol, streptomycin, kanamycin, neomycin, ampicillin and dihydrostreptomycin have all been found to be inactivated by enzymes from R factor-bearing microorganisms and the products have been characterized.

R factors mediate resistance to streptomycin by one of two mechanisms, adenylation or phosphorylation of the 3'-OH of the N-methyl-glucosamine moiety (19,20). The adenylated or phosphorylated streptomycin is biologically inactive. Smith has found two R factor-mediated phosphorylases, one specific for streptomycin, the other specific for kanamycin and neomycin. The streptomycin phosphorylase has in vitro and in vivo activity against gentamicin; however, the in vivo gentamicin resistance thus far is lower than concentrations clinically attainable. Unfortunately, such R factors can mutate at high frequencies to high levels of streptomycin and presumably gentamicin resistance. Chloramphenicol resistance appears to be due to enzymatic acetylation (21). *E. coli* and klebsiella-enterobacter which are kanamycin-resistant are usually resistant to 4 to 7 other drugs, and in particular chloramphenicol, due to the linkage of the loci mediating kanamycin and chloramphenicol resistances. Resistance to ampicillin, through the enzyme penicillinase, is also R factor-mediated (22). Smith demonstrated that resistance to ampicillin was often transferable whereas that to cephalothin was not.

Whereas R factor-mediated resistance to the antibiotics mentioned above has been ascribed to inactivation of the antibiotic, such has not been demonstrated for tetracycline (23). Arima and Izaki demonstrated that an R factor-bearing strain of *E. coli* had a greatly reduced uptake capacity for tetracycline and postulated a permeability defect (24).

This mechanism of antibiotic resistance differs notably from that of the classic model in that (1) acquisition of drug resistance is not random or spontaneous but occurs only through contact of sensitive and R^+ bacteria; (2) multiple resistance is acquired at a single, rapid event; (3) multiple resistance to antibiotics can be "infectious"; (4) the transmission of multiple antibiotic resistance can occur between all genera of enteric bacteria; (5) the genetic apparatus responsible for the multiple antibiotic resistance is self-regulated and can be eliminated from the host bacterium without affecting bacterial survival.

The potential spread of R factors among enteric bacteria was immediately recognized as a threat. Concern increased during the ensuing years as R factors were associated with the rapid emergence of antibiotic-resistant shigella in Japan (25), salmonella and *E. coli* in Great Britain (26), and were found to play the major role in the mediation of antibiotic resistance among enteric bacteria (associated with nosocomial infections) in the United States (27). Recent studies indicate that R factors now infect approximately 85% of all shigella in Japan (25), 60% of the salmonella isolated in England (28), and 20% of those in the United States (29,30), 25% of all enteric bacteria and 60 to 70% of all resistant enteric bacteria isolated at medical centers in the United States (27, 31). Of 18 strains of *Shigella dysenteriae* type 1 isolated during the epidemic of dysentery in Central America and Mexico during 1969-1970, all transferred the complete resistance to *E. coli* (32). Seventeen strains were resistant to sulfonamides, streptomycin, tetracycline and chloramphenicol.

Less is known about the epidemiology and clinical role of R factors, however. The prevalence of R factors has been correlated generally with the commercial usage of antibiotics in Japan (25), and it was originally presumed that R factors arose solely because of the selective force of antibiotics used by man. This thesis was found to be an overstatement since R factors have been found in bacteria isolated before the antibiotic era (33). That antibiotics play a major role in the selection of R^+ bacteria, however, has been demonstrated by preliminary experiments (25,34).

Despite the rapidity of interbacterial transfer in in vitro cultures, R factor transfer in nature may be much less frequent than originally anticipated. Smith demonstrated antibiotic resistance could be transferred to the resident *E. coli* in the alimentary tract of a volunteer when cultures of *E. coli* of animal and human origin were taken in large doses (35). The amount of transfer was small and the resistant resident organisms did not persist. Similarly, Jarolmen and Kemp induced experimental infections in weanling pigs with both nalidixic acid sensitive and resistant strains of *S. cholera suis* (36). Transfer of drug resistance in vivo was rare.

SPECIFIC DISEASE CONSIDERATIONS

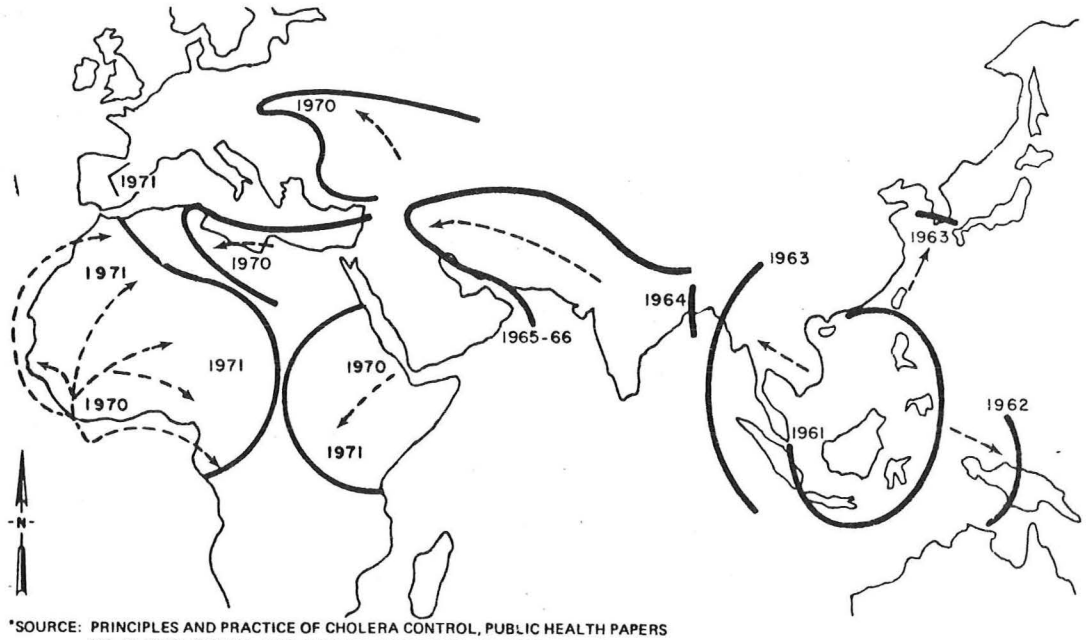
Cholera

The current pandemic of cholera began in 1961 in the Philippines. This particular pandemic is caused by a variant of *Vibrio cholerae*, designated as El Tor. This organism has slightly different cultural characteristics but is as toxigenic as the classic cholera vibrios. Since 1961, cholera has spread across Asia and in 1970 moved into Africa and in 1971 isolated cases occurred in Spain (Figure 3) (37).

