Specialty Conference

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Plague in San Diego

JAMES D. CONNOR, MD:* *Bubonic plague occurs most frequently in children and adolescents. In some areas of California and the Southwest, insect vectors and wild rodents together provide endemic foci for plague, from which there is occasional distribution to persons traveling to those areas. The clinical syndrome of bubonic plague fits very well within a group of syndromes of febrile origin in pediatrics; therefore, the usual clinical presentation of plague is difficult to recognize unless the index of clinical suspicion is high. The clinical syndrome and the bacterial infection are treatable by readily available means. Diagnostic laboratory procedures are available in San Diego county; the diagnosis is easily made once the necessity of making a diagnosis is recognized. The bacterial infection and clinical syndrome yield to treatment quickly with a low mortality; if the infection is not recognized, the mortality is very high and the syndrome time is very short. For these reasons we felt that we as pediatricians should become acquainted with plague.*[1-3] *The recent plague death in the county is the only recorded case of the plague in San Diego. This conference discusses the various aspects of plague in children: pathogenesis, pathology, clinical diagnosis, bacteriologic diagnosis and treatment. Doctor Daley will present the case for us.*

SANDRA DALEY, MD:† The patient is a white girl, aged 3 years and 9 months, who was in good health until five days before admission to hospital. While on vacation with her family at Lake Tahoe, she became ill, with fever, delirium and vomiting. Her parents administered aspirin, but the child was unable to keep any medicine down. The fever persisted; at the height of fever, brief jerky and kicking movements, which lasted a few seconds, were noted. She was lucid, and her parents did not notice any rolling back of the eyes. Because of her illness, the family returned to San Diego. On the evening of their return, she was seen in the emergency room of a local hospital, where it was noted that she had a temperature of 38.9°C (102°F), a heart murmur and tonsillitis. Penicillin was prescribed at 125 mg four times a day and an aspirin suppository was given, which promptly reduced her fever. The following day, although she ate poorly and

*Professor of Pediatrics.

Dr Thomas Quan of the Center for Disease Control Plague Laboratory in Fort Collins, Colorado, shared slides that allowed us to compose tables of biochemical reactions. He also supplied slides showing phage test results and fluorescent antibody stain reaction, along with specific conjugate and phage test strips that made identification of the isolate possible.

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vomited a dose of aspirin, her parents felt she was somewhat improved. Two days before admission to hospital she was notably improved and was able to sit at the table with the family and eat. She remained febrile throughout this time, however. One day before admission to hospital she appeared worse to the family. She complained of generalized pain as well as pain in her left elbow. She was taken to the emergency room of a second local hospital where an analysis of urine was ordered but no urine was obtained. A blood test was interpreted as suggestive of infection. An x-ray study of the left elbow was said to show no abnormalities and the parents were instructed to continue with the administration of penicillin. The morning of admission she awoke again with fever; in the left axilla was noted a lump that was not erythematous and was nontender. She was taken to see her private physician, who noted the left axillary mass, the fever and a significant left shift of the complete blood count done in the emergency room the night before. He then referred the child to Childrens Hospital for admission.

Her past history was remarkable for Hemophilus influenzae B cellulitis at the age of 9 months. Growth and development had been normal and she lacked immunization boosters for diphtheria-pertussis-tetanus immunization and oral polio-vaccine. Review of systems revealed she had not been around any ill children. She had received no recent injuries and had ingested nothing unusual. She had been constipated for several days but had had a normal bowel movement early in the day of admission.

Physical examination revealed a well-developed girl, with a heart rate of 140 per minute, shallow respiration at a rate of 70 per minute, blood pressure of 120/80 mm of mercury and temperature of 39.3°C (102.7°F). Her skin appeared to be somewhat dry and mottled. There were no rashes, petechiae or purpura noted. Results of ear, nose and throat examination were essentially normal. The chest was clear to auscultation. The liver was palpated approximately 4 cm below the right costal margin and was smooth and nontender. A spleen tip was barely palpable. A 3-cm left axillary mass was nontender and nonerythematous and was not warm to touch. Neurologic examination showed an alert, awake and active child who was otherwise normal.

Approximately 30 minutes after admission to hospital, she experienced increasing tachypnea. Re-examination at that time revealed no other differences from results of the initial examination. She had a second normal bowel movement at that time.

An hour after admission, her skin appeared to be somewhat more mottled than previously, but she remained alert with appropriate behavior while an intravenous infusion was being started. Because of the difficulty in starting the intravenous infusion and concern about increased mottling with continued tachypnea, she was transferred to the intensive care unit for closer monitoring and placement of a cutdown. Immediately after transfer she vomited, suffered a generalized tonic-clonic seizure with stiffening of all extremities and arching of the neck, became cyanotic and had a cardiopulmonary arrest. She was promptly intubated and resuscitated. A cutdown was placed in the right saphenous vein. She was given 100 percent oxygen and was given bicarbonate, epinephrine, calcium and isoproterenol hydrochloride (Isuprel®). In spite of vigorous cardiac pulmonary resuscitation, the patient did not respond; she was pronounced dead after an hour and 20 minutes. Subsequent laboratory data on the day of admission revealed a leukocyte count of 41,000 per cu mm, hemoglobin of 11 grams per dl and Gram-negative rods were reported seen on the peripheral smear with Wright stain.

DR. CONNOR: What I would like to do in a few minutes is to point out the pathogenesis of plague starting with the biting flea. I would like to also point out the milestones that we can identify as being important in the cycle of pathogenesis and in some way relate to that cycle the clinical events that might be recognizable and helpful in the development of a diagnostic suspicion that would allow case diagnosis.

Figure 1 is the kind of scheme I have used to acquaint myself with pathogenesis of plague. At the top of the figure is shown an event that is generally uncommon in pathogenesis of disease; that is, an injection of nonvirulent bacteria progressing to generalized fatal infection through mechanism and factors contributed by the infected host.[4] Most of the 1,000 to 12,000 bacteria that are injected during the regurgitant feeding of the vector flea are killed at the site by phagocytosing neutrophilic leukocytes. There is usually no inflammation at the bite site; sometimes a minute abscess develops but that is in-

frequent. However, despite phagocytosis by the host of most of the infected bacilli, an essential step in the survival and ultimate progression of the infection also occurs at the site or within inguinal lymph nodes; that is, engulfment by monocytes but survival of intracellular bacilli allowing replication in the host at a higher temperature. Therefore, during the incubation period of three to seven days, there is initial replication within the host's monocytes at a temperature that provides increasing virulence. The differential between flea temperature of 28°C and temperature of 37°C (82.4°F and 98.6°F) in the host provides for a change—not a mutation—in the bacterium from avirulent to virulent form. During that time, plague bacilli become highly encapsulated and acquire factors known as virulence factors V and W. The incubation period thus is the first and essential phase in pathogenesis of plague.

