Facts concerning plague epidemiology in the United States are presented, emphasizing the potential danger of outbreaks. While transmission of the infection to man from commensal rats is virtually unknown in the United States, a permanent focus of sylvatic plague exists in the western part of the country. The significance of this focus as a threat to public health is stressed.

RECENT OBSERVATIONS ON THE EPIDEMIOLOGY OF PLAGUE IN THE UNITED STATES

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A SEEMINGLY paradoxical situation exists today in the United States with respect to the status of bubonic plague. On the one hand, we recognize that plague is a serious world health problem, with cases occurring in 1965 in North and South America, in Asia, and in Africa. In that year there were at least 766 reported cases, with 95 of these being fatal.[1] Past and present experience with this disease has caused it to be listed as one of the six internationally quarantinable diseases, and thus subject to the most stringent regulations concerning the reporting of its occurrence, the quarantine of endemic and epidemic areas, and so on.

On the other hand, we have had only about two cases of plague, on the average, each year in the United States, if we exclude those cases which resulted from the few urban epidemics this country has seen.[2] From 1908 to the present time, there have been 111 reported human infections contracted from wild rodents or rabbits, or from their fleas, with 64 of these resulting in death.[3] This very small case rate, together with the fact that the disease can be cured if diagnosed and treated properly, would lead one to believe that plague does not present any great problem to the health of this country.

But this is not the case. Plague exists, in its sylvatic form, in over 130 counties of 15 western states. Potentially, it may break out among humans at any time, as it did most recently in New Mexico and California in 1965.

The importance of the occurrence of a human plague case in the United States cannot be measured by frequency of incidence. In terms of probability, such an event is statistically insignificant and may suggest disregard. However, one case of pneumonic plague could pose an epidemic threat if it were to occur in a community in which health workers are not cognizant of such a possibility. Such a situation occurred in Oakland, California, in 1919, when a squirrel hunter developed a secondary plague pneumonia subsequent to being infected by contact with diseased wild rodents. A self-limited epidemic among friends and other contacts followed, in which a total of 14 cases with 13 deaths occurred.[4] The sporadic, widely sepa-

rated cases of bubonic plague which still occur should serve to remind us that this disease continues to be a real threat to the public health in this country. It is clear that the reservoir of enzootic infection, entrenched in the vast hinterland of our western recreational regions, constitutes a disease potential that must be recognized by public health and medical authorities.

The investigation of bubonic plague in the United States today is essentially an exercise in clinical epidemiology defined in broad terms.[5] The prevalence of human cases of plague has changed so radically since the early days of urban epidemics, that at present the single clinical case becomes a focus for epidemiological investigation. During the past 35 years or more, human cases have been exclusively associated with wild rodents or rabbits and their fleas in the western states, i.e., with the sylvatic form of the infection. Investigations of the epizootiology of sylvatic plague constitute a basic research activity in our attempt to understand the factors responsible for the focal persistence of enzootic infection. Studies of such a nature may reveal the potential for human cases, but the human case per se, when it occurs, is now the point of departure for an epidemiologic study. Thus every case of human plague offers a unique opportunity not unlike that awaiting a detective at the scene of a crime.

Starting with the sick individual, in whom infection with Pasteurella pestis has been diagnosed and confirmed, the investigator records the history of the patient before onset of his clinical illness and carries out a detailed study of the total environment associated with the victim. In many cases the investigation will reveal important epidemiologic factors and ecological relationships directly related to the human case. Thus the present public health approach to the study of bubonic plague in the United States must be one in which the victim is not regarded as an isolated sick individual, but rather is placed within the setting in which the infection was contracted. Adherence to this principle in the discussion which follows, and applying it to a number of human cases, should reveal salient epidemiologic circumstances affecting the occurrence of human infection.

Recent Human Plague Data

During the period from 1956 to 1965, a total of 20 cases of human plague were reported in the United States. All of these were associated with foci of sylvatic plague in four western states (New Mexico—13, California—4, Colorado—2, Arizona—1). Figure 1 shows the geographic distribution of these cases and indicates that two of the cases traveled a considerable distance from the infective source before the onset of symptoms.