Despite this widespread pandemic, it is unusual for tourists to develop cholera even after visits to highly endemic areas.

FIGURE 3

*EXTENSION OF EL TOR CHOLERA - 1961-1971**



*SOURCE: PRINCIPLES AND PRACTICE OF CHOLERA CONTROL, PUBLIC HEALTH PAPERS NO. 40, WHO, GENEVA, 1970. REVISED ACCORDING TO WEEKLY EPIDEMIOLOGICAL RECORD, VOL. 45, NOS. 1-52, 1970, AND VOL. 46, NOS. 1-33, 1971.

The first American tourist became ill in Japan after a trip to Hong Kong in 1962 (38). The second documented case follows:

A 79-year-old American tourist developed cholera in Australia in early December after visiting Bombay, India. The patient, a known diabetic, was accompanied by his wife, son, and daughter-in-law on a journey from the United States to Rome, Johannesburg, and Bombay. In Bombay, they spent 1 day, December 5, and 2 nights prior to leaving for Australia. During the time they were in India, no food was eaten other than that obtained in their hotel or restaurants recommended for tourists. The man became ill about 2 a.m. on December 6 and was admitted to the Fairfield Infectious Diseases Hospital, Melbourne, at 4 p.m. the same day. Signs and symptoms at that time included cardiovascular collapse, dehydration, aphonia, severe muscle cramps, and mental disorientation. His stool had the "rice water" appearance typical of cholera.

During the first 24 hours, 11 liters of intravenous electrolyte solutions were administered and subsequently 9 to 10 liters per day were required for 3 days to balance stool losses. He was also treated with intravenous chloramphenicol and oral tetracycline. His diabetes was controlled with insulin. On December 9, he developed auricular fibrillation. He responded well to treatment and was discharged after 16 days, completely recovered.

Diagnosis was proved by isolation of *Vibrio cholerae* biotype El Tor, Ogawa serotype on plain nutrient agar, blood agar, and MacConkey's media. The laboratory isolate was confirmed by serologic and biochemical tests.

The other three members of the tour group did not become ill, and there were no secondary cases. The patient had received two doses of cholera vaccine about 2 weeks before he left the United States (39).

This case emphasizes that the cholera vaccine provides only relative protection. In a controlled field trial conducted in East Pakistan, the vaccine was shown to be 75% protective during the first 3 months after vaccination (40).

Despite this infrequency, it is entirely possible that individuals with cholera might return to the United States and subsequently seek medical attention. Following recovery from clinical cholera, some individuals become chronic carriers (41-43). Although large numbers of vibrios could be found in duodenal fluid, probably as a consequence of being sequestered in the gallbladder, normally passed fecal specimens were usually vibrio-free. However, purged stools, or diarrheal stools associated with spontaneous diarrhea, often yield a positive culture (Figure 4) (43).

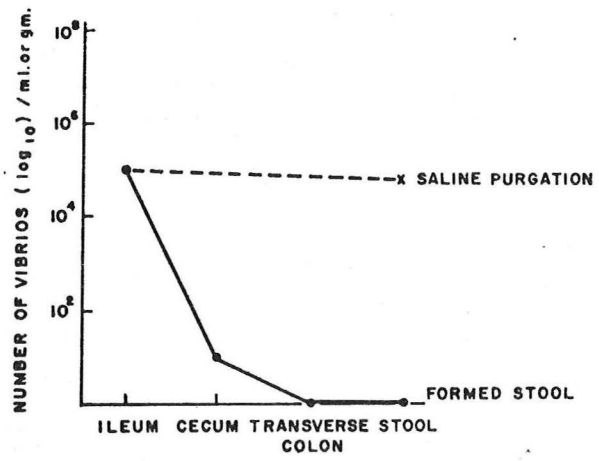


FIGURE 4

Concentrations of *V. cholerae* in the terminal ileum and colon during passage of formed stool and during saline purgation

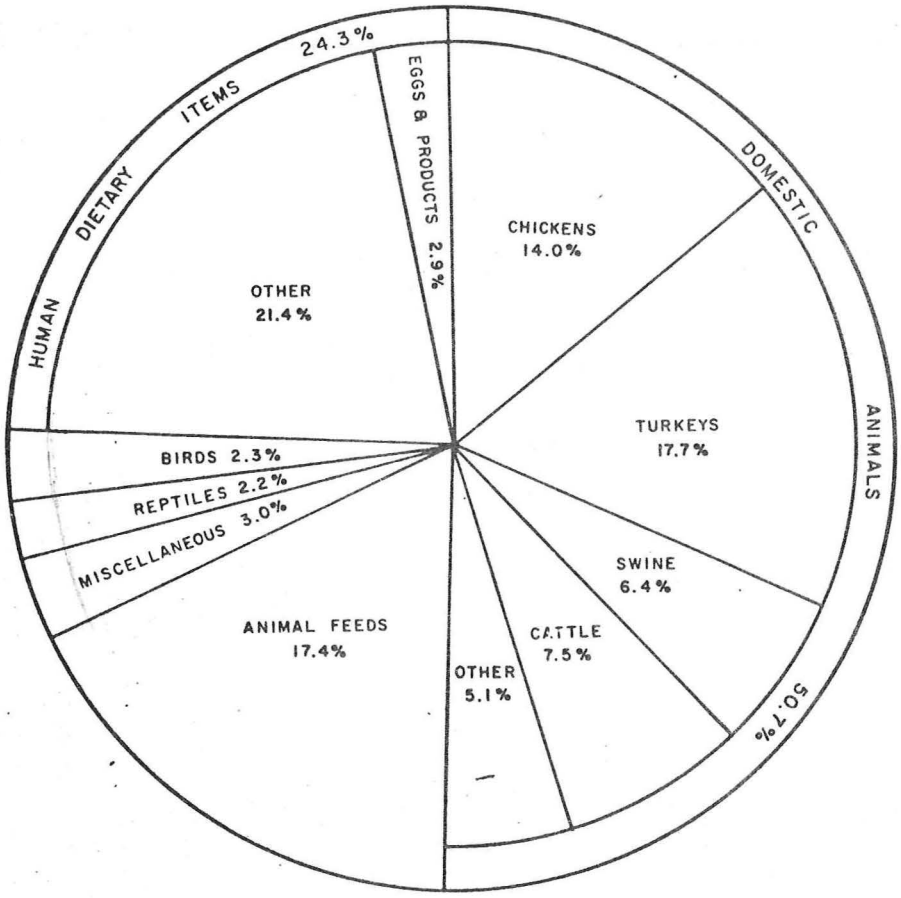
Imported cholera cases might well not be recognized because the usual media for the isolation of enteric pathogens are suboptimal for the isolation of *V. cholerae*. When suspected, TCBS (thiosulfate, citrate, bile, sucrose) agar should be employed.

