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MISCELLANEOUS PUBLICATION 39

HUMAN ORAL DOSE FOR TEN SELECTED FOOD- AND WATERBORNE DISEASES

James A. Kime
Edwin P. Lowe

APRIL 1971

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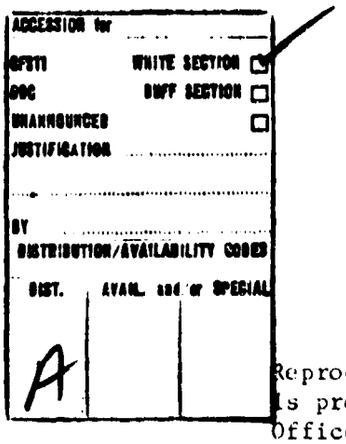

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ABSTRACT

The available data on human oral dose for 10 illnesses commonly implicated in food- and waterborne outbreaks are assembled and discussed. Seven of the illnesses are bacterial infections; the other three are bacterial intoxications.

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I. INTRODUCTION

Man acquires a number of diseases by the oral route, i.e., by ingesting the causative agent in food and water. In public health reports these are commonly grouped in a category identified as "food- and waterborne illnesses." Although information on oral dose should be useful in a number of ways, the accumulation of such data has proceeded at a slow rate for many years and is still sparse in many respects. For example, brucellosis was a major health problem during the first half of the present century, yet an examination of numerous reports and several well-known books on this disease yielded no data or estimates of the number of Brucella organisms required to produce infection in man. Another example is cholera, sometimes identified as the oldest plague. Since resurgence of the disease in the early 1960's, it has been the object of worldwide research, but again the literature apparently is devoid of documented estimates of the number of vibrios required to infect man.

During recent decades new data on oral dose are finding their way into the literature. It seemed worthwhile, therefore, to present the available information in convenient summary form for ready reference. With two illnesses the authors have estimated a dose based on information as to the probable number of infecting organisms per gram of food and an assumption as to the amount consumed. The purpose of this presentation is not to set guidelines for acceptability of a food or beverage for human consumption but to provide a convenient summary and key references to oral dose for ten food- and waterborne illnesses.

II. SCOPE OF REPORT

Seven bacterial infections commonly implicated in food- and waterborne outbreaks are described in tabular form in Table 1. The disease, its causative agent, the incubation period, and the nature of the illness are given. Table 2 contains similar information for three bacterial intoxications usually acquired by ingesting contaminated food. In compiling this report, generous use was made of information in the manual Control of Communicable Diseases in Man.[1]

This report does not include information on infective dose of virus by the oral route although the potential problem of waterborne virus disease has received considerable attention in recent years by medical and scientific investigators. At the symposium on this subject convened at the Robert A. Taft Sanitary Engineering Center in 1965, Plotkin and Katz[2] reviewed the literature on infective dose of several viruses by different routes and made this general observation: "Since we cannot provide much exact data,

TABLE 1. SELECTED FOOD- AND WATERBORNE BACTERIAL INFECTIONS

Illness	Causative Agent	Incubation Period	Nature of Illness
Bacillary dysentery, shigellosis	Members of genus *Shigella*	Usually 2-3 days; extremes 12 hours to 7 days	Diarrhea, bloody stools, fever in severe cases
Brucellosis, undulant fever	*Brucella abortus*, *B. melitensis*, *B. suis*	Extremely variable, usually 5-21 days	Protracted illness, fever, chills, sweats, weakness, muscle and joint pains
Cholera	*Vibrio comma*	Usually 3 days; extremes a few hours to 5 days	Sudden onset, diarrhea, vomiting, muscular cramps, dehydration, collapse
Hemolytic streptococcal infections (scarlet fever or streptococcal sore throat)	*Streptococcus pyogenes* group A of at least 40 serological types	Usually 2-5 days	High fever, nausea, vomiting, sore throat, rash
Typhoid fever	*Salmonella typhosa*	Average 14 days, usual range 1-3 weeks	Acute infectious fever lasting 3 to 4 weeks, persistent headache, bronchitis
Salmonellosis	Members of genus *Salmonella*	Average 12 hours, usual range 6-48 hours	Abdominal pain, diarrhea, chills, fever, vomiting
Tularemia	*Pasteurella tularensis*	About 3 days; extremes 1-10 days	Sudden onset with headache, chills, body pains, vomiting and fever

TABLE 2. SELECTED FOODBORNE BACTERIAL INTOXICATIONS

Illness	Causative Agent	Incubation Period	Nature of Illness
Botulism	Toxins of *Clostridium botulinum*	Usually 12-36 hours; extremes 2 hours to 6 days	Headache, double vision, respiratory paralysis, death
Paralytic shellfish poisoning	*Gonyaulax catenella*	Symptoms in 5-30 minutes; in fatal cases, death in 2-12 hours	Numbness of extremities, muscular incoordination, paralysis, death
Staphylococcal food poisoning	Exterotoxin-producing strains of *Staphylococcus*	Usually 2-4 hours; extremes 1-11 hours	Sudden onset, nausea, vomiting, diarrhea, and acute prostration

we will express an opinion and then try to justify it. The opinion is that there is no reason to believe that the human is any less susceptible than the tissue culture. In other words, in general one 50% human infective dose is equal to one 50% tissue culture dose."