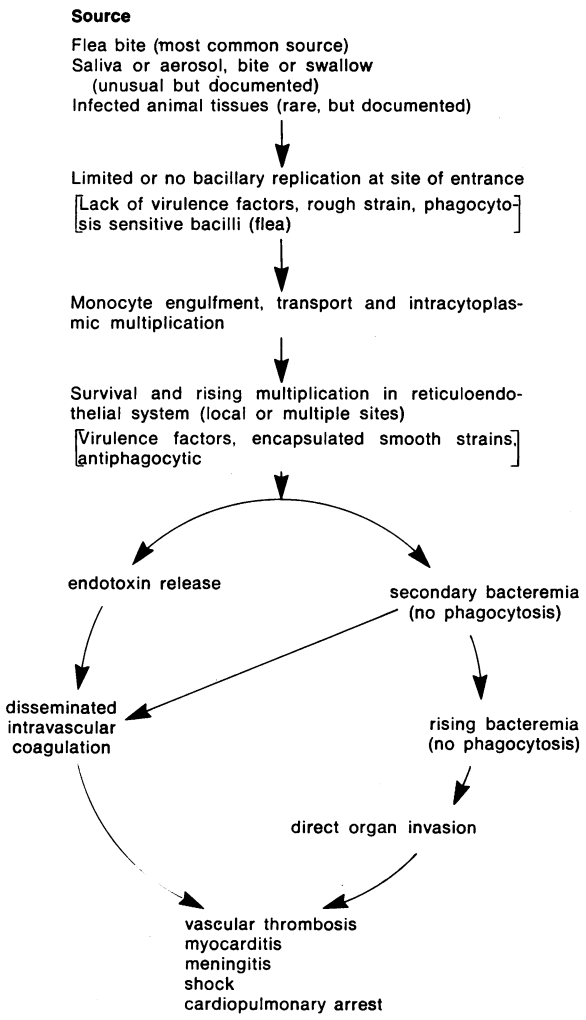

Figure 1.—Pathogenesis of plague.

TABLE 1.—*Differential Diagnosis of Bubonic Plague*

Lymphadenitis, acute
streptococcal
staphylococcal
granuloma inguinale
lymphopathia venereum
Pasteurella tularensis
cat-scratch disease
Pasteurella multocida
mycobacteriosis (atypical, fast grower)
Pharyngeal diphtheria
Acute parotitis
Peritonsillar abscess
Appendicitis
Hip-joint pyogenic arthritis
Mesenteric lymphadenitis

During the second phase, rapid bacterial replication occurs within one or more lymph nodes, provided for by the antiphagocytic nature of the virulence factors. Encapsulated plague bacteria, replicating at animal body temperature, are highly resistant to phagocytosis and killing. Therefore, the progression of the infection within the regional lymph node is relatively rapid and virulent, leading to development of local inflammatory signs and concomitant systemic complaints, usually at the same time.

In 95 percent of all cases of plague, patients present with one enlarged node, a regional lymph node draining the bite site.[3] Enlarged nodes may be found at different locations throughout the body, most commonly in lower extremities where they are more frequently femoral and inguinal nodes, less commonly in upper extremities where they are more frequently axillary and less frequently epitrochlear. Nodes appear less commonly in the neck and are least frequent in the anterior cervical region. The lesson is that almost any area of regional adenopathy may present, including deep glands such as the iliac or deep cervical, making the immediate diagnosis sometimes very complicated.

Due to the rapidly expanding node infection, pain at the site and in the area of involvement may be most severe; the pain may be so great at the site or within the quadrant of involvement that the lymph gland involved may be overlooked or thought not to be the cause of pain. I think such findings should increase the index of suspicion more than the similar ones that occur in a broad, recognized etiologic spectrum of lymphadenitis (Table 1). The infected lymph gland

that is involved may be the site of so much pain that the entire joint or quadrant may be immobilized from the day of onset. The pain of the lymph gland, upon examination, is usually exquisite particularly in the early phase, regardless of size. As the gland expands and finally suppurates, the pain may be less. This is easily confused with pyogenic arthritis, deep inguinal adenitis of streptococcal origin and similar syndromes in deep nodes. Frequently in bubonic plague no involvement of soft tissue is recognized; later involvement of soft tissue is usually characterized by inflammatory edema with or without erythema. These findings, exquisite pain and tenderness with immobilization of the quadrant or an extremity would point toward adenitis of plague infection as well as toward other kinds of frequent diagnoses we make in pediatric patients.

To return to continuing pathogenesis: A systemic reaction is also occurring at the time, depending upon production by replicating bacteria of typical Gram-negative bacterial endotoxin or an exotoxin peculiar to the plague bacillus, as yet poorly characterized. The progress of this stage is rapid due to the fact that phagocytosis does not work in either monocytic cells or neutrophilic cells. Therefore, rapid replication continues; bloodstream invasion occurs secondarily, and bacterial replication occurs there also. This stage is accompanied by a feeling of intense illness in the patient. Right from the first day of illness the patient may have high fever, a sense of prostration, a feeling of impending doom, lethargy, chilly feelings or overt chills, and may be septic out of proportion to what you may find on physical examination at that time.

If untreated, the last stage of this progressive syndrome goes on to be marked bacteremia. Some findings out of the Vietnam experience of the 1960s reported by Butler[5] point out rising bacteremia with maximum bloodstream infection with 10^2 to 10^6 bacteria per ml of blood. Shock and death are common consequences of that condition as contrasted to nonbacteremic bubonic plague, in which mortality is much lower.