Salmonellosis

Salmonella are a major cause of bacterial gastroenteritis in the United States. While typhoid fever is declining in incidence in the U.S., salmonellosis is increasing and is much more common than is generally appreciated (Figure 5). While man is the natural host for *Salmonella typhosa*, virtually all of the remaining serotypes have non-human hosts or sources (Figure 6).

FIGURE 6

NONHUMAN SALMONELLA ISOLATIONS FROM THE INDICATED SOURCES IN THE UNITED STATES, 1970

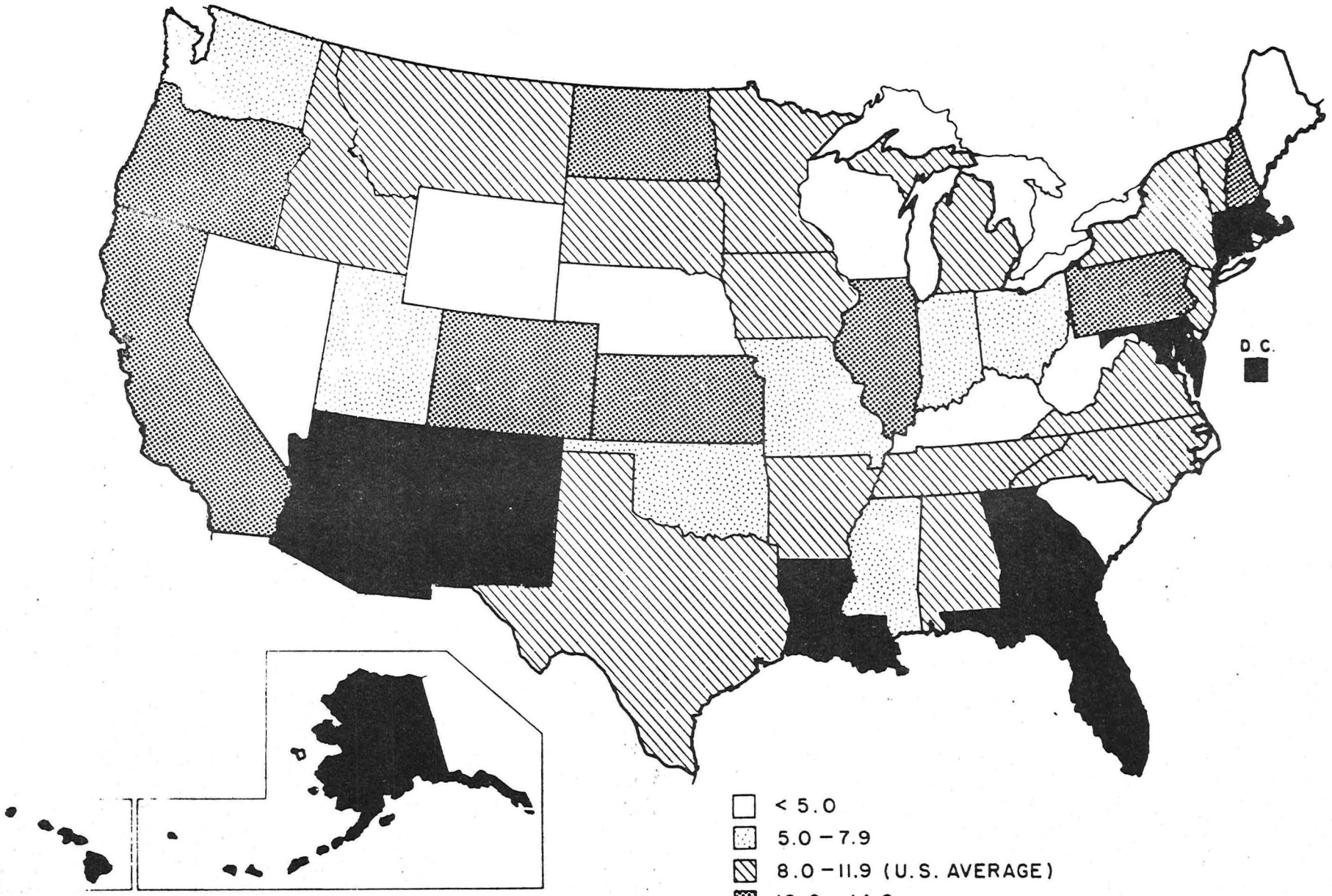


Important sources include not only foodstuffs, but also domestic animals and pets, e.g., dogs, turtles, Easter chicks, etc. (44-46).

Despite almost continuous exposure to salmonella, disease is uncommon since most salmonella are killed by gastric acidity. In normal persons, a dosage of 100,000 salmonellae or more is required to produce symptoms in even 25% of volunteers. (In comparison, < 200 shigella will produce disease in 25% of subjects and > 1000 organisms will produce disease in 80-90%.). However, in the

FIGURE 5

NUMBER OF HUMAN ISOLATIONS OF SALMONELLA PER 100,000 POPULATION IN THE UNITED STATES, 1970



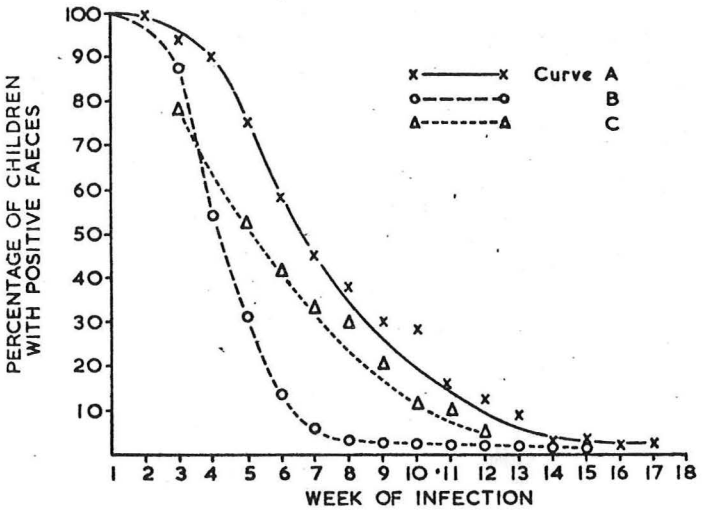
SOURCE: CURRENT POPULATION REPORT'S SERIES P-25, NO. 414

patient with achlorhydria or post-gastrectomy, the infectious dose of salmonella is much less, hence the increased prevalence in patients with pernicious anemia and in post-operative patients, especially when the latter are placed on eggnog, etc.