III. ORAL DOSE

The scientific and medical literature dealing with food- and waterborne diseases is abundant. In general, however, the reports are not particularly helpful in quantifying the oral dose in man. From the standpoint of public health, this situation is understandable because the primary concern is the minimum infective dose (MID). The public official needs to know, and to be able to state on the basis of scientific fact, whether a food product can be consumed without hazard or should be condemned as dangerous. The number may be a range of values dependent on strain and virulence (or toxicity) and on the variation in resistance of people ingesting the causative agent. What may be highly dangerous to the health of an infant, an aged person, or one with an altered gastrointestinal tract may not affect a normal healthy adult.

The literature was rather extensively searched for data on human oral dose of the causative agents of illnesses listed in Tables 1 and 2. The findings are summarized below with additional information on the diseases produced.

IV. BACTERIAL INFECTIONS

A. BACILLARY DYSENTERY OR SHIGELLOSIS

This acute bacterial disease of the intestine is characterized by diarrhea, accompanied by fever and often vomiting, cramps, and tenesmus. It occurs in all parts of the world: arctic, temperate, and tropical. The reservoir is man; the source of infection is feces from an infected person.

The work on vaccines by Shaughnessy et al.[3] in 1946 apparently provides the only available data on oral infective levels of shigellae for man. Those authors fed 39 human volunteers with various doses involving five strains of Shigella paradysenteriae (Flexner W). Strain FWI, although the most virulent for mice, was not virulent enough to produce a clean-cut clinical infection in man even at doses of 50×10^9 organisms. Mixed

fresh cultures of four other strains of Flexner W (FWII, FWIII, FWIV, and FWV) were fed to volunteers. A dose of 10 x 10^9 organisms produced clinical illness in all of four volunteers. In a repeat experiment, two of three volunteers who received 2.5 x 10^9 organisms had a moderate form of clinical dysentery. The investigators also observed that virulence decreased with increase in age of culture.

The results were inconsistent in some respects, to the extent that a firm estimate of the oral dose was not suggested by the authors. The response recorded in the tests cited do suggest that an ED_{50}* in normal adults would be of the order of 1 x 10^9 organisms of a fresh virulent culture.

B. BRUCELLOSIS OR UNDULANT FEVER

Brucellosis is primarily a disease of domestic animals. Man becomes infected by drinking contaminated milk, by handling meat or organs of diseased animals, or by physical contact with diseased animals. In man the illness is a systemic disease with insidious onset, characterized by continued, intermittent, or irregular fever of variable duration. Occurrence is worldwide. Three species of Brucella are involved. Brucella melitensis is found most frequently in goats, B. suis in swine, and B. abortus in cattle. Brucella melitensis is the most invasive and produces the most serious infections. Brucella suis is also very invasive and characteristically causes necrosis and suppuration in the tissues of the host. Brucella abortus is the least invasive of the three species and causes a milder disease.[4]

More than 60 years ago the British Mediterranean Fever Commission discovered B. melitensis in milk of apparently healthy goats on the Isle of Malta. In 1907, goats' milk was banned from the diet of military forces on this island and the incidence of brucellosis (Malta fever) dropped precipitously. Obviously, the disease had been acquired by consumption of contaminated milk. Since this pioneering discovery, numerous outbreaks have been described in which milk was the vector for transmitting the disease from animal to man. A report-by-report examination of the extensive literature on brucellosis to ferret out data on oral dose in man is beyond the scope of this study. Several well-known books and numerous articles were examined, however, but no definitive data were located. This lack was confirmed in conversations with persons knowledgeable in the field.**

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* In this report ED_{50} is defined as the amount of agent required to produce illness in 50% of an exposed population.

** Norman B. McCullough, National Institutes of Health, Bethesda, Maryland, personal communication.

One approach to approximating oral dose is to calculate potential exposure. Some data on the numbers of Brucella organisms in milk from infected cows were found in the literature, but, unfortunately, the concentrations were not reported and related to the attack rate in a specific outbreak. It did seem worthwhile, however, to present the data and quantitate the hazard by simple assumptions.

In a discussion of Brucella in cheese, Harris[5] referred to milk from heavily infected cows as containing 600 to 800 B. abortus organisms per milliliter. Huddleson[6] reported that nine samples of whole milk after 24 hours in an ice box contained from 140 to 400 organisms of B. abortus per milliliter. In a duplicate set of samples, the cream that rose to the top was skimmed off and analyzed. The counts of B. abortus ranged from 890 to 5,200 organisms per milliliter.