The 20 cases are summarized in Table 1. Plague was observed more frequently in males (15 cases). Although infection was more common in younger individuals, no specific age group predominated (0-9 years, 4; 10-19, 2; 20-29, 5; 30 and over, 4). The five females involved were all children, one 12 years old and 4 under 5. As stated above, plague is currently confined to sylvatic locations. It is therefore to be expected that men would be exposed more often than women, due to differences in occupational and/or recreational activities. In several instances occupational demands were directly associated with increased risk of exposure (field biologist, telephone lineman, geologist, sheepherder). At least six of the patients had engaged in hunting as a form of recreation. Squirrels were hunted for sport, whereas rabbits and prairie dogs were sought for sport, and sometimes for food as well.

A history of being bitten by a flea,

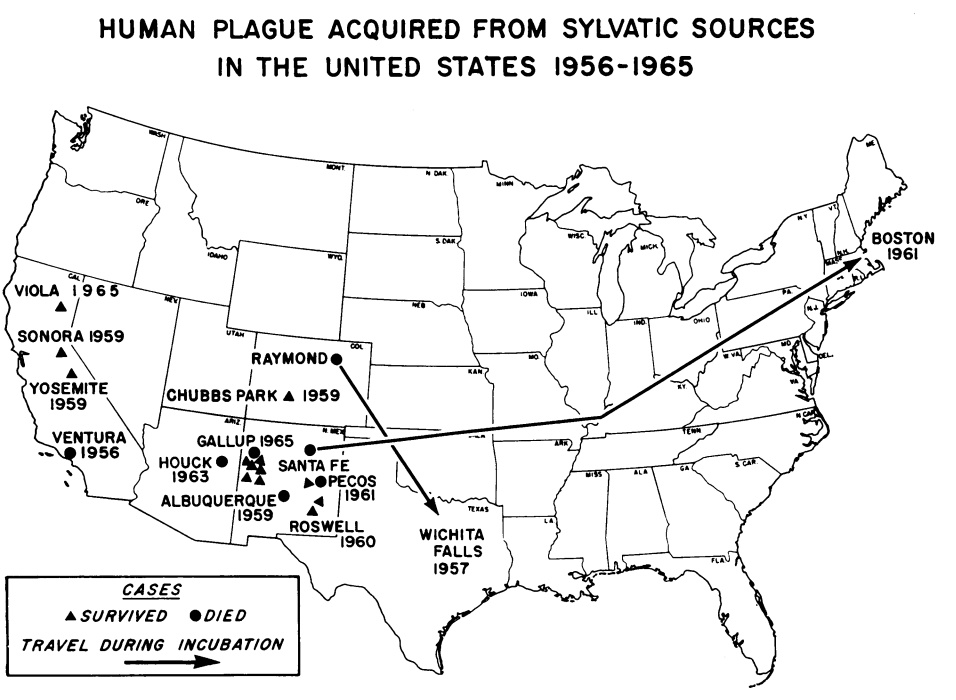

Figure 1—Cases of human plague due to contact with wild rodents, rabbits, or wild rodent fleas.

presumably a wild rodent flea, was elicited from three patients. Direct contact with animals was reported for 12 others (8, wild rodent; 4, rabbit) with no clear-cut history of flea bite. It was uncertain what the infective source may have been in the remaining five cases, although the circumstances suggested wild rodents.

The majority of infections occurred in the summer and early fall months (June—5, July—4, August—6, September—2). All those with onset during the winter (December—1, February—2) were associated with rabbits.

Each of the 20 infections was classified clinically as bubonic plague. None presented the pneumonic form initially, although two of the seven fatal cases were known to have developed a secondary pneumonitis. In this series of cases, the case-fatality rate was 35 per cent (7/20). Certain epidemiologic details associated with several of these cases will be described below.