In the patient with typhoid fever, there is no question that antibiotic therapy (chloramphenicol) has significantly decreased mortality, 12% to 4% (47). However, even the earliest studies suggested that the carrier state developed with its usual frequency in patients who received specific antimicrobial therapy (47).

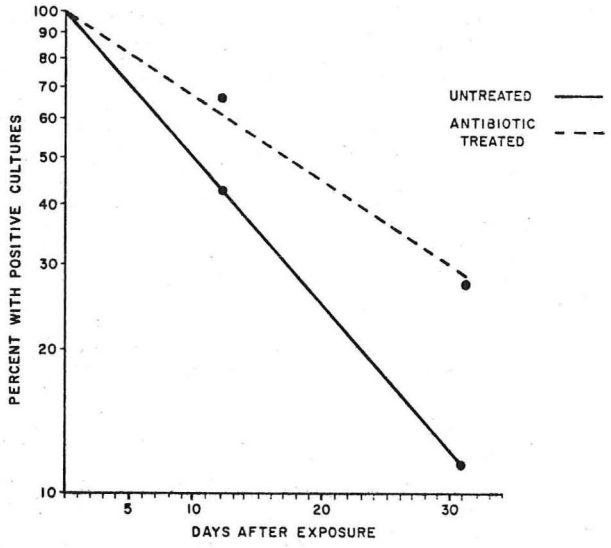
However, because of the prevalence of salmonellae, the question often arises as to appropriate management of the patient with a positive culture for a non-typhosa salmonella. There are studies which demonstrate that, at least in children, treatment with chloramphenicol had no effect in influencing the rate of clinical recovery (48). Furthermore, there has been the suggestion that antibiotic treatment may lengthen the period of excretion (Figs. 7, 8) (49-51).

FIGURE 7



Duration of excretion of *S. typhimurium* in the feces of children infected in two outbreaks. Curve A, treated children (Suffolk); Curve B, untreated children (Wales); Curve C, Suffolk children examined by less sensitive techniques.

FIGURE 8



Duration of excretion of *S. typhimurium* after acute gastroenteritis

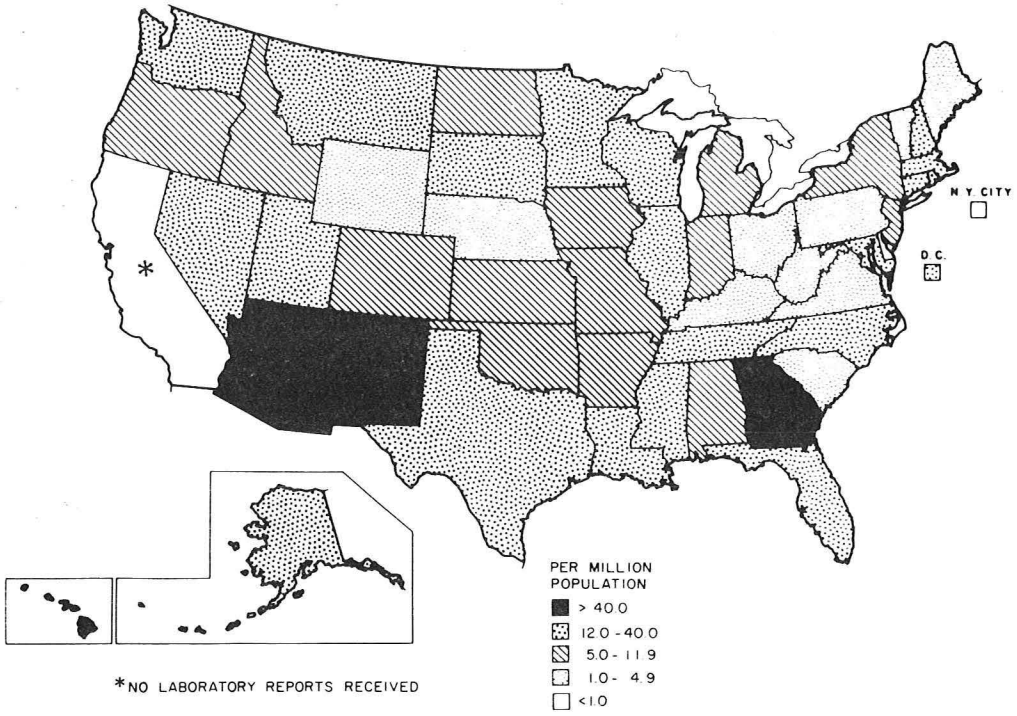
Thus, while therapy should not be withheld from the patient with systemic illness, diarrhea alone or a mere positive culture is not an indication for therapy.

Shigellosis

There are several facets of shigellosis which merit emphasis. Shigellosis is a not uncommon cause of diarrheal disease in the United States (Fig. 9) (52).

FIGURE 9

ATTACK RATES OF SHIGELLOSIS, BY STATE, JULY-SEPTEMBER 1970



The question frequently arises as to whether antibiotics are of benefit in shigellosis. This is particularly pertinent since the treatment of shigellosis is occasionally extrapolated from that of salmonellosis. Haltalin and Nelson, in a series of well designed studies, have shown unequivocally in children that the course of shigellosis is shortened when an appropriate antibiotic which is absorbed from the GI tract is administered (Table 5) (53,54).

Two factors are involved in the decision to treat patients or carriers. One relates to the good of the individual patient, the other to the public health. On clinical grounds alone "The necessity for antibiotic treatment of patients with milder forms of disease has not been conclusively established" (54). But the effect of treatment in limiting excretion of organisms and spread of infection to others is well established. Small children who are excreting shigellae should be treated to protect their siblings and parents. Food handlers and nurses with shigellosis pose a similar threat to others, and they should be treated.

So-called shigella carriers are not a homogeneous group. The vast majority of carriers either have an asymptomatic, self-limited infection or are in the convalescent phase of a symptomatic infection. Some are in an incubatory phase just prior to the onset of symptoms. Long-term carriage of shigella is unusual.