If an approximate average is assumed to be 500 organisms per milliliter of whole milk, a person consuming a pint a day for 10 days would ingest $500 \times 473 \times 10 = 2.4 \times 10^6$ organisms. Before the introduction of homogenized milk, the cream layer that rose to the top on standing was often decanted and used for breakfast food, desserts, etc. If this contaminated cream contained 2,500 organisms per milliliter, and a person consumed 2 ounces per day for 10 days, the total ingested dose would be $2,500 \times 28.35 \times 2 \times 10 = 1.4 \times 10^6$ organisms. No information was found on the concentration of B. melitensis in milk from infected goats or of B. suis in milk of cows that had become infected by close association with swine that carried the disease. It is logical to expect that fewer organisms of these two species would be required to produce infection in man because both are more invasive than B. abortus and cause more serious complications.

This analysis obviously does not establish an oral ED_{50} for Brucella in man. It does provide limited support for estimating the ED_{50} for B. abortus to be in the order of 1×10^6 organisms. As indicated above, the number may be less for B. melitensis and B. suis.

C. CHOLERA

This serious, acute, intestinal disease is characterized by sudden onset, vomiting, profuse watery stools, rapid dehydration, and collapse. Severity differs greatly from place to place and within epidemics. Case fatality is 5 to 15% in endemic cholera and as high as 75% in explosive epidemics. Adequacy of rehydration can markedly reduce fatality rate. Cholera due to the classical Vibrio species is endemic in parts of India and East Pakistan, from which it has spread in epidemic form from time to time. During the early 1960's, a strain of the El Tor group suddenly expanded its area of attack and has replaced Vibrio comma as the principal cause of cholera. The source of infection is feces and vomitus of patients, and, to a lesser extent, the feces of persons incubating the

disease, and the feces of convalescents. The causative agent persists in feces 7 to 14 days after onset, and occasionally for several months, depending on the strain.

Transmission in the initial wave of an epidemic is regularly by contaminated water and uncommonly by food. Later cases ordinarily occur by direct contact, by food contaminated by soiled hands or utensils, and by flies. The stability of the El Tor Vibrio in various vehicles of transmission was reported by Pesigan.[7]

Data on the oral infective dose of cholera organisms for man apparently are nonexistent. At the 1965 Cholera Research Symposium, Flynn[8] commented: "Recent reports by Zafar at Dacca, Orth in Thailand, and Bhaskaran at Calcutta have shown frequent contamination of water by cholera organisms and NAGs,* yet there were no new cholera cases in the area supplied by the water. Is this a question of immunity of persons using the water, or of the size of the infecting dose? Or is it easier to recover organisms from water recently contaminated by large numbers of recently infected persons?

"Size of infective dose -- Determining the infecting dose in water has posed an important problem. The response of individuals to even large numbers of cholera organisms is very variable. The rare instances of the disease in personnel of western military forces living in cholera areas is a measure of perhaps their discipline and their vaccination status and their own resistance because of their good standard of nutrition, but what happens when an individual is debilitated or is not vaccinated? How can we determine the size of the infecting dose in water for various states of nutrition and health? Perhaps we can carry out experiments on volunteers to determine infective dose size with cholera organisms in water, as Professor Woodward has done with typhoid."

Recovery from disease affords some short-term protection. Immunity artificially induced by vaccines is of unknown degree and short duration, not more than 6 months.

D. HEMOLYTIC STREPTOCOCCAL INFECTIONS

Group A hemolytic streptococci cause a wide variety of diseases differentiated clinically according to the portal of entry, tissue of localization of the infectious agent, and presence or absence of a scarlatinal rash. The more important conditions are scarlet fever, streptococcal sore throat, erysipelas, and puerperal fever.

Scarlet fever is a streptococcal sore throat in which the infectious agent is capable of producing erythrogenic toxin and the patient has no antitoxic immunity. If the organism is not a good toxin producer, or

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* Nonagglutinable vibrios.

if the patient is immune to the toxin, streptococcal sore throat results. The distinguishing characteristics of scarlet fever are fever, sore throat, exudative tonsillitis, tender cervical adenopathy, leukocytosis, strawberry tongue, and rash (exanthema).

The reservoir is man—an acutely ill person, convalescent patient, or carrier. Sources of infection are discharges from nose, throat, or purulent lesions, or objects contaminated with such discharges.

Explosive outbreaks of streptococcal sore throat may follow the ingestion of contaminated milk or other food. Although such incidents may be infrequent, they do happen. Three are described in brief, two that occurred in 1968 and one in 1943.

Group A streptococcal pharyngitis struck about 600 cadets at the U.S. Air Force Academy in April 1968. Illness was characterized by high fever, headache, and sore throat. The apparent vehicle was hard-boiled eggs presumably contaminated by a food handler.[9]

Group A streptococci involved 172 of 502 students at a Vermont college in October 1968. The main symptoms were sore throat, headache, chills, and fever. Egg salad was the suspected food vehicle.[10]

An epidemic of tonsillitis and pharyngitis caused by beta-hemolytic streptococci of group A type 5 involved troops at Fort Bragg, North Carolina, in 1943.[11] Epidemiological evidence incriminated creamed eggs served at breakfast as the probable vehicle of infection. The outbreak was sudden in onset with a median incubation period of 38 hours and a primary attack rate of 42%. The secondary attack rate was 30%, of which half were cases and half were carriers.