Some Factors Affecting Plague Epidemiology

The epidemiologic cycles of plague have been the subject of numerous publications and there is little need to reiterate the facts here. However, we present a summary of these cycles in the form of a diagram, Figure 2. This shows the relation of wild rodent plague to rat-borne plague and to the accidental involvement of the human victim. Both wild rodent and domestic rat infections are shown as cyclic phenomena, a circumstance that suggests them to be "permanent" enzootic pockets. In the historical sense this is mainly applicable to wild rodent plague. Rat-borne plague, although quite often a long-term infec-

Table 1—Cases of human plague reported in the United States, 1956-1965

Case	Identity	Age	Sex	Onset	Location	Probable Source	Original Diagnosis	Outcome
1	A.S.	40+	M	June '56	Ventura Co., Calif.	Wild rodent flea	Plague	Fatal
2	L.B.	4	F	Sept. '57	Boulder Co., Colo.*	Wild rodent flea	Meningitis	Fatal
3	J.T.	27	M	June '59	Park Co., Colo.	Prairie dog	Tularemia	Recovered
4	J.L.	11	M	June '59	Yosemite Nat'l Pk., Calif.	Wild rodent flea	Plague	Recovered
5	L.B.	12	F	July '59	Bernalillo Co., N.M.	Cottontail rabbit	Plague	Fatal
6	L.B.	40	M	July '59	Tuolumne Co., Calif.	Ground squirrel	Plague	Recovered
7	D.S.	24	M	Feb. '60	Chaves Co., N.M.	Cottontail rabbit	Plague	Recovered
8	J.J.	23	M	Feb. '60	Chaves Co., N.M.	Cottontail rabbit	Plague	Recovered
9	S.D.	38	M	June '61	San Miguel Co., N.M.	Uncertain	Plague	Fatal‡
10	J.M.	38	M	July '61	Santa Fe Co., N.M.†	Uncertain	Tularemia or RMSF**	Fatal
11	D.F.	23	M	Aug. '61	San Miguel Co., N.M.	Uncertain	Plague	Recovered
12	T.S.	28	M	Dec. '63	Apache Co., Ariz.	Rabbit	Plague	Fatal
13	P.N.	3	F	June '65	McKinley Co., N.M.	Prairie dog	Meningitis	Recovered
14	J.C.	2	M	July '65	McKinley Co., N.M.	Prairie dog	Meningitis	Recovered
15	L.M.	9	M	Aug. '65	McKinley Co., N.M.	Prairie dog	Plague	Recovered
16	E.M.	4	F	Aug. '65	McKinley Co., N.M.	Prairie dog	Mumps?	Recovered
17	A.I.	3	F	Aug. '65	McKinley Co., N.M.	Prairie dog	Plague	Recovered
18	B.M.	3	M	Aug. '65	McKinley Co., N.M.	Prairie dog	Plague	Recovered
19	L.R.J.	14	M	Aug. '65	McKinley Co., N.M.	Prairie dog	Plague	Fatal‡
20	J.C.	5	M	Sept. '65	Shasta Co., Calif.	Ground squirrel	Plague	Recovered

* Died in Wichita Falls, Tex.
† Died in Boston, Mass.
‡ Secondary pneumonic involvement.
** Rocky Mountain Spotted Fever.