TABLE 5

COMPARISON OF RESULTS OF TREATMENT IN TWO CONTROLLED STUDIES OF SHIGELLOSIS

	PLACEBO (Study #1) 16 patients	*NEOMYCIN (Study #2) 15 patients*	*AMPICILLIN (Study #1) 18 patients*	*AMPICILLIN (Study #2) 15 patients*
No. of patients with shigellae in stools more than 48 hrs after therapy begun ("Bacteriological failure")	12	13	1	2
Mean no. of days after start of therapy				
Until culture negative	5.0	5.4	1.9	2.2
Until diarrhea stopped	6.0	4.2	3.3	3.2
Until afebrile	2.6	2.3	1.3	1.5
No. of patients removed from study	6	5	0	1
No. of patients with diarrhea for more than 5 days after therapy begun	6	6	0	1
One or both of the above ("Clinical failure")	9	9	0	2

In a study of 29 volunteers experimentally infected with shigellae, duration of excretion ranged from 1 to 78 days, with an average of 27 days if antibiotics were withheld (55). Surveillance to detect carriers in a home for retarded children showed that the vast majority of shigellosis patients excreted the organism for less than a month; only 3.5% excreted shigellae for more than 18 months (56). Control of shigellosis in custodial institutions is a particularly difficult problem. Antibiotics will usually stop excretion in individual patients, but they do not prevent later re-infection. In addition, the propensity of shigellae to develop multiple antibiotic resistance is accentuated in institutions where shigellosis is endemic and antibiotic usage is extensive.

Special mention must be made of the problems in treating infections due to *Shigella dysenteriae* type 1. This organism has been responsible for severe epidemics of dysentery in Central America since early in 1969. Travelers have from time to time returned to this country infected with *S. dysenteriae* type 1 after travel to Mexico or Central America (57). Isolates of this epidemic strain have been notably resistant to sulfathiazole, tetracycline, streptomycin, and chloramphenicol. They have been sensitive to ampicillin, cephalothin, nalidixic acid, nitrofurantoin, gentamicin, neomycin, colistin and kanamycin (58). The relative clinical efficacy of these antibiotics has not yet been reported in this epidemic. In infections of United States tourists reported to the CDC, ampicillin has been consistently effective, if used at the recommended dosage of 50 mg/kg/day. This form of dysentery can be severe and prolonged, if not treated properly, as noted in the following case (59).

A 78-year-old woman from Dade County, Florida, returned from Nicaragua on May 7, 1970, with a chief complaint of bloody diarrhea of 3 weeks' duration. She was hospitalized directly from the airport. She had been in her usual state of good health until April 13, 1970, two weeks after arriving in Nicaragua, when she had the onset of diarrhea with up to 20 bloody and mucoid stools each day accompanied by tenesmus. Her symptoms persisted in spite of treatment in Nicaragua with tetracycline, another antibiotic, and intravenous fluids.

On admission, she was lucid and moderately dehydrated. Her vital signs were normal. She had atrial fibrillation with a ventricular rate of 80 and tenderness in both lower quadrants of the abdomen; the rest of the physical examination was within normal limits. The white blood cell count was 13,200 with a shift to the left; sodium was 110, BUN 90, CO 18, and chlorides 86 mEq/L. The admitting diagnosis was diarrhea of undetermined origin with amebic and ulcerative colitis as the most likely possibilities. Shigella infection was considered but was dismissed as unlikely. Sigmoidoscopy and barium enema revealed nonspecific findings. A single blood culture on the day of admission grew a gram-negative rod identified as a shigella A strain. It was referred to the state laboratory and to the CDC for further identification.

The patient's dehydration improved markedly with intravenous fluids. Although amoebas could not be identified in stool examinations and a rectal swab was negative for amoebas, she was treated with metronidazole (Flagyl) for 3 to 4 days for amoebic colitis with no relief of her bloody diarrhea. She subsequently received chloramphenicol, kanamycin, penicillin, Azulfidine, steroids, and Mandelamine with no apparent benefit. For this reason and because other findings were negative, she was treated for ulcerative colitis until May 17 when she developed fever and symptoms of pneumonia; she died on May 18. A postmortem examination was not performed.

The gram-negative rod isolated from this patient's admission blood culture was later identified as *Shigella dysenteriae* 1, the classic Shiga bacillus. The additional history was obtained after her death that the community she had visited in Nicaragua, a city called Granada, had, at the time of her visit, experienced a severe outbreak of a similar dysenteric illness which resulted in many deaths. In retrospect, this woman's diagnosis was Shiga bacillary dysentery.

This case emphasizes several important points: Persons returning from any of the Central American countries or Mexico with symptoms of bloody diarrhea with or without tenesmus should be presumed to have Shiga bacillus dysentery until proved otherwise. This diagnosis is commonly confused with amebiasis and ulcerative colitis and is often missed on culture even when stools are streaked on enteric media commonly used in bacteriology laboratories. The Shiga bacillus is more fragile than other shigella and is often inhibited on the commonly used SS agar and other inhibitory media. Recent studies at the CDC have shown that Tergitol-7 agar, XLD, and MacConkey's agar are the media of choice for primary isolation. This organism is usually resistant to chloramphenicol, tetracycline, and sulfa drugs and is intermediate in its sensitivity to penicillin. As of this date, all strains isolated from Mexico, Guatemala,

Honduras, El Salvador, and Nicaragua have been sensitive to ampicillin, which is generally considered the drug of choice. In a fully developed case, such as this, with extensive tissue involvement and ulceration of the descending colon, sigmoid and rectum, response to treatment is slow; large doses should be given over many days to ensure eradication of the organism and to permit healing. Other drugs may be used, but it is important to recognize the possibility of compromised renal function in patients who have experienced prolonged dehydration. Cases should be promptly reported to health authorities so that a search can be made for secondary spread. To date, there have been no endogenously acquired cases in the United States associated with the epidemic in Central America and Mexico.

In that shigellosis should be treated, while most cases of salmonellosis should not, the question of clinical differentiation becomes critical. Nelson and Haltalin have presented data which indicate that at least in children, reasonable accuracy is possible (Tables 6 and 7) (60).