No estimate was made in the report of the Fort Bragg incident of the number of organisms consumed by personnel at risk. As so often happens when the agent is foodborne, the contaminated eggs had been consumed or destroyed by the time the attack rate became significant. With assumptions, however, a plausible estimate of the number consumed may be made. It seems obvious from the high attack rate that the creamed-egg fluid provided a favorable environment for the streptococcal organism. After the uncooked mixture stood overnight in a warm place, the concentration could have been 1×10^5 organisms/g.* During cooking, a 2-log decrease could be expected. If the average serving was equal in a fluid volume to that of two whole eggs, or about 50 g, then the average amount ingested would have been $1 \times 10^3 \times 50 = 5 \times 10^4$ organisms. This rationale suggests an ED_{50} of 1×10^4 to 1×10^5 cells of beta-hemolytic streptococci.

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* Harold V. Leininger, Director, National Center for Microbiological Analysis, Food and Drug Administration, suggested that a fluid milk product inoculated with a streptococcal organism of the species discussed here might contain up to 4×10^5 organisms/g after overnight incubation (personal communication, 1970).

E. TYPHOID FEVER

Typhoid fever is a systemic infectious disease characterized by continued fever, malaise, anorexia, slow pulse, involvement of lymphoid tissues, especially ulceration of Peyer's patches in the intestine, enlargement of the spleen, rose spots on the trunk, and constipation more often than diarrhea. It occurs throughout the world and is common in many countries of the Far East, Middle East, Eastern Europe, Africa, and in Central and South America. The causative bacteria are excreted in the fecal discharges of patients ill with the disease, as well as by occasional individuals who have fully recovered from this illness, the so-called typhoid carriers. Principal vehicles for spread of disease are contaminated water and food.

Of the several diseases commonly transmitted by contaminated water or food, the most complete information on oral dose required to produce illness is that of Woodward et al.[12,13] on typhoid fever. They challenged immunized and nonimmunized volunteers with several strains of Salmonella typhosa in a study of the efficacy of vaccines prepared by different procedures. Their results, with particular reference to oral dose, are summarized in Tables 3, 4, and 5. The experimental evidence shows that 1×10^5 organisms, Quailes strain, caused infection in 28% of controls, i.e., persons without a previous history of disease or vaccination. A dose of 1×10^7 organisms caused infection in 50% of the individuals challenged, including those who had been vaccinated. A dose of 1×10^9 organisms caused infection in 100% of the unprotected volunteers and 75% of those who had been vaccinated.

F. SALMONELLOSIS

The most common clinical manifestation of Salmonella infections is an acute gastroenteritis, particularly in salmonellosis that arises from contaminated food. It is an acute infectious disease with sudden onset of abdominal pain, diarrhea, and frequent vomiting. Fever is nearly always present. Deaths are uncommon. Occurrence is worldwide.

More than 1,000 serological types may be involved in food poisoning. On a world basis, S. typhimurium is the most common. The reservoir of pathogenic Salmonella is domestic and wild animals, including pets such as turtles and chicks, and man, including patients and convalescent carriers. The source of infection is feces of animals and infected persons; whole eggs, particularly duck eggs, and egg products; meat and meat products, including poultry; and animal feeds and fertilizers prepared from meat, fish meal, and bones.

Man is generally susceptible. Severity of disease is greatest at extremes of life and is related to size of dose and to a slight extent to species of infectious agent. There is no active or passive artificial immunization.

TABLE 3. VIRULENCE OF S. TYPHOSA STRAINS IN UNIMMUNIZED CONTROLS

Strain[a]	No. Requiring Treatment/ No. Challenged	Infection Rate, %
Quailes	16/32	50
TY2-V	2/6	33
TY2-W	4/19	21
0901	6/20	30

a. Oral dose: 1×10^7 organisms.

TABLE 4. DOSE RESPONSE IN UNIMMUNIZED CONTROLS OF QUAILES STRAIN

Oral Dose, No. Organisms	No. Requiring Treatment/ No. Challenged	Infection Rate, %
10^9	40/42	95
10^8	8/9	89
10^7	15/30	50
10^5	24/84	29
10^3	0/14	0

TABLE 5. EFFICACY OF TYPHOID VACCINE AGAINST ORAL CHALLENGE WITH QUAILES STRAIN

Dose, No. Organisms	Vaccine K No.[a]	K %	Vaccine L No.[a]	L %	Controls No.[a]	Controls %
10^9	2/3	67	3/4	75	4/4	100
10^7	12/28	43	13/24	54	15/30	50
10^5	2/35	6	3/39	8	20/72	28

a. No. = Number of persons requiring treatment/number challenged.