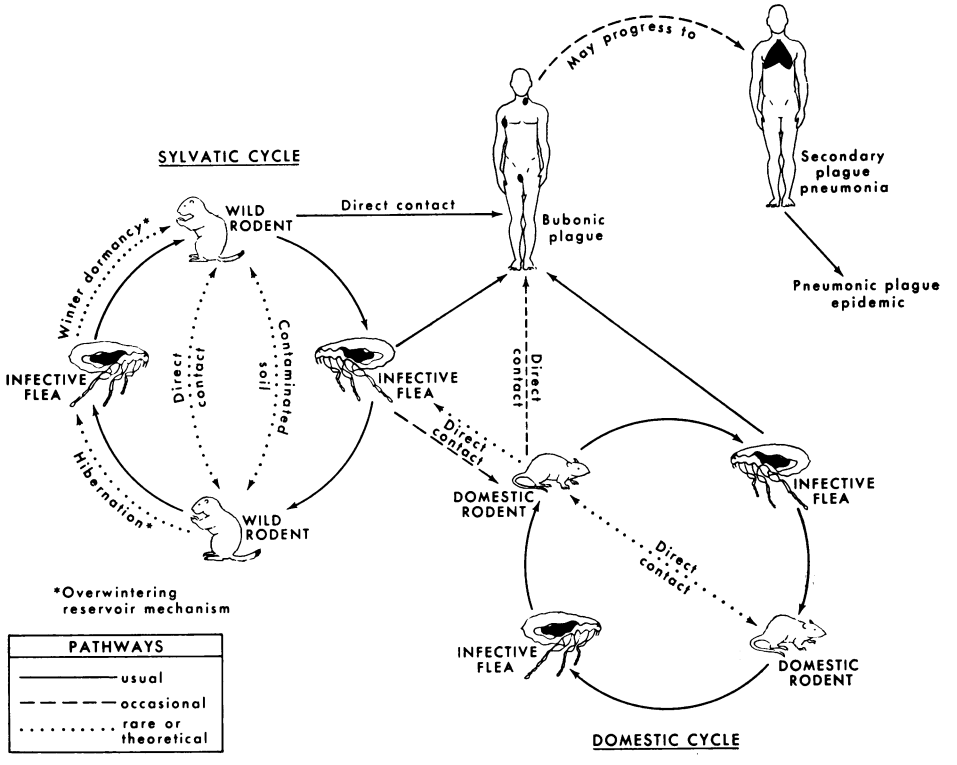

Figure 2—Epidemiology of Pasteurella pestis infection in the United States, showing the cyclic nature of the infection and some of the mechanisms responsible for its maintenance in nature.

tion in nature, is not considered to have the inveterate character associated with natural foci of disease that antedate human history.

Mammalian Host

For many, the mention of plague conjures up the image of a classic disease, with human deaths associated with deaths among domestic rats in a concurrent epidemic and epizootic. Among many of the mammalian hosts of sylvatic plague, however, the presence of P. pestis infection may not be as obvious. As is the case with other infectious agents (e.g., poliovirus, staphylococci), P. pestis infection does not always result in disease. Wild rodent species believed to be of prime importance in the maintenance of sylvatic plague are often able to withstand inoculation with doses of plague bacilli that are hundreds or thousands of times greater than the lethal dose for man or the domestic rat. An epizootic of plague infection may spread through a population of an insusceptible wild rodent species without producing any symptoms of disease. Of particular interest is the fact that, although no noticeable symptoms occur, a transient bacteremia results which permits fleas on such hosts to become infected.[6] Therefore, an extensive epizootic of P. pestis infection may exist in a population of highly resistant rodents and may never be detected except by laboratory means.

Very marked differences in the ability to survive infection with virulent P. pestis cells have been found between

species and, in some cases, between different populations within a species. Although the exact LD_{50} for a given host population will vary somewhat, depending on the route of inoculation and the virulence of the P. pestis strain being used, certain broad categories of susceptibility can be seen.

The standard animals used in the laboratory are the albino mouse and guinea pig, each being highly susceptible to P. pestis infection ($LD_{50}<10$ organisms inoculated I.D. or S.Q.). Western harvest mice (Reithrodontomys megalotis) collected in California,[7] New Mexico,[8] and Utah[9] have been found experimentally to be highly susceptible. At the other extreme, Ord kangaroo rats (Dipodomys ordii) from New Mexico and Utah were highly resistant ($LD_{50}<10^6$ organisms).

Within each of the above species, a similar degree of susceptibility to plague has been exhibited, regardless of the geographic area. However, it cannot be assumed that the susceptibility pattern established in one area necessarily will hold true for another. Deer mice (Peromyscus maniculatus) are considered to be important reservoirs of P. pestis in enzootic areas of California[7] and Utah,[10] yet the population in the former state is highly resistant ($LD_{50}<10^7$) while in the latter it is somewhat less resistant ($LD_{50}=10^4$-10^6). Still another deer mouse population, in New Mexico,[8] was even more susceptible ($LD_{50}<10^3$).