TABLE 6

CLINICAL FEATURES OF ACUTE DIARRHEAL DISEASE USEFUL IN DIFFERENTIAL DIAGNOSIS

Clinical Features	*Shigella*	*Enteropathogenic E. coli*	*Salmonella (excluding typhoid fever)*	*Nonbacterial*
Age	6 mo. to 5 yr. (rare in neonate)	Less than 2 yr.	Any age	Any age
Diarrhea in household	Common (> 50%)	No	Variable	Variable
Onset	Abrupt	Gradual	Variable	Abrupt
Vomiting as a prominent symptom	Absent	Uncommon	Common	Common
Fever (> 102°F)	Common	Absent	Variable	Uncommon
Respiratory symptoms	Common (bronchitis)	Absent	Uncommon (except in septicemic form)	Common (upper respiratory)
Convulsion	Common	Rare	Rare	Rare
Anal sphincter	Lax tone (rarely, rectal prolapse)	Normal	Normal	Normal
Stools:				
Consistency	Watery	Loose, slimy	Loose, slimy	Loose
Odor	Relatively odorless	Foul	Foul (rotten egg)	Unpleasant

[*Continued*]

Clinical Features	*Shigella*	*E. coli*	*Salmonella*	*Nonbacterial*
Stools:				
Blood	Common	Rare	Rare	Rare
Color	Yellow-green (almost colorless in severe cases)	Green	Green	Variable
Mucus	Present	Variable	Variable	Absent
Time after onset when seen by physician	Early	Several days	Several days	Early
Early course, untreated	Slight or no improvement	Persistent or relapsing	Persistent	Daily improvement

TABLE 7

ACCURACY OF PREDICTION OF TYPE OF DIARRHEAL DISEASE AT THE FIRST EXAMINATION

	Bacterial vs nonbacterial		*Specific bacterial diagnosis*	
	No. correct guesses/ No. families examined	*% Accuracy*	*No. correct guesses/ No. families examined*	*% Accuracy*
A	11/18	61	11/18	61
B	16/22	73	13/22	59
C	7/11	64	6/11	55
D	8/13	62	8/13	62
E	11/13	85	9/13	69
F	19/24	79	18/24	75
G	17/21	81	17/21	81
Total	89/122	73%	82/122	67%

Travellers Diarrhea (Turista)

Travellers diarrhea is a disease which attacks the person newly arrived in a foreign country, usually within 14 days of arrival.

Of 600 of the scientific visitors to a medical congress held in Teheran in 1968, 28% had diarrhea. The syndrome was similar to the travellers diarrhea, or "turista", affecting U. S. visitors to Mexico (Table 8) (61). Only 8% of the 163 travellers from tropical countries (where diarrhea is considered to be common) became ill, wheras 41% of those from countries with more temperate climates had diarrhea. Only 1 out of 48 Iranians was affected.

TABLE 8

COMPARISON OF SYNDROME IN U.S. CITIZENS IN TEHERAN AND IN MEXICO

	Of those having diarrhea:	
	Teheran	*Mexico*
No. U. S. citizens	94	208
Positive for diarrhea	41%	33%
Abdominal pain	45%	71%
Fever	37%	76%
Nausea	22%	65%
Myalgia	28%	25%
Vomiting	8%	22%
Headache	5%	21%
Chills	5%	52%
No. days after arrival diarrhea began	4 (1-10) days	14 (2-31) days
Duration of diarrhea (days)	3 (1-9) days	2 (1-10) days
No. bowel movements peak day	1-10	2-39
More than 10 bowel movements on one day	3% (1)	19%

In a series of studies reported by Kean, the efficacy of two antimicrobial agents in the prevention of tourist diarrhea among newly arrived college students in Mexico City was reported. In a two-week "double-blind" study, 473 students took one of three drugs in prophylaxis: a lactose placebo, neomycin sulfate (1 gm/day), or phthalylsulfathiazone (2 gm/day) (Table 9).

Diarrhea occurred in 23.8% of those who took the placebo, in 16.1% of those who took neomycin and in 6.6% of those who took phthalylsulfathiazole. Both results were statistically significant.

TABLE 9

DRUG STUDY: INCIDENCE AND SEVERITY OF DIARRHEA

	Total completing study	*Total sick*		*Students with diarrhea*		
				Mild	*Moderate*	*Severe*
Students receiving:		*No.*	*%*	*No.*	*No.*	*%*
Placebo	168	40	23.8	11	29	17.3
Neomycin	137	22	16.1	15	7	5.1
Phthalylsulfathiazole	168	20	11.9	9	11	6.6

Recent studies suggest that specific strains of *E. coli* which are either enterotoxigenic or invasive may be responsible for at least part of the syndrome. A group of 540 British soldiers travelled by air from England to Aden. 38 had an attack of diarrhea during their first 14 days after arrival; fecal specimens were investigated from 35 (62). Salmonellae were isolated from 2 cases (5.7%), but in the remaining 33 cases salmonellae and shigellae were not isolated. A new serotype of *E. coli* with antigenic structure O148K?H28 was isolated in the acute phase from 19 (54.3%) of these cases. In the remaining 14 (40%) cases a number of different *E. coli* serotypes were isolated, including serotypes which cause infantile diarrhea; these were not related to travellers diarrhea. The peak of the isolations of *E. coli* O148K?H28 corresponded with the peak incidence of travellers diarrhea, and this serotype was never isolated from a healthy subject. A year later, in a laboratory in England, a technician working with this serotype developed a severe attack of diarrhea, and *E. coli* O148K?H28 was recovered in pure culture from his stools.

It is noteworthy that Formal found this strain to be toxigenic in the rabbit ileal loop (Table 2). Similar observations were made on two strains of *E. coli* isolated from the small bowel of U. S. soldiers in Vietnam. Gorbach and associates studied the microflora of the small and large intestine in 17 adults with acute undifferentiated diarrhea in Calcutta, India (63). On the basis of bacteriologic findings, the patients could be divided into two groups: those with a predominant flora of *E. coli* (8 patients) and those with a mixed coliform flora (9 patients). In the former group, *E. coli* were distributed throughout the small and large bowel. Broth filtrates of these isolates contained an enterotoxin which caused fluid accumulation in the rabbit intestinal loop model. Toxigenic *E. coli* were cleared rapidly from the small bowel during the acute period; some patients had only the "hot" strains in their fecal effluent. During convalescence, the serotypes of *E. coli* changed and the new strains did not elaborate enterotoxin. Only 1 of the 8 patients had a serotype previously associated with diarrhea. Acute undifferentiated diarrhea in the remaining cases was apparently caused by untypable *E. coli* or by typable strains not generally considered pathogenic.

Clostridium perfringens

Clostridium perfringens has been associated with two diarrheal syndromes, a lethal necrotizing enteritis known as "Darmbrand" in Germany and as "pig-bel" in New Guinea and not seen in the United States, and self-limited non-fatal food-borne disease. In the U. S., *Clostridium perfringens* is the prevalent cause of outbreaks of food-borne diarrhea (Figure 1).