At this stage, San Diego's patient had a marked bacteremia, and bacteria were noted in a peripheral smear of her blood (Figure 2). In such a smear polymorphonuclear cells are characteristically found in large numbers without any evidence of phagocytosis. The plague bacillus also induces an anti-opsonin factor in blood and progressively arranges for itself "free" replication within tissues, organs and blood. In lethal infections, the end comes as a direct result of massive bacterial invasion in blood and tissue; relative to that, plague endotoxin activity is probably of lesser relative importance.[6] Vascular thrombosis, myocarditis and meningitis all occur, as well as shock and cardiopulmonary arrest, as developed in the patient we are discussing. The rapidity of the lethal infection is brought out by this case. Physicians have precious little time to act; a period of only three to five days to mount an appropriate diagnostic and therapeutic response is not unusual.

Differential diagnosis of bubonic plague includes a number of childhood infections (Table 1). Some characteristics of these infections do match up with plague diagnosis, some obviously do not. I offer the list only to indicate that this is the kind of pediatric infectious disease spectrum we might think about and to stress that plague should be included in it, in San Diego, regardless of the fact that we have only seen one case and that in 1977. We need to develop an index of suspicion and appropriate screening for plague along with other conditions in the differential diagnosis of cellulitis and lymphadenitis.

Unlike most hard, tender, nonfluctuant lymph glands, the plague-infected gland should be needled to make an immediate diagnosis; the diagnosis can be established by providing the laboratory with appropriate specimens. Needle aspiration of the nonfluctuant node or excision should probably be done under antibiotic therapy to prevent bacteremia as a result of manipulation. It should be done immediately upon developing

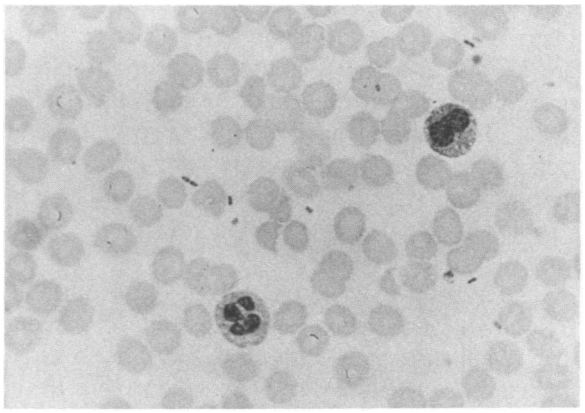

Figure 2.—Peripheral blood smear illustrating massive bacteremia.

TABLE 2.—*Epidemiological Circumstances Favoring Diagnosis of Plague*

Nonurban residence (particularly southwestern part of United States)
Domestic cats or dogs known to have wild animal contact
Sick animal contact, recently
Recent camping or sleeping on the ground
Known flea bites
Known plague area, visit or residence
Plague in the family or community, recently

a clinical index of suspicion. The node should be entered with a needle and a saline wash of the gland should be sent to the diagnostic laboratory for stain and culture. If removed surgically, the node should be used also to make imprints on a slide to search for plague bacteria. This situation is unusual to pediatricians and surgeons alike in that we usually do not aspirate small, tender, hard nodes but wait for fluctuation. However, it is not appropriate to wait for staging or fluctuation in plague. When node fluctuation is present, pus can be taken for an immediate diagnosis. If the lymph gland involved is deep, a physician may not be suspicious of plague; clinical suspicion is usually based upon characteristic physical findings. In some cases published in the radiological literature, deep lymph nodes involved by bubonic plague were visualized on radioscan.[7,8]

When the clinical index of suspicion has been reached, epidemiological factors may obligate prompt consideration of plague in the differential (Table 2). Such factors are important in developing an appropriate differential diagnosis. Considering experience in California and the southwestern United States, there should have been some recent contact by the family group of the patient with the outdoors or with animals that are in contact with the outdoors or with wild animals, or travel to an area of endemic animal plague where insect vector and the rodent host are known to come together in order for plague to be considered strongly in the differential diagnosis. However, recent reports also tell about sick domestic cats transmitting plague to owners and children. Doctor Ginsberg will talk more about such epidemiological factors in the latter part of this conference.

The mortality of bubonic plague, appropriately treated with antibotics, is low, less than 5 percent. The diagnosis can be established in time to arrive at that satisfactory result. The syndrome and the bacterial infection respond dramatically to antibiotics. Pharyngeal plague, a subset of bubonic plague that occurs in adults, is a mild condition also called pestis minor and is the only non-life-threatening variety of this disease recognized. Primary septicemic plague comes from already virulent sources of plague infection, such as an infected animal host—from the lick of a dog or from a cat with adenitis in which the infecting bacteria already have achieved encapsulation and virulence. No symptomatic node infection develops. The patient is very soon drastically ill with septicemia and bacteremia and dies in three or four days. Pneumonic plague is a similar kind of syndrome in which human-to-human transmission brings about devastating, rapidly fatal disease. A California veterinarian died recently of this form of disease acquired from an infected dog—not a person—transmitted during postmortem examination of the animal carcass.

Streptomycin probably is the drug of choice even yet—with 20 to 50 mg per kg of body weight per day by intramuscular injection yielding a low mortality in bubonic plague. With streptomycin, there is some controversy about the problem of Jarisch-Herxheimer reaction, but this probably is not clinically important. It may be important to add a systemic antibiotic by the intravenous route since meningitis has been reported to have developed in patients receiving streptomycin intramuscularly. Although tetracycline is a very good drug, it is difficult to give intravenously; moreover, among other disadvantages, it is painful, stains teeth, and is stored in bone. Chloramphenicol by the intravenous route is probably the drug of second choice as it rapidly controls bacteremia and prevents the late occurrence of meningitis. It is important to use two drugs in bubonic plague and these are the drugs of choice.

ROGER A. WILLIAMS, MD:* Doctor Connor has discussed the pathogenesis of plague, and I think you will see that this particular case demonstrates well the pathogenic mechanisms that result in fatal bubonic plague.

The presence of large numbers of plague bacilli seen in the peripheral blood smear (Figure 2) illustrates the massive, uninhibited multiplication of these bacteria after they have been activated and have become resistant to phagocytosis by the phagocytic cells of the host.

In the axillary bubo, other pathogenic features of the plague bacilli can be seen in the extensive

*Chief, Pediatric Pathology, Childrens Hospital and Health Center.

hemorrhagic tissue necrosis caused by large numbers of bacilli (Figure 3). On high-power examination of the lymph node we can see tremendous numbers of bacilli forming sheets of organisms which replace the previously existing lymph node architecture, notably without much of a suppurative reaction (Figure 4).