Bushy-tailed wood rats (Neotoma cinerea) in Utah were moderately resistant in experimental tests.[9] However, an extensive die-off occurred in 1961 in a population of this species inhabiting the Lava Beds National Monument, Siskiyou County, California (San Francisco Field Station, unpublished observations). No experimental data are available to establish the susceptibility of the wood rats of the Lava Beds area, although it appears from the field observations that there was little resistance to P. pestis infection. Deaths due to plague have been observed in whitethroat woodrats (Neotoma albigula) in New Mexico.[11] Laboratory tests showed these rodents to be highly susceptible.[8]

Plague was recognized in the brush rabbit (Sylvilagus bachmani) and desert cottontail (S. auduboni) in California, in the hare (Lepus californicus) and desert cottontail in New Mexico, and in the mountain cottontail (S. nuttalli) in Washington.[11] Experimental data on hares from Utah showed them to be susceptible ($LD_{50}<10^4$).[9]

Differences in susceptibility were detected between two populations of California ground squirrels (Citellus beecheyi), apparently related to differences in the extent of selection for natural resistance influenced by the presence of P. pestis. A striking example of variation in resistance correlated with the presence or absence of P. pestis was seen in two California vole (Microtus californicus) populations in the San Francisco Bay area. Voles tested from an enzootic area were highly resistant ($LD_{50}<10^7$), whereas individuals from a plague-free population less than ten miles away were susceptible ($LD_{50}=10^2$).[7]

Norway rats (Rattus norvegicus) trapped in San Francisco were susceptible to plague ($LD_{50}=10^2$). In contrast, Norway rats collected in Hawaii showed somewhat greater resistance, depending upon the locality. Populations from urban areas around Honolulu and Pearl City on the island of Oahu were moderately susceptible, whereas rats from a formerly enzootic area on the island of Hawaii were significantly more resistant. Significant differences were also noted in populations of the Hawaiian rat (R. exulans); those from Oahu were more susceptible than those from Hawaii. Black rats (R. rattus) were found to be equally susceptible in both areas.[12]

Epizootics of plague have occurred

in populations of numerous other species for which no experimental data are now available. The mortality rates in these epizootics were suggestive of high susceptibility. Some of these species, such as the Gunnison prairie dog (Cynomys gunnisoni), black-tailed prairie dog (C. ludovicianus), yellow-belly marmot (Marmota flaviventris), Richardson ground squirrel (Citellus richardsoni), and golden-mantled ground squirrel (Cit. lateralis) are particularly important in the ecology of plague.

The presence of asymptomatic infections in resistant host populations may go unnoticed unless tissues are submitted to the laboratory for examination. Another clue to this phenomenon is the finding of infected fleas on healthy animals. However, epizootiologic studies need no longer be limited to tissue and flea collections and the subsequent isolation of P. pestis. Serologic investigations utilizing the passive hemagglutination test have added considerably to our understanding of the epizootiology of inapparent plague infections. A definite seasonal pattern of infection was detected in Microtus californicus in the San Francisco Bay area, with its peak in mid-winter. At this peak, infection rates of 65 per cent or greater were noted serologically, while very little infection was measurable by bacterial isolation technics.[13]

The role of carnivores in the ecology of plague is still undefined. Coyotes (Canis latrans) have been shown to be highly resistant.[9] A half-grown bobcat (Lynx rufus) showed no evidence of infection when examined 33 days after feeding on three guinea pigs infected with P. pestis.[9] Dogs in areas of Arizona and New Mexico, where epizootics in prairie dogs have occurred, were found to have hemagglutinins against P. pestis antigen. Generally it may be assumed that carnivores are relatively insusceptible to plague. However, it is possible that they may play a role in the transport of infected rodent fleas from one area to another.

Certain rodents survive the adverse conditions of winter through the process of hibernation. Wayson[14] discussed the possibility that "plague may be carried through the winter as a subacute or chronic infection of the hibernating animal, and that an acute recrudescence may occur in the animal . . . upon the termination of hibernation in the spring."