Hobbs, Smith, Oakley, Warrack and Cruickshank in 1953 published the results from epidemiological and laboratory studies on outbreaks of food poisoning due to *Cl. welchii* (64). After an incubation period of 8 to 24 hours, there was abdominal pain and diarrhea but rarely vomiting, with an absence of signs of infection such as pyrexia and headache. The medium or vehicle of infection was almost invariably a cold or warmed-up meat dish, boiled, braised, steamed or stewed for 2 to 3 hours on the previous day or some hours before required, and allowed to cool slowly in the kitchen or larder. The remains of the meat eaten by those affected were usually normal in appearance, taste and smell, and only occasionally were they sour and gassing.

It is of note that an enterotoxin has been demonstrated (Table 3) (65).

Vibrio parahemolyticus

In Japan the high incidence of summer food poisoning has been related to the custom of eating uncooked seafish and shellfish (sushi). This has been associated with an enteropathogenic halophilic marine bacterium, *Vibrio parahemolyticus*, carried by fish and shellfish (66). Noteworthy is the observation that *V. parahemolyticus* has a generation time as short as 10 minutes at appropriate salt concentration and temperature, hence it can rapidly reach high concentrations. *V. parahemolyticus* was isolated from 33% of patients suspected of having shigellosis during the summer months, and also from 30% of patients with enteritis without other pathogens, but from only 0.8% of healthy subjects. During the summer months, 87% of food materials and 82% of utensils used in the preparation of sushi had positive cultures. The organism requires special medium for isolation, e.g., TCBS, which is also recommended for cholera. In studies off the coast of Washington State, organisms were isolated from 78 to 100% of sediment samples and all oysters and clams (10^5 to 10^7/gm) (67). During subsequent marine ecological studies, the organism was found virtually worldwide: Hong Kong, Taiwan, Philippines, Hawaii, Germany (Baltic Sea), the Gulf and South Atlantic U. S. coasts (68). Likewise, 56 of 60 samples of processed meat of Chesapeake Bay blue crabs were positive (68).

Despite these frequencies, gastroenteritis was not recognized in the United States until the summer of 1971. Between August 14 and 16, 1971, approximately 320 of 550 persons attending a picnic at the U. S. Naval Training Center in Bainbridge, Maryland, had onset of acute gastroenteritis. Their symptoms included diarrhea (98%), severe abdominal cramps (78%), nausea (76%), vomiting (74%), fever (26%), headache (25%), and chills (10%). Onset of symptoms was documented for 100 patients. Median incubation period was 15 hours (range 8-22 hours), and median duration of illness was 2 days (range 1-5 days). Approximately 60% of the patients sought medical attention, and 2% were hospitalized. There were no deaths.

On August 14, approximately 20 of 30 guests at another picnic in nearby Elkton, Maryland, experienced a similar clinical illness.

Cultures of foods served at both picnics and of stool specimens from an estimated 30 ill persons were negative for enteropathogenic *E. coli*, salmonella, and shigella. However, cultures of stool specimens from 4 patients, two from each picnic, and of two steamed crabs served at the smaller picnic were positive for *Vibrio parahemolyticus*. Steamed crabs had also been served at the larger picnic.

The implicated crabs at both picnics had been obtained from a crab supply house in Chesapeake Bay, Maryland. There, they had been steamed, placed in a truck with baskets of other live crabs on top, and delivered to Elkton. Some were then delivered to the smaller picnic and some to the larger picnic in Bainbridge.

Among the symptoms, the 10% frequency of chills is striking. In an outbreak which occurred on a resort island off the coast of Australia, the frequency of symptoms was strikingly similar, including 4 of 19 patients (21%) who recalled "shivers" which required blankets despite ambient temperatures of 30 to 38°C (69). In that outbreak, a few patients had apparent relapses within 2 or 3 days of recovery.

The recognition of *Vibrio parahemolyticus* as a potential etiologic agent in the U. S. can be expected to lead to the definition of a number of previously undefined episodes. Certainly, culture material from outbreaks with a salmonella-like illness and epidemiologic data implicating a seafood vehicle should be processed specifically for *V. parahemolyticus*, e.g., on TCBS medium.

Cadmium and Arsenic Poisoning

It is essential to remember that both arsenic and cadmium poisoning may present as a diarrheal syndrome, as illustrated by this report:

Alleged food poisoning occurred in a family of two adults and two children. According to the report given by the father, within 1 hour after the evening meal the previous day all members of the family experienced headaches followed almost immediately by severe nausea and vomiting. The symptoms persisted until midnight, when they began to subside. No ill effects were noted the next day.

The meal, eaten by the family at 7 p.m., was prepared out of doors and consisted of the following items: boiled potatoes, tossed green salad without dressing, commercially canned string beans, steaks grilled over an outdoor barbecue, soft drinks for the children, and one glass of beer for each adult. No dessert was eaten.

Since none of the food was available for analysis, a careful epidemiological investigation was made. It was learned that all foods were freshly prepared under sanitary conditions. The salad and drinks were prepared in glass containers. The string beans were commercially canned and were freshly opened. The steak, of the prepackaged type, appeared fresh. It had been purchased 4 days earlier

at a local supermarket and had been kept under refrigeration until the time of use.

The father had not eaten his noon meal at home and yet was affected by the illness. All members of the family ate portions of all the foods except the beverages. The investigation did not reveal the presence of any obvious staphylococcal lesions on members of the family.

On further questioning, it was learned that the steak was grilled on an improvised outdoor barbecue. The grill consisted of an old refrigerator shelf which was being used for this purpose for the first time. Cadmium poisoning was suspected, and the shelf was submitted for chemical analysis of the plating remaining on the unburned portions. This examination revealed that the metal contained cadmium in greater than trace amounts.

Ingestion of as little as 10 mg of cadmium results in headache, nausea, vomiting, diarrhea, salivation, abdominal and muscular pains which occur within 1/2 to 2 hours (70). In contrast to most bacterial toxins, cadmium usually affects 100% of persons ingesting the material. Exposure may occur from "boiled" ice trays and coated containers.

Solanine Poisoning

The ingestion of green or sprouting potatoes may be followed in several hours by gastroenteritis characterized by colic, diarrhea, headache, anxiety, cold and clammy skin, weakness and vascular collapse (71-74). The pupils may become dilated and fixed, and hyporeflexia occurs. These symptoms are due to solanine, a glycoalkaloid which inhibits cholinesterases, and is especially high in the sprouts and sun-greened skin of potatoes (*Solanum tuberosum*).

Attached is a list of other considerations (Table 10) (75).