The classic work of McCullough and Eisele[14-16] provides authoritative data on the pathogenicity of six serotypes of Salmonella. All serotypes produced illness in healthy male volunteers, but the number of organisms required varied widely (Table 6). Salmonella bareilly, S. newport, and two strains of S. anatum were the most virulent, causing illness in 50% of the exposed volunteers with doses of 8.6×10^5 to 1.3×10^6 organisms.

Carmine is an inert dye widely used as a stool marker in gastrointestinal investigations. Carmine contaminated with Salmonella cubana was the cause of numerous cases of salmonellosis at the Massachusetts General Hospital.[17] Those involved were predominantly debilitated and aged patients, infants, and persons with altered gastrointestinal function. The investigators concluded that as few as 15,000 S. cubana organisms may be sufficient to begin significant and even fatal infection in persons with impaired resistance.

G. TULAREMIA

Tularemia is an infectious disease of animals and man. In man the onset begins with chills and fever and the patient usually is prostrated and confined to bed. Tularemia occurs throughout North America and in many parts of Europe, Russia, and Japan. The disease is transmitted by inoculation of the skin during the handling of infected animals, as in skinning, dressing, and performing necropsies, through bites of arthropods, by ingestion of contaminated water, and by inhalation. People of all ages are susceptible but permanent immunity follows recovery. Vaccines prepared from viable, nonvirulent strains offer good protection against infection.

The reservoir and source of infection, with particular reference to the United States, was concisely described by Jellison et al.[18] in summarizing their years of experience with tularemia in animal populations: "In North America two kinds of tularemia can be distinguished by epidemiological pattern and virulence of isolates:

1. Tickborne tularemia of rabbits, Lagomorpha, which frequently affects other animals, may be transmitted by other arthropods, and is the source of 90% of the human infections.

2. Waterborne tularemia of true rodents, Rodentia, which also affects other animals, and is the source of 5 to 10% of human infections."

The first reported outbreak of tularemia due exclusively to water was observed in Russia in 1935 by Karpoff and Antonoff.[19] Those who became ill had worked in a hay field and drunk water from a contaminated stream. Water samples inoculated into guinea pigs showed the presence of P. tularensis. Cultures isolated from water samples and from the lymph glands of patients were of equal virulence. Water rats and mice were

TABLE 6. ORAL DOSE OF *SALMONELLA* IN HUMAN VOLUNTEERS

Salmonella Serotype	Challenge Dose, No. Organisms	No. Ill/ No. Exposed	Approximate ED_{50}, No. Organisms
S. meleagridis			
Strain I	24×10^6	1/5	4×10^7
	50×10^6	4/6	
Strain II	10×10^6	1/6	3×10^7
	20×10^6	2/6	
	41×10^6	5/6	
Strain III	7.7×10^6	1/6	$>1 \times 10^7$
	10×10^6	2/6	
S. anatum			
Strain I	5.9×10^5	2/6	8.6×10^5
	8.6×10^5	3/6	
Strain II	44.5×10^6	1/6	6.7×10^7
	67×10^6	4/8	
Strain III	1.3×10^6	2/6	3×10^6
	4.7×10^6	4/6	
S. newport	1.5×10^5	1/6	1.4×10^6
	3.9×10^5	1/8	
	1.4×10^6	3/6	
S. derby	6.4×10^6	0/6	1.5×10^7
	15×10^6	3/6	
S. bareilly	1.3×10^5	1/6	1×10^6
	7.0×10^5	2/6	
	1.7×10^6	4/6	
S. pullorum			
Strain I	1.8×10^9	0/6	$>1 \times 10^9$
	10×10^9	6/6	
Strain II	1.6×10^8	0/6	$>1 \times 10^9$
	6.7×10^9	4/5	
Strain III	1.3×10^9	0/6	$>1 \times 10^9$
	7.6×10^9	6/6	
Strain IV	1.1×10^8	0/6	$>1 \times 10^9$
	4.0×10^9	2/6	
	1.3×10^9	3/6	

known to frequent the vicinity of the stream. The disease apparently spread during the late 1930's, and for the 1940 to 1942 period thousands of cases were reported in various districts of Russia. Many outbreaks were believed to have arisen from streams and wells that were contaminated by water rats.

"Contamination of Natural Waters and Mud with Pasteurella tularensis and Tularemia in Beavers and Muskrats in the Northwestern United States" is the title of a summary report by Parker et al.[20] published by the United States Public Health Service in 1951. Among other things, the authors were concerned with "the degree to which contaminated water is a danger to man." Although much useful information is presented, the question was not resolved. One incident of tularemia was reported in a household, apparently caused by a contaminated water supply. The presence of tularemia organisms was established but not the concentration.

Data on which to judge the potential hazard from ingestion of specific numbers of tularemia organisms have recently become available in the evaluation of vaccines and immunization procedures.[21] The resistance of the gastrointestinal tract to infection by P. tularensis SCHU S4 strain is shown by the results obtained in human volunteers.