Similar hemorrhagic and necrotizing changes were noted in the heart, involving myocardium, endocardium and epicardium, again with large numbers of organisms present in the necrotic foci. As before, no significant suppuration was noted. These foci of hemorrhage can be seen grossly as petechial hemorrhages or small ecchymoses.

In the lungs, similar areas of hemorrhage and necrosis with multiplication of organisms were noted, most prominently in a perivascular distribution related to large and medium-sized pulmonary arteries and veins. In addition, the lungs demonstrated another mechanism of pathogenesis of plague, that of disseminated intravascular coagulation. In many of the small pulmonary blood vessels are thrombi in which moderate to large numbers of plague bacilli are enmeshed (Figure 5).

Microthrombi related to disseminated intravascular coagulation were widespread in a variety of other organs including the liver, spleen and kidneys. On gross examination, the spleen and liver were found to be enlarged; microscopic examination of these organs showed clusters of organisms in the sinusoids. The kidneys were severely affected, with a number of petechial hemorrhages over the surface and widespread involvement of glomerular capillaries and renal arterioles with microthrombi incorporating variable numbers of bacteria (Figure 6).

In summary, the pathogenic mechanisms of plague are well demonstrated in the pathologic anatomy of this patient, manifested by uninhibited multiplication of large numbers of bacteria, hemorrhagic tissue necrosis and disseminated intravascular coagulation.

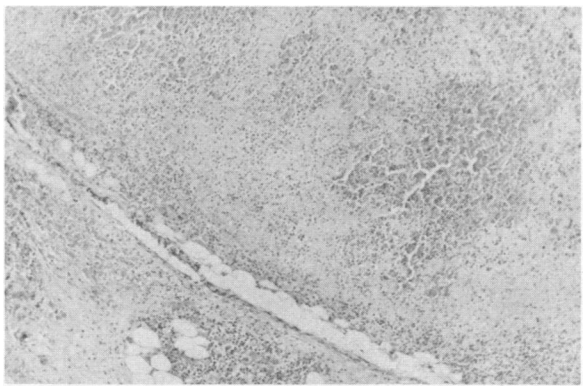

Figure 3.—Hemorrhagic tissue necrosis with massive tissue invasion by plague bacilli.

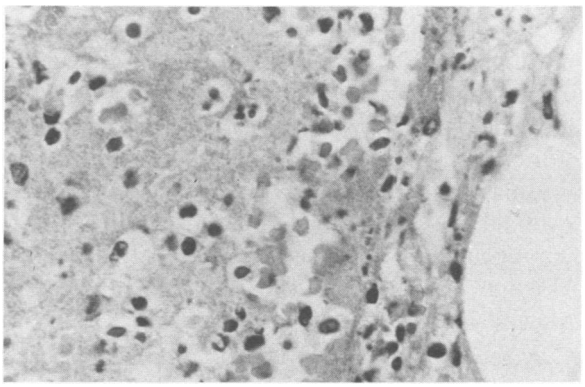

Figure 4.—Numbers of bacilli forming sheets of organisms which replace the previously existing lymph node architecture, without much suppurative reaction.

MURIEL A. THOMPSON, DR PH:† Regarding laboratory aspects of Yersinia pestis identification, the specimens that come to the laboratory for diagnosis may consist of aspirates, blood, sputum, throat swabs or autopsy material; or, as in this particular case, the isolation may come from spinal fluid. I think that the hospital microbiology laboratory is to be commended for the identification and for rapid assistance in the diagnosis of this case. I stress the need to pass along the case history with specimens submitted to the laboratory; in this case, the accompanying history prompted personnel of the hospital

†Chief, Public Health Laboratory.

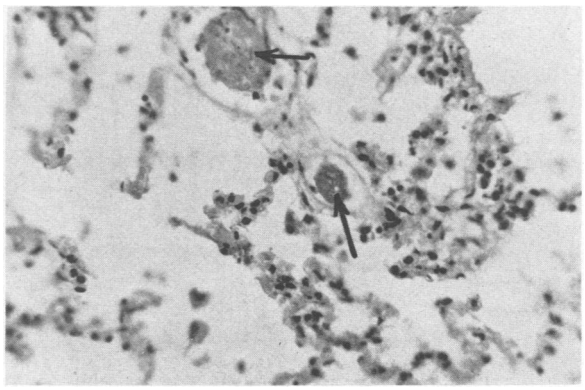

Figure 5.—Thrombi enmeshed with plague bacilli in small pulmonary vessels.

laboratory to consider plague in the differential diagnosis.

The bacteriology of plague began in 1894 in Hong Kong, with the discovery of the organism by Alexandre Yersin, who identified and classified the bacillus. The organism is a Gram-negative, aerobic, facultative-anaerobic, non-spore-forming coccobacillus, relatively large, with slightly pointed ends, a characteristic that helps to differentiate it from other bipolar-staining organisms. Wayson stain,[9] a combination of carbol-fuchsin and methylene blue, is better than Wright stain to show up the bipolar characteristic. The organism grows easily and readily on most media. The colonies at 24 hours are tiny, but at 48 hours they measure 1 to 2 mm and are quite easily recognizable. They grow well in most hospital laboratories upon a 5 percent blood agar base. The optimum temperature of growth is 28°C. However, for a number of the diagnostic tests, the organisms must be cultivated at about 30°C. Our laboratory procedures usually call for 35°C so that fraction I (the capsular or envelope, heat-labile, protein antigen of Y. pestis),[10] which is important in diagnostic tests, will be found. The organism is of the Enterobacteriaceae group and resembles Pasteurella. However, the pasteurellae are oxidase-positive and since the plague bacterium is oxidase-negative, it has been recently reclassified as a member of the Yersinia genus. Also reclassified are Y. pseudotuberculosis and Y. enterocolitica, all of which are oxidase-negative. The organisms are routinely nitrate reducers and attack carbohydrates.