Classification of Illnesses Attributable to Foods

A. FOOD INFECTIONS (Bacterial)

Illness	Causative agent	Foods usually involved	Other modes of transmission	Incubation period	Signs and symptoms	Measures to prevent spread by food
Bacillary dysentery (Shigellosis)	Members of the genus *Shigella*	Moist prepared foods, milk, or other dairy products contaminated with excreta	Direct or indirect contact with case or carrier, or contaminated water	Usually 2-3 days; extremes, 12 hours to 7 days	Diarrhea, bloody stools; fever in severe cases	Strict personal cleanliness in food preparation; refrigeration of moist foods during storage periods; cooking of foods prior to serving; elimination of flies
Bacillus cereus poisoning	*Bacillus cereus*	Prepared foods containing eggs and starches, such as puddings, pie fillings, and sauces		8-22 hours	Acute abdominal pain and diarrhea	Adequate cooking followed by rapid cooling and refrigerated storage
Clostridium perfrigens infection	*Clostridium perfrigens* (*welchi*)	Meat which has been boiled, steamed, braised, stewed, or insufficiently roasted and allowed to cool slowly and served the next day, either cold or reheated		8-22 hours	Acute abdominal pain and diarrhea; nausea and vomiting rare; fever, shivering, and headache seldom seen	Exclude from food handling, known carriers; cook meat immediately before consumption, or rapid cooking and refrigerate between cooking and use
Hemolytic streptococcal infections (scarlet fever or septic sore throat)	Certain strains of beta hemolytic streptococci	Food contaminated with nasal or oral discharges from case or carrier; milk from cows having udder infections caused by these organisms	Direct contact with case or carrier	Usually about 3 days; extremes, 1-7 days	Fever, sore throat; rash occasionally	Pasteurization of milk and other dairy products; excluding persons with known streptococcal infections from handling food; isolation of carriers; prophylactic antibiotic treatment of contacts of known cases
Streptococcal food infection	Enterococcus group *S. fecalis* (Lancefield group D.), Pyogenic group *S. pyogenes* (Lancefield group A)	Food products contaminated with excreta. Foods contaminated by respiratory discharges of case or carrier	Contact with contaminated persons or fomites. Wound infection, or contact with discharges of infected wounds	2-18 hours	Nausea; sometimes vomiting, colicky pains, and diarrhea; usually milder than staphylococcal food poisoning	Cooking of food thoroughly; refrigeration of moist foods during storage periods
Salmonellosis a) Typhoid fever	*Salmonella typhi* (typhosa)	Any milk, shellfish, or other food product contaminated with excreta from human case or carrier	Water polluted by human excreta	Usually 7-21 days; extremes, 3-38 days	Insidious onset with malaise, lack of appetite, headache, fever, diarrhea. In children, onset may simulate early pneumonia	Pasteurization of milk and other dairy products; certification of shellfish; chlorination of water; prohibit carriers from handling food; elimination of flies; examination of stools of food handlers who have history of having had typhoid fever
b) Paratyphoid A	*S. paratyphi* A	Same as for typhoid fever	Contact with unrecognized case or carrier	Usually a few days; extremes 1-10 days	Fever, malaise; may resemble milk typhoid	Same as typhoid fever
c) Other types	Members of the genus *Salmonella, e.g., S. typhimurium, newport, oranienburg, montevideo, newington, enteritidis, choleraesuis, pullorum,* and others, including Arizona group	Meat and poultry salads, eggs and egg products	Direct or indirect contact with human or animal carriers	Usually 12-24 hours; extremes, 5-72 hours	Abdominal pain, diarrhea, chills, fever, frequent vomiting, prostration	Cooking of food thoroughly; strict sanitation in food preparation; refrigeration of moist foods during storage periods; wash hands frequently; protect foods from animal excreta; prohibit carriers from handling food

B. FOOD INFECTIONS (Viral)

Illness	Causative agent	Foods usually involved	Other modes of transmission	Incubation period	Signs and symptoms	Measures to prevent spread by food
Acute non-bacterial gastroenteritis*	Coxsackie and ECHO viruses; viral agents as yet unidentified	Possibly food-borne but as yet this mode of transmission is unestablished	Case or carrier	27-60 hours (average)	Fever; constitutional symptoms; headache; abdominal pain, vomiting, and diarrhea	Probably the same as for poliomyelitis

C. FOOD INTOXICATIONS (Bacterial)

Illness	Causative agent	Foods usually involved	Incubation period	Signs and symptoms	Measures to prevent spread by food
Botulism	Toxins	Home-processed foods; contaminated canned foods with pH over 3.5; smoked fish; canned liver paste	Usually 12-36 hours; extremes, 2 hours to 6 days	Dizziness; lassitude; double vision; loss of reflex to light; muscular weakness; difficulty in swallowing, speeech, and respiration; frequently fatal	Cook foods thoroughly before serving (boil 15 min. with stirring to insure heating of all parts, or pressure cook)
Staphylococcal food poisoning (intoxication)	Enterotoxin-producing staphylococcus (preformed enterotoxin)	Cooked ham or other meats; cream-filled or custard pastries, and other dairy products; bread puddings; potato salad, and other salads of protein foods; Hollandaise sauce; "warmed over" foods	Usually 2-6 hours; extremes, 1-11 hours	Nausea, vomiting, diarrhea, and acute prostration; abdominal cramps	Exclude from food handling persons with nasal discharges or purulent local skin infections; cook foods thoroughly; refrigerate moist foods during storage; reheat custard pastries; wash hands frequently
Scombroid poisoning	*Proteus morganii*	Tuna, Bonita, Skipjack, and other tuna or mackerel-like fish	½-3 hours	Reddening of the face and upper half of the body, exanthema like those of allergy, severe headache, palpitation and diarrhea	Proper handling and refrigeration of fish at 45 F or below

E. CHEMICALS

Illness	Causative agent	Foods usually involved	Incubation period	Signs and symptoms	Measures to prevent spread by food
Arsenic poisoning	Insecticides and rodenticides	Any foods accidentally contaminated	1 hour or less	Vomiting, diarrhea; occasionally fatal	Use of colored pesticides and proper storage of same
Cadmium poisoning	Plating metal	Any food contaminated by leaching of containers and trays by acid foods including fruit juices	½ hour or less	Nausea, vomiting, cramps; often fatal	Discontinue use of cadmium-plated utensils as food containers
Chlorinated hydrocarbon poisoning	Chlorinated hydrocarbon insecticides aldrin, chlordane, DDE (DDD), DDT, dieldrin, endrin, heptachlor, lindane, toxophene, others	Any food or utensil accidentally contaminated	½ hour or longer	Headache, nausea, dizziness, confusion, convulsions	Wash leafy vegetables; prevent contamination by protecting food and utensils when using insecticides

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