Route of Challenge	No. of Organisms
Respiratory	10 to 50
Intradermal	10 to 50
Oral	100,000,000

These numbers of organisms caused clinical infection and serological conversion.

Tolerance to the large oral dose apparently is not due to a rapid die-off of P. tularensis in the stomach. This organism does survive the acidity of the stomach, as shown by the ease of isolation from the gastric washings of patients with the typhoidal-pneumonic forms of illness.

V. BACTERIAL INTOXICATIONS

A. BOTULISM

Botulism is a highly fatal afebrile bacterial intoxication (not an infection) characterized by weakness, dizziness, headache, and constipation, followed soon by paralysis. About two of three patients die of respiratory or cardiac failure within 3 to 7 days. The disease occurs sporadically in all countries and always in relation to some perishable food product so

prepared or preserved as to permit toxin formation. Six types of toxin are recognized, but most human cases are caused by type A or type B, with a few due to type E. Soil and the intestinal tract of animals and fish are the reservoirs of Clostridium botulinum, which produces the toxin. Home-canned vegetables inadequately sterilized lead the list of known causes of botulism outbreaks in the United States. A manual containing a tabular summary of outbreaks in the United States from 1899 through 1967 and procedural information for the epidemiologist, clinician, and laboratory worker is available from the U.S. Public Health Service.[22]

Morton[23] summarized information available in the open literature on the toxicity of type A toxin for various species of animals, including man. He examined 10 reports of 18 cases of botulinus poisoning caused by eating contaminated food. Four of the 18 persons exposed received antitoxin and three survived; the other 15 cases were fatal. From the reported estimates of the amounts of type A toxin consumed, Morton concluded that the oral MLD* for man may be assumed to be about 7,000 mouse IPMLD.** He also estimated the LD_{50}*** to be about 80% of the MLD. On the assumption that 50% pure type A toxin contains 15×10^9 mouse $IPLD_{50}$ per gram, the LD_{50} dose would be 0.37 μg.

B. PARALYTIC SHELLFISH POISONING

This disease is caused by the ingestion of toxic shellfish. The symptoms begin with numbness in the lips and fingertips, followed by progressive paralysis and death from respiratory failure in 2 to 12 hours, depending on the dose. If a person survives for 24 hours, the prognosis is good. Those who survive usually show no lasting effects from the ordeal.

The original source of the poison in shellfish is in certain species of unicellular marine organisms of which the dinoflagellate Gonyaulax catenella is perhaps the best known. The organism is free-swimming, multiplies by the formation of dark orange or greenish-brown chains, and lives like a true plant cell by photosynthesis. The principal types of shellfish that reach dangerous levels of toxicity and may be consumed by man are mussels and clams. The poison accumulates mainly in the digestive gland of mussels and clams and in the siphons of butter clams, but is apparently harmless to the shellfish. If a large number of Gonyaulax is present in the water, toxicity of the shellfish may rise to dangerous levels in a few days. In the absence of the organism, the stored poison is slowly eliminated.

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* Minimum lethal dose.
** Intraperitoneal minimum lethal doses.
*** The amount that causes death in 50% of an exposed population.

Practical procedures have been developed for isolating paralytic shellfish poison in pure form.[24] Its toxicity is about 5,500 mouse units per milligram.

The human lethal dose of shellfish poison has been estimated from epidemiological investigations. In a review article by McFarran et al.[25] the findings and conclusions of several investigators were summarized as follows:

1) Some people have a natural tolerance to the poison. Some people in shore communities who consume shellfish more or less regularly may acquire a tolerance to doses of poison that would produce severe symptoms in susceptible persons.

2) Tennent, Naubert, and Corbeil[26] reported an outbreak involving seven persons. In tabular form the calculated doses and observed responses were:

Dose		No. Deaths/	No. Severely Ill/
Mouse Units	Pure Toxin, mg	No. Exposed	No. Exposed
5,800	1.05	1/1	1/1
2,400	0.44	1/2	2/2
650 to 1,000	0.12 to 0.18	0/4	4/4

3) Bond and Medcof[27] furnished additional information on the quantity of poison that would cause intoxication, based on an epidemic of shellfish poisoning involving 33 persons:

a) A 2-year-old child was seriously ill from ingesting only 600 mouse units, or about 0.11 mg.

b) Two adults experienced mild symptoms from doses of only 1,900 mouse units (0.35 mg) and 2,150 mouse units (0.39 mg), respectively.

c) The most severe case resulted from eating clams containing 5,500 mouse units, or 1.0 mg of pure poison.

The above findings suggest that an oral human dose of 0.5 to 1.0 mg of pure toxin would be lethal for 50% of the exposed population.