Approximately 30 to 40 biochemicals may be used in the laboratory in order to come to a final bacteriologic identification (Tables 3, 4 and 5). Bacteriologists should note that, in the chart on page 224 of the *Manual of Clinical Microbiology,* second edition,[11] the salicin reaction is indicated to be positive for Y. pestis; our culture was negative, a result that coincided with reference information from Dr. Thomas Quan of the Center for Disease Control (this may be a variable reaction, according to *Bergey's Manual,* eighth edition[12]). A summary of the biochemical reactions most helpful in differentiating the three species of the genus Yersinia is shown in Table 5.

TABLE 3.—*Biochemical Reactions of Yersinia pestis After 48 Hours of Incubation at 37°C*

Biochemical	*Reaction*
Triple sugar iron agar	No change to slight A/A
Kliglers iron agar	No change to slight A/A
Nitrate reduction	+
Methyl red	+
Voges-Proskauer	−
Indol	−
Esculin hydrolysis	+
Litmus milk	No change
Gelatin hydrolysis	−
Salicin	−

A = acid

NOTE: Reactions noted were shown on 35-mm color film supplied by Thomas Quan, PhD, Plague Branch, Center for Disease Control, Fort Collins, Colorado. (This table reprinted by permission from Dr. Quan.)

In a 24-hour broth culture at room temperature, the organisms tend to adhere to the side of the tube and thus appear to be motile, although the organism is nonmotile. If such a culture is gently shaken, the growth simply settles to the bottom of the tube.

The phage lysis test is helpful in the specific identification of Y. pestis versus the other Yersinia. In the phage test, all strains of Y. pestis and also Y. pseudotuberculosis grown at 35°C will be lysed by the phage. Y. pseudotuberculosis, however, is not lysed at 20°C, whereas Y. pestis is. There is a simple procedure: Single streaks of the unidentified organism and of each control organism (for example, Y. pestis and Y. pseudotuberculosis) are made on blood agar plates. The streaks are overlaid with a filter-paper strip that has been impregnated with the specific bacteriophage (Figure 7). The organisms are then allowed to grow at both room temperature and at 37°C.

A second test that is especially useful in early diagnosis is the fluorescent antibody (FA) staining technique. In the direct FA procedure, the organisms are stained with antiserum to Y. pestis

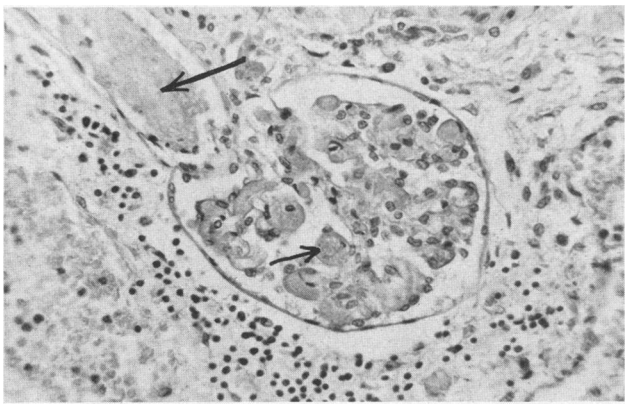

Figure 6.—Widespread involvement of glomerular capillaries and renal arterioles with microthrombi incorporating numbers of bacteria.

TABLE 4.—*Biochemical Reactions of Yersinia pestis After 24 Hours of Incubation at 37°C*

Biochemical	*Reaction*	*Biochemical*	*Reaction*
Triple sugar iron agar	No change to slight A/A	Mannitol	+
Kligers iron agar	No change to slight A/A	Mannose	+
Oxidase	−	Arabinose	−(V)
Catalase	+	Fructose	+
Phenylalanine deamination	−	Galactose	+
Glucose	A, no gas	Melibiose	weak+
Glucose fermentative (OF)	A	Raffinose	−
Glucose oxidative (OF)	A	Rhamnose	−
Urea	−	L-sorbose	−
Citrate	−	Trehalose	+ (V, usually +)
Arginine dihydrolase	−	Xylose	+
Lysine decarboxylase	−	Adonitol	−
Ornithine decarboxylase	−	Dulcitol	−
Lactose	−	Inositol	−
Sucrose	−	Sorbitol	+

A = acid
V = variable

NOTE: Reactions noted were shown on 35-mm color film supplied by Thomas Quan, PhD, Plague Branch, CDC, Fort Collins, Colorado. (This table reprinted by permission from Dr. Quan.)

that has been conjugated with fluorescein isothiocyanate. Only Y. pestis will fluoresce if specific conjugate is used. Y. pseudotuberculosis and Y. enterocolitica used as controls should not stain. In the case under discussion, we ran into some problems. We had received antisera designated as specific for Y. pestis. We did the FA stain procedure in our laboratory on the culture forwarded to us. We observed varying levels of fluorescence with the various Yersinia species available; that is, unidentified organisms showed 4+ fluorescence, whereas the Y. enterocolitica and Y. pseudotuberculosis used as controls showed 2+ readings. Then we learned that the one reference laboratory that had furnished conjugate had used mixed Yersinia antigen in developing the diagnostic antisera. They did not absorb it, and as a result all organisms of the genus stained with the tagged antibody. The other reference laboratory, from which we were able to get conjugate within a couple of days, had a specific reagent that stained only Y. pestis. Once so standardized, the FA test is an excellent diagnostic procedure. It is currently available in our laboratory if you should have a problem identifying or excluding Y. pestis in clinical isolates.

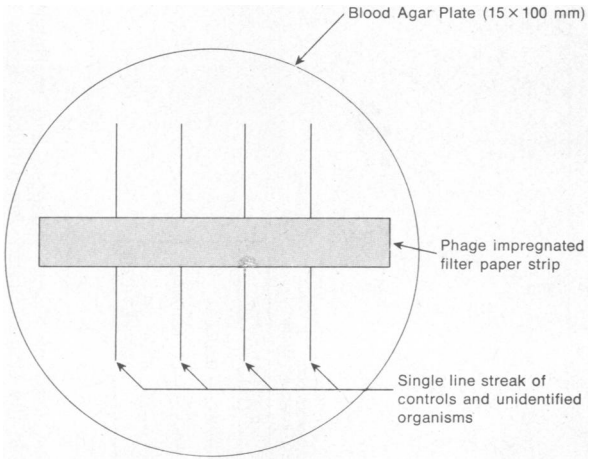

Figure 7.—Procedure for setting up phage test for Yersinia pestis. Prepare 2 identical plates. Incubate one at 20°C and one at 35-37°C.