We would hesitate to call such a phenomenon "a subacute or chronic infection"; perhaps a better term would be "delayed infection." Be that as it may, we have found this phenomenon to take place in experimental studies using Belding ground squirrels (Citellus beldingi). Our experiments involved three points: first, the effect of hibernation on the "normal" course of the disease; second, the occurrence of disease during the period of hibernation; and third, the ability of the organism to survive in the host animal through hibernation.

With regard to the first point, we found that the lethal dose among the hibernating animals was more than 20 times the number of organisms required to kill normal controls. Later in the study, we found squirrels succumbing to plague several weeks after infection. Apparently the plague bacilli were able to survive in vivo for an extended period of time, producing disease long after their counterparts in nonhibernating hosts could do so. Finally, we have seen squirrels come out of hibernation and then sicken and die of plague infections 19 weeks after being inoculated.

We can therefore say that hibernation seems to provide an interepizootic pathway for the plague bacillus which differs from "reservoiring mechanisms" either in so-called classic rat-borne plague or in sylvatic plague involving non-hibernators such as voles.

The maintenance of enzootic plague in natural foci depends in a fundamental way upon the commingling of insusceptible and susceptible individuals within populations of single species of rodents, and upon its polyhostal character, i.e., the circulation of the plague organism in two or more rodent species in a given locality during a given period. Some observers have maintained that plague basically is monohostal.[15] Our work has supported the idea of its polyhostal nature as suggested by Kalabukhov.[16] In the San Francisco Bay region, Microtus californicus and Peromyscus maniculatus commingle, and they are both found to be relatively insusceptible to plague but susceptible to infection with P. pestis which circulates in these vole and deer mouse populations and their fleas.[13,17] Historically, the ground squirrel, Citellus beecheyi, was an important host in this area in the past. Extensive poisoning campaigns drastically reduced the ground squirrels, but the infection remained in the voles and field mice. A similar situation occurred at Fort Ord, California in 1943-1944 where ground squirrels were controlled but P. pestis continued to be isolated from Microtus and Peromyscus populations.

The commingling of rodent or other mammalian species of differing susceptibility is of basic epidemiologic importance because the insusceptible species does not succumb to plague, whereas it acts as a reservoir of the infection which, when transferred to a susceptible species, results in clinical disease that may in turn be a source for human infection via the flea or by direct contact. In Roswell, New Mexico, during the winter of 1960, two human plague cases were associated with the handling of rabbits, Sylvilagus auduboni. Investigation revealed a close association of the cottontail rabbits with wood rats, white-footed mice, grasshopper mice, cotton rats, and kangaroo rats. A plague epizootic had wiped out the wood rats, Neotoma albigula, and the infection had transferred to the highly susceptible rabbits. Insusceptible species such as the kangaroo rats and white-footed mice were relatively unaffected. Thus the rabbits were the epidemiologic link in the chain of infection from wood rats to man.[11] Similarly, in 1959 a human case in Yosemite National Park was associated with chipmunks that are quite susceptible to plague. The chipmunks commingled with ground squirrels, Citellus beldingi, that are less susceptible and in which asymptomatic infection was found. Besides, the ground squirrels, as noted above, hibernate during the winter and may carry the infection over to the next spring-summer period.

The commingling of wild rodents and domestic rats in an enzootic plague area has a serious potential for human infection since the relatively more susceptible rat can serve as a direct avenue of infection to man. Such a situation was noted many years ago in southern California where the flea, Diamanus montanus, transferred the infection from ground squirrels to rats.[18] In the San Francisco Bay region Norway rats have been found dead from plague in situations where the infection transferred from vole and deer mouse populations undergoing an epizootic of infection.[19,20]

Ectoparasite Vector

Various ectoparasites of mammals such as ticks, lice, mites, and "kissing bugs" have on occasion been found to either harbor plague organisms in nature or to be receptive to infection in the laboratory. Nevertheless these parasitic bloodsucking arthropods have never been shown to play a significant role as biological vectors of P. pestis. The flea is the vector that is considered basic for the perpetuation of P. pestis in nature. Theoretically, one might assume that a priori every flea is a potential

vector. In actuality, it has been found that species of fleas show wide differences in their efficiency as vectors and that, within a species, individual fleas differ in their capacity to transmit P. pestis. Comprehensive summaries of flea species that have been implicated in plague throughout the world are available in the literature.[21,22]