C. STAPHYLOCOCCAL FOOD POISONING

This is an intoxication of abrupt and sometimes violent onset with severe nausea, cramps, vomiting, severe diarrhea, and prostration. This type of food poisoning is widespread and relatively frequest. The toxic agent is an enterotoxin produced by staphylococci. The reservoir and

source of poisoning in most instances are staphylococci of human origin. Transmission may occur in a variety of food products. The enterotoxins that cause illness are simple proteins and are classified enterotoxin A, enterotoxin B, etc., on the basis of their reactions with specific antibodies. Type A is most frequently identified with food poisoning. The estimates published on oral dose in man are speculative in that human volunteer studies have not been performed. Data gathered in natural outbreaks are helpful, but the interpretation is complicated by a number of factors. People who consumed the same contaminated food displayed various degrees of tolerance. Other factors that must be evaluated in drawing conclusions are previous experience of individuals and differences in potency of toxin produced by various strains of staphylococci.

The rationale by Bergdoll[28] suggests that the minimum emetic dose for man is 0.015 μg per kg for an average individual, or 1.13 μg for a person weighing 75 kg. He summed up the situation as follows:

"There is no absolute proof of the minimum amount of the enterotoxin required to make a sensitive individual ill. Some evidence is available to indicate that the amount required may be less than one μg of enterotoxin A, which is the enterotoxin most apt to be involved in food poisoning outbreaks. This amounts to about 0.015 μg per kg for the average individual, which is about one-hundredth as much as is required to make a monkey vomit (about 2 μg per kg). Relating this to food it means that a sensitive person might get sick from drinking a pint of milk which contained as little as one μg of enterotoxin or 0.0022 μg per ml of milk. To make a monkey sick would require 2500 ml for a 2.5 kg animal."

Angelotti[29] estimated human susceptibility from data on concentration of toxin in contaminated foods, as determined by gel diffusion methods. Investigators added enterotoxins A and B to food, then extracted and concentrated the antigen. The minimum that could be detected by gel diffusion techniques was 0.02 to 0.05 μg/g of food. Using the same methods, they detected one or both enterotoxins in foods involved in natural outbreaks. If the minimally detectable concentrations of toxin were present in these foods and 100 g of the contaminated food was consumed, the dose necessary to cause illness might be estimated at 1 to 5 μg. Angelotti compared this estimate with data obtained by Casman and Bennett.[30] They reported 50 to 200 million staphylococci per gram in foods responsible for food-poisoning incidents. Using the slide gel-diffusion test they also reported finding 2 to 4 μg of enterotoxin per milliliter of brain heart infusion broth containing 15 to 20 billion organisms. If one assumes a direct correlation and disregards differences between media, the calculated concentration of enterotoxin in the food is 0.01 to 0.04 μg/g. Again assuming that 100 g of food are consumed, the calculated dose is 1 to 4 μg.

Raj and Bergdoll[31] reported that 20 to 25 μg of pure enterotoxin B can produce clinical manifestations of enterotoxemia in man. This estimate was based on the response of three young adult volunteers who consumed 50 μg of 50% pure enterotoxin B. A 120-lb. female became ill during the 3rd hour from zero time. A 135-lb. male became ill during the 4th hour from zero time. A 145-lb. male became ill during the 6th hour from zero time. His illness was the most severe because he accidentally consumed 850 μg of the toxin preparation 3 hours after zero time.

Obviously additional studies in man are needed to permit firm estimates of the oral dose.

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LITERATURE CITED

1. Gordon, John E. (ed.) 1965. Control of communicable diseases in man. 10th Ed. American Public Health Ass., Inc., New York, N.Y.

2. Plotkin, S.A.; Katz, M. 1967. Minimal infective doses of viruses for man by the oral route, p. 151-166. In Gerald Berg (ed.) Transmission of viruses by the water route. Interscience Publishers, Inc., New York, N.Y.

3. Shaughnessy, H.J.; Olsson, R.C.; Bass, K.; Friewer, F.; Levinson, S.O. 1946. Experimental human bacillary dysentery: Polyvalent dysentery vaccine in its prevention. J. Amer. Med. Ass. 132(7):362-368.

4. Spink, Wesley W. 1956. The pathogenesis of brucellosis, Chapter 6. In The nature of brucellosis. The University of Minnesota Press, Minneapolis, Minnesota.

5. Harris, Harold J. 1950. Brucellosis (undulant fever), p. 54. 2nd Ed. Harper and Bros., New York, N.Y.

6. Huddleson, I. Forest. 1943. Brucellosis in man and animals, p. 43. Rev. Ed. The Commonwealth Fund, New York, N.Y.

7. Pesigan, T.P. January 1965. Studies on the viability of El Tor vibrios in contaminated foodstuffs, fomites, and water, p. 317-321. Proceedings of the Cholera Research Symposium.

8. Flynn, Michael. January 1965. Needs for research upon the role of water in the transmission of cholera, p. 314-316. Proceedings of the Cholera Research Symposium.