TABLE 5.—*Key Differential Biochemical Reactions of the Genus Yersinia*

*Biochemical Reactions**	*Y. pestis*	*Y. enterocolitica*	*Y. pseudotuberculosis*
Oxidase	−	−	−
Catalase	+	+	+
Motility at 22°C	−	+	+
Motility at 37°C	−	−	−
Urease (Christensen)	−	+	+
Indol	−	+or−	−
Methyl red	+	+	+
Voges-Proskauer	−	−	−
Citrate (Simmons)	−	−	−
Lactose	−	Slow A	−
Sucrose	−(V)	A	−
Melibiose	Weak A	−	A
Sorbitol	A (V)	A	−
Salacin (48 hours)	−(V)	−(A)	A
Esculin (48 hours)	+	−	+
Adonitol	−	−	A (−)
Ornithine decarboxylase	−	+	−
Triple sugar iron agar	ALK/A	A/A	ALK/A

A = acid
ALK = alkaline
V = variable
*Cultures incubated at 35°C for 24 hours unless otherwise indicated.

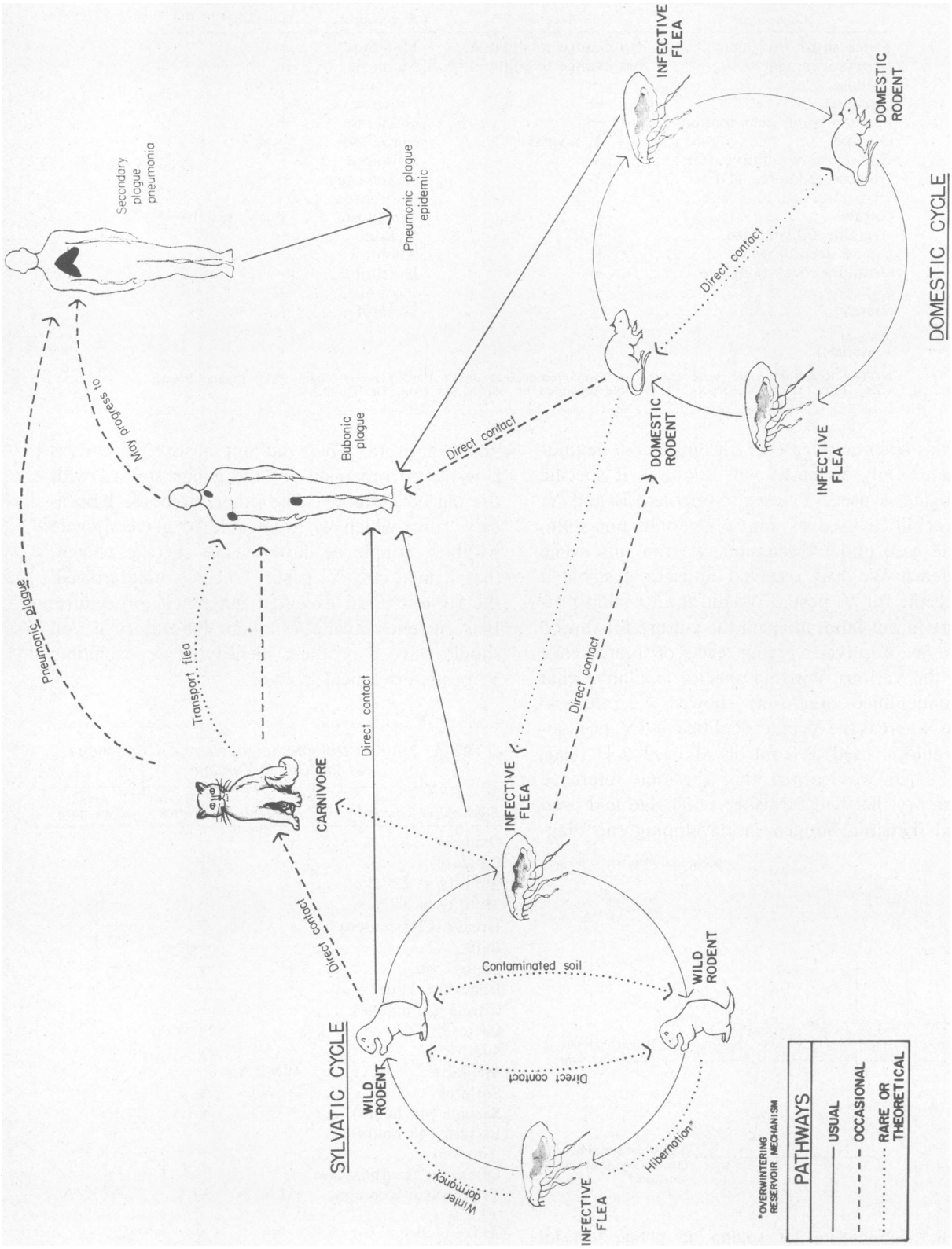

Figure 8.—Cycles of plague (adapted and reprinted with permission from Kartman L, Goldenberg MI, Hubbert WT: Recent observations in the epidemiology of plague in the United States. Am J Public Health 56:1554-1569, Sep 1966).

The passive hemagglutination procedure is also available and is an excellent test to assist in diagnosing plague. The organism with fraction I^2 present will cause the development of antibodies that will be demonstrated by this procedure; current infection is indicated if a fourfold rise is shown. Since a very low percentage of the population has the antibody, even a titer of 1:16 is presumptive of a current or recent infection with Y. pestis.

MICHELE GINSBURG, MD:* As has already been indicated, plague is an aggressive disease. It has been called black death and the great pestilence. Since the 13th century BC, it has been a decimator of human populations. It remains so today but is a relatively infrequent cause of death in developed countries.

Plague in the United States must be considered in three cycles: in the sylvatic or wild rodent population, in the domestic or urban rodent population and in the human population (Figure 8). Y. pestis, the plague bacillus, can survive in the flea-rodent cycle without involvement of humans. However, when a person is bitten by an infected flea, bubonic plague develops initially. If the person does not receive prompt, specific attention, sepsis occurs and secondary plague infection of the lung may follow. Once lung infection develops, plague may be transmitted as an airborne disease and has the potential of infecting many people without an insect vector.