The differences in vector efficiency of various flea species have important epidemiologic implications. First of all, it is imperative to differentiate between vector capacity among animal hosts and in human populations. Vector efficiency studies obviously have been conducted with rodent hosts. On the other hand, a flea that readily feeds upon a rodent and transmits P. pestis will not necessarily feed upon a human host as readily. It is known that most wild rodent fleas are reluctant to feed upon man, whereas the cat and dog fleas, the so-called human flea, and the Oriental rat flea will feed upon humans fairly avidly. The Oriental rat flea, Xenopsylla cheopis, is the "classic" vector in urban, rat-borne epidemics of plague. In experimental studies it has been shown to be the most efficient vector.[23] Fortunately, in the United States, rat-borne epidemics of plague have not occurred since the first decade of this century. Thus, although X. cheopis is found on rats in urban and other areas, the threat is currently a potential one as long as rats and rat fleas are adequately controlled and kept from commingling with wild rodents on a large scale in areas of enzootic plague. Dog and cat fleas have never been associated with plague outbreaks and they are very poor vectors in the laboratory. The human flea, Pulex irritans, is a vector in North Africa and possibly in South America primarily because of human customs and habits that are absent in our own culture.

Without going into a detailed recital of the facts, it is clear that the vector efficiency and the host preference of a given flea species are two critical epidemiologic factors. The relatively low vector efficiency and restricted feeding habits of most wild rodent fleas account in part for the very few human cases of plague in this country that are traceable to sylvatic sources and authenticated as due to flea bite. On the other hand, the high vector efficiency of the Oriental rat flea and its catholicity of feeding habits have been, and continue to be, two of the main factors in urban epidemics of plague.

Two additional points about fleas should be mentioned here. The first is the habit of fleas to transfer from one rodent to another within a host species, as well as between individual hosts of different species that commingle.[24] This habit accounts for the spread of infection in rodent populations and its spread from wild to domestic rodents, as noted above. In the case of the Oriental rat flea it was found many years ago that the fleas would attack man after the rat host had died. Thus during rat-borne epidemics it became very important to kill the fleas first, or certainly to kill them concomitantly with rat poisoning. This same principle applies to certain wild rodent control campaigns even though the direct danger to man is less.

The second point is that fleas may act as reservoirs of P. pestis as well as vectors. In the laboratory most wild rodent fleas can be kept alive for many weeks while infected. As a matter of fact, in most wild rodent fleas the plague organism may take two months or longer to reach a stage of multiplication in which the flea is infective. (Some wild rodent fleas never reach this stage, but transmit the pathogen mechanically by contaminated mouth parts; a situation in which one or two fleas cannot transmit but where transmission takes

place en masse.) This ability to harbor the plague organism for considerable periods seems to reach high efficiency in fleas of deep burrowing rodents such as ground squirrels and prairie dogs. Field studies in Colorado have demonstrated that infected prairie dog fleas were capable of remaining alive in burrows for from 12 to about 15 months after their hosts had died from plague.[25] Thus, like a hibernating rodent, certain species of fleas can maintain P. pestis during the interepizootic period or through the rigors of the winter season.

The Etiologic Agent

The causative agent of all forms of plague, Pasteurella pestis, was discovered by Yersin[26] and Kitasato[27] in 1894, making this one of the oldest known disease agents. After over seventy years of examination we still have a great deal to learn about this organism. However, certain information has recently become available which may be of interest in this discussion.

We ordinarily think of plague as a severe illness, sweeping through populations of animals or, historically, humans, and being associated with high rates of morbidity and mortality. In support of this generalization, we may note that all of the isolations of P. pestis made in our laboratory in recent years have been fully virulent for mice and guinea pigs, with calculated LD_{50} values in the range of 1-50 organisms (San Francisco Field Station, unpublished observations). However, it has been shown that there exist in nature strains of P. pestis which are but weakly virulent when compared to our usual isolates, or which are virulent for some susceptible rodent species but ineffective against others.[10,28,29] If a population of rodents is infected by one of these weakly-virulent strains, the animals can develop antibodies which protect them in the event of a subsequent infection with a virulent strain. Thus the establishment of what we consider a normal plague bacillus in a given area may be thwarted because of the earlier presence of one of these weakly-virulent strains.