9. Morbidity and mortality weekly report. 1968. National Communicable Disease Center, USDHEW, 17, No. 21, May 25, 1968.

10. Morbidity and mortality weekly report. 1968. National Communicable Disease Center, USDHEW, 17, No. 44, November 2, 1968.

11. Commission on Acute Respiratory Diseases, Fort Bragg, North Carolina. 1945. A study of a food-borne epidemic of tonsillitis and pharyngitis due to β-hemolytic Streptococcus, type 5. Bull. Johns Hopkins Hosp. 77:143-210.

12. Commission on Epidemiological Survey. Annual Report to the Armed Forces Epidemiological Board. Fiscal Year 1965.

13. Commission on Epidemiological Survey. Annual Report to the Armed Forces Epidemiological Board. Fiscal Year 1966.

14. McCullough, Norman B.; Eisele, C. Wesley. 1951. Experimental human salmonellosis: I. Pathogenicity of strains of Salmonella meleagridis and Salmonella anatum obtained from spray-dried whole egg. J. Infect. Dis. 88:278-289.

15. McCullough, Norman B.; Eisele, C. Wesley. 1951. Experimental human salmonellosis: III. Pathogenicity of strains of Salmonella newport, Salmonella derby and Salmonella bareilly obtained from spray-dried whole egg. J. Infect. Dis. 89:209-213.

16. McCullough, Norman B.; Eisele, C. Wesley. 1951. Experimental human salmonellosis: IV. Pathogenicity of strains of Salmonella pullorum obtained from spray-dried whole eggs. J. Infect. Dis. 89:259-265.

17. Long, D.J.; Lawrence, J.K.; Martin, A.R.; Schroeder, S.A.; Thomson, L.A. 1967. Carmine as a source of nosocomial salmonellosis. New England J. Med. 276:829-832.

18. Jellison, William L.; Owen, Cora R.; Bell, J. Frederick; Kohls, Glen M. 1960. Tularemia and animal populations: Ecology and epizootiology. Presented as Annual Mid-West Wildlife Conference, Toronto, Canada. December 6, 1960.

19. Karpoff, S.P.; Antonoff, N.I. 1936. The spread of tularemia through water as a new factor in its epidemiology. J. Bacteriol. 32:243-258.

20. Parker, R.R.; Steinhaus, Edward A.; Kohls, Glen M.; Jellison, William L. 1951. Contamination of natural waters and mud with Pasteurella tularensis and tularemia in beavers and muskrats in the Northwestern United States, (Bulletin No. 193). National Institutes of Health, Washington, D.C. 61 p.

21. Hornick, R.B.; Dawkins, A.T.; Eigelsbach, H.T.; Tulis, J.J. 1966. Oral tularemia vaccine in man, p. 11-14. In Robert A. Day (ed.) Antimicrobial agents and chemotherapy. American Society for Microbiology.

22. Botulism in the United States. Review of cases, 1899-1967 and handbook for epidemiologists, clinicians, and laboratory workers. Public Health Service, U.S. Department of Health, Education, and Welfare.

23. Morton, Harry E. 1961. The toxicity of Clostridium botulinum type A toxin for various species of animals including man, (Contract DA-18-064-CML-2757, October 1961). The Institute of Cooperative Research, University of Pennsylvania, Philadelphia, Pennsylvania.

24. Schantz, Edward J. 1960. Biochemical studies of paralytic shellfish poisons. Ann. N.Y. Acad. Sci. 90(3):845-855.

25. McFarren, E.F.; Schafer, M.L.; Campbell, J.E.; Lewis, K.H.; Jensen, E.T.; Schantz, E.J. 1960. Public health significance of paralytic shellfish poison. Advances in Food Research 10:135-179.

26. Tennent, A.D.; Naubert, J.; Corbeil, H.E. 1955. An outbreak of paralytic shellfish poison. Can. Med. Ass. J. 72:436-439.

27. Bond, R.M.; Medcof, J.C. 1958. Epidemic shellfish poisoning in New Brunswick. Can. Med. Ass. J. 79:19-24.

28. Bergdoll, Merlin S. 1968. Bacterial toxins in foods. Presented: Institute Food Technologists, May 1968, Philadelphia. Pa. Reproduced in FRI News, No. 4, Nov. 15, 1968, Food Research Institute, University of Wisconsin, Madison.

29. Angelotti, Robert. 1969. Staphylococcal enterotoxin, Chapter IX. In Hans Rieman (ed.) Food-borne infections and intoxications. Academic Press, New York, N.Y.

30. Casman, E.P.; Bennett, R.W. 1965. Detection of staphylococcal enterotoxin in food. Appl. Microbiol. 13:181-189.

31. Raj, H.D.; Bergdoll, M.S. 1969. Effect of enterotoxin B on human volunteers. J. Bacteriol. 98:833-834.

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The available data on human oral dose for 10 illnesses commonly implicated in food- and waterborne outbreaks are assembled and discussed. Seven of the illnesses are bacterial infections; the other three are bacterial intoxications.

14. Key Words

Foodborne illness
Waterborne illness
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