Plague first entered the United States in 1894 by means of ships from Asia that docked at the port cities of San Francisco, New Orleans and New York. Infection became established in the domestic rodent population. The last outbreak of pneumonic plague in this country occurred in Los Angeles in 1924.[13] During that outbreak, of 32 patients with pneumonic plague, 30 died. Seven bubonic plague cases were identified as well.

As plague in the domestic rat population was controlled, it became established in the wild rodent population, where it has remained endemic. Since 1924, all known instances of plague in humans in the United States have resulted from contact with the wild animal population. In California alone, plague has been identified in 136 persons, of whom 71 died, a 52 percent mortality rate.[14]

Domestic (urban) plague is not a thing of the past. As recently as 1968, domestic rodents in Denver were identified as being infected with plague. Domestic rats acquired their infection through mingling with the rural rodent population

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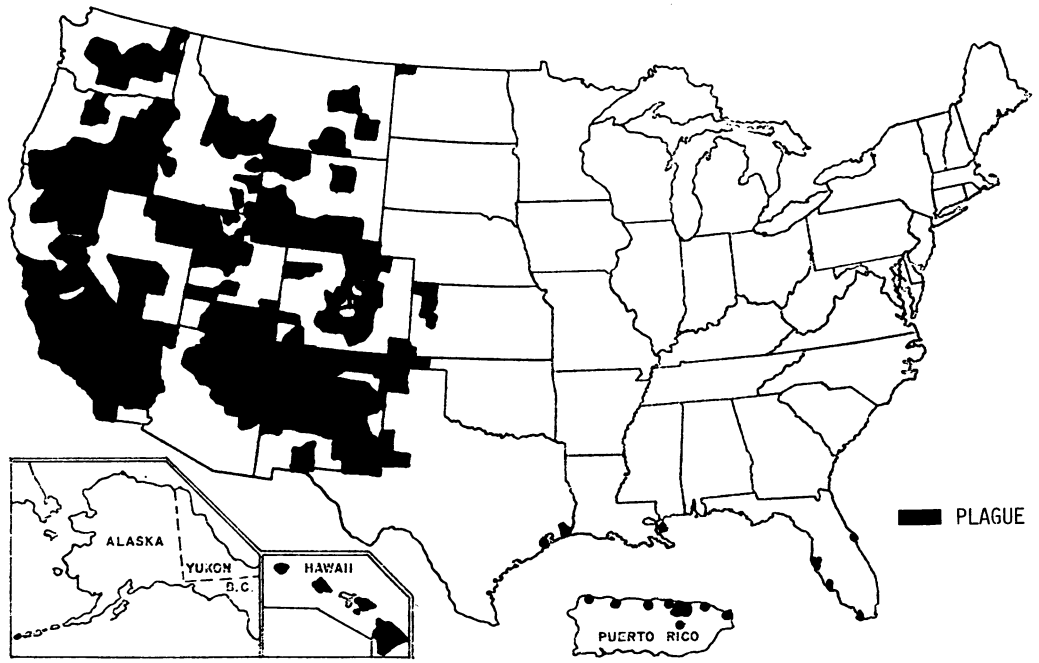

Figure 9.—Endemic areas of plague infection in animals in the United States from 1908 to 1969. (Adapted with permission from Center for Disease Control, Plague Surveillance Report No. 1, 1970.)

of that mountain city. Only through an active surveillance and rodent-control program was an outbreak of plague in humans prevented.

In order for plague to persist in wild animals, it must infect a relatively resistant animal population. Since fleas can survive the winter in animal burrows, young rodents can become infected and perpetuate the cycle of wild rodent infestation each spring. In the western United States, plague infection has been found in ground squirrels, prairie dogs, chipmunks, rabbits, mice and rats, as well as in larger carnivores, such as bobcats and coyotes.[15]

Humans become involved with plague when they enter into the sylvatic cycle. For example, a person may become infected by handling a dead squirrel or by skinning a rabbit or a bobcat. On the other hand, an infected flea may leave a dead or dying rodent and attach itself to a human for a blood meal (a contact resulting in a case of bubonic plague). When people take pets into the wild or woodland area, the pets may catch infected animals and transport fleas back to their masters. Dogs are relatively resistant to plague and after exposure may show seroconversion without evidence of clinical illness. Cats, on the other hand, are quite susceptible to plague, and

TABLE 6.—*Human Plague Cases in the United States, Incidence and Mortality, 1975-1977*

Year	Males		Females		Total Cases
	Cases	Deaths	Cases	Deaths	
1975	5	1	15	3	20
1976	8	2	8	1	16
1977	12	1	6	1	18
Total ..	25	4*	29	5*	54

*Mortality: males, 16 percent; females, 17 percent.

two of the 18 cases of plague in humans reported in 1977 by Allan M. Barnes, PhD, Chief, Plague Branch, Bureau of Laboratories, Vector-borne Diseases Division, Center for Disease Control, Fort Collins, Colorado (personal communication, November 1977) resulted from contact with infected cats.[16,17]

The endemic areas of plague infection in the United States are illustrated in Figure 9. Fifteen western states on both sides of the Rocky Mountains have been extensively involved with plague in the wild rodent population. Because plague persists in these wild rodent populations, it is possible for plague to be reintroduced into the cities as a result of animal commingling. In San Diego, plague was identified in wild rodents dur-

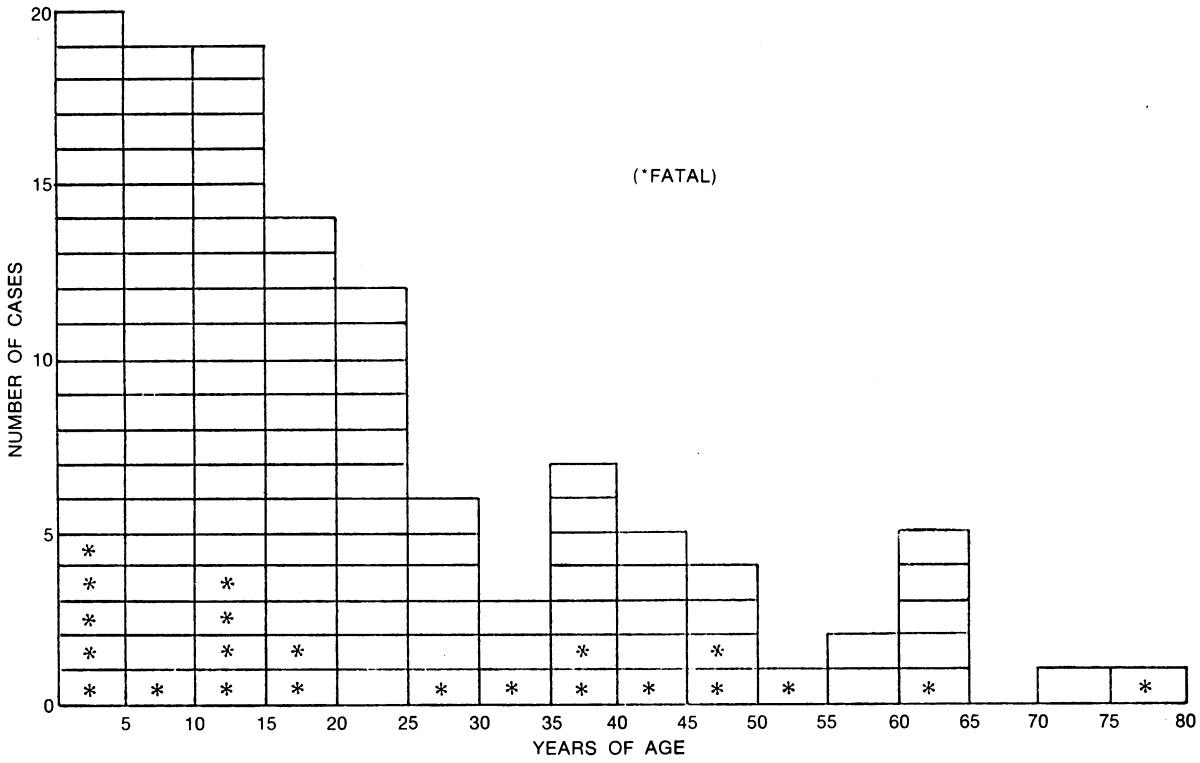

Figure 10.—Plague cases in United State from 1950 to1977.

ing the 1940s; but, as Dr. Connor indicated, no plague infection in persons has originated through animal contact in San Diego County.

Plague is actually an international disease found in countries on most continents, including Canada, Brazil, India and Russia. For example, an annual incidence as high as 6,500 cases of plague was reported in Vietnam during the 1960s. Plague may occur throughout the year; but, in this country, most infections have occurred in the period from June through September.

Figure 10 represents the 119 plague cases reported in this country from 1950 through 1977. All age groups are represented, but three fourths of the cases have involved patients under the age of 25. No age group is spared from mortality from this disease.

The sex distribution of plague cases in the United States during a recent three-year period is illustrated in Table 6. It was formerly believed that males were much more likely to be affected by the plague than females, but now that females participate more in wilderness activities, their incidence rates have approached male rates. Mortality rates have been about the same for both sexes. Of the 54 patients with plague reported during the three-year period shown in Table 6, 15 developed pneumonic involvement and with it the risk of person-to-person transmission.

It is important for clinicians to consider plague in the differential diagnosis, especially in young persons with enlarged lymph nodes and fever after camping or hunting in the western states. Once the diagnosis is considered, the physician is obligated to treat the patient with specific drug therapy, collect the appropriate specimens, such as by aspiration of a bubo, and then attempt to rule out the diagnosis using the specific fluorescent antibody test as well as culture of the specimen. The Health Department must be notified; it can assist in making the specific diagnosis of plague from the clinical material and can help in defining exposure to other contacts.

In the hospital, the patient must be placed in strict isolation until the extent of infection is established. Since Y. pestis is transmitted by droplets, airborne spread can occur between persons who have had prolonged close contact. It is noteworthy that no secondary cases have occurred in the United States since 1924, even though many patients in recent years have developed pneumonic complications. We can probably attribute this absence of secondary cases to the fact that extensive prophylaxis has been offered to contacts.

Once the diagnosis of bubonic plague is established, there is usually little risk to contacts since treatment is effective against the bacterial infection. However, strict isolation should be observed, and contacts should be placed under surveillance, which should include determination of temperature twice a day. In addition, specific therapy (tetracycline or streptomycin or both) should be initiated at the first sign of fever or other illness. If a diagnosis of pneumonic plague is established either by clinical presentation or by autopsy examination (as in the patient discussed today), chemoprophylaxis in contacts should be instituted immediately. In our case, all 48 persons who had contacts with the child during the last 24 hours of her life were located, and all were treated with tetracycline or sulfadiazine. Therapy should continue for ten days and temperature of contacts should be taken twice daily, with immediate reporting of elevation of temperature. In a child contact, tetracycline should be avoided; sulfadiazine is recommended, 75 mg per kg of body weight per day in four divided doses for a ten-day period. For adults, 250 mg of tetracycline every six hours may be administered for ten days.

Once a diagnosis is established, the source of infection must be identified. For this case, two of the three campgrounds visited by the family showed flea pools positive for Y. pestis. Both these areas were treated by exterminators to reduce the infected animal population and, it is hoped, to prevent future infection of persons.

Appropriate precautions can be taken to minimize the risk of exposure to plague. Vaccination is not recommended for campers, but patients should be advised not to handle sick or dead animals in the woods or at home. Sleeping bags should not be placed directly on the ground, and tents or sleeping bags should not be placed near entrances to animal burrows. Insect repellents can be used in the woodland areas and pets should be kept leashed and should be deflead after returning home.

A physician must be alert to the possibility of plague infection. Patients should be asked about exposure to wild animals and about camping or hunting experience in a plague endemic area

within the preceding week. The only way to defend against plague and to reduce mortality is by suspecting the problem, making an early diagnosis, and initiating treatment as soon as the diagnosis is suspected.

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Thick Nasal Antral Walls in Chinese

I HAVE A GOOD FRIEND who practices in Taiwan. He tells me that when he is doing a sinus irrigation on his countrymen, he always has a little mallet on the tray. This is to hammer the trochar through the medial wall of the sinus in very young, delicate Chinese ladies. Apparently the antral wall in the Chinese is often much thicker than in Caucasians.

—PAUL J. DONALD MD, *Davis, California*

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