Furthermore, in cases where a balance has been established between a weakly-virulent plague organism and a population of rodents, the introduction of a stress situation—e.g., a sharp temperature change or an increase in numbers which leads to competition for food and space—may allow the resistance of the rodents to drop and thus initiate the production of overt disease. This type of reaction has been produced experimentally,[30] and may explain the occasional death from plague seen in populations of resistant rodents.[17]

While it may be true that certain minor differences exist with respect to the antigenic composition of various strains of P. pestis, all are sufficiently alike so that we have no need for serological subclassifications such as are found in the Salmonellae, Streptococci, and some other bacterial genera. However, the antigenic make-up of the plague bacillus is particularly important from several points of view, especially (1) in the manifestation of virulence, (2) for improvement in clinical methods of identification, and (3) for differentiating the plague bacillus from the closely related species, P. pseudotuberculosis.

First of all, the virulence of the plague organism is dependent, among other things, upon its possession of several specific antigens. Among these are the so-called V and W antigens, which are thought to be associated with the prevention of phagocytosis by the host cells.[31] Another antigenic component is an endotoxin, the protein responsible for the harmful effects of the infection.[32] Lastly, the plague bacillus is surrounded by a protein-polysaccharide complex which contains the antigen termed Fraction I, preeminently involved in the protection of the bacterium.[33] The presence of all of these antigens does not guaran-

tee the virulence of the organism, but the absence of any one of them will render that strain avirulent.

The second point of view, that of improved identification methods, is primarily concerned with the Fraction I antigen. The classical methods of bacterial identifications are often too slow to be of practical value in human cases of plague, since P. pestis is a slow-growing organism and plague is often a fulminating disease. At the present time, however, we can make use of the fluorescent antibody technic for the rapid identification of P. pestis cells. While this technic, which uses fluorescein-conjugated antibodies against Fraction I,[34] has been shown to be reliable in practiced hands, it assumes the Fraction I antigen to be unique to P. pestis. This assumption has recently been found to be unwarranted.[35,36]

In the half-dozen years that the fluorescent antibody has been in use, we have seen only one false negative and two false positives. The false negative, a strain of P. pestis isolated from a fatal human case in 1957, was found to possess very little Fraction I antigen. While the identity of this strain was confirmed in the laboratory by our routine cultural, biochemical, and pathological tests, difficulty was encountered in producing a positive immunofluorescent reaction.[37]

In 1963, an organism isolated from a snowshoe hare in Alaska was found to produce a positive reaction, albeit an atypical one, with our fluorescent antibody conjugate. An intensive examination[35] showed that this isolate was a strain of P. pseudotuberculosis, an organism closely related to P. pestis. So close is this relationship that, as reported in a recent article,[38] of 18 antigens distinguishable by gel-precipitation methods 13 are common to both species. The envelope antigen (i.e., Fraction I) was one of the antigens thought to be unique to the plague bacillus until the isolation of the Alaskan organism. This isolate was found to possess a surface antigen so closely related to Fraction I that serological cross-reactions were found.

This isolation, plus a second made in California in early 1965 which produced these same difficulties, has caused a revision in the criteria applied in the interpretation of the fluorescent antibody test. Rather than the simple presence or absence of staining, greater emphasis must be placed on the intensity and distribution of fluorescence and the morphology of the stained organism.[35]

The rodent-flea-rodent chain of infection thought to be the principal pathway in the transmission of plague in nature leaves unexplained many facets of the epizootiologic picture. For instance, an infected area may go through an extended "quiescent period"—during which no evidence of the disease can be found—and then show a resurgence of infections. Attempts to explain these quiescent periods have suggested the flea as a long-term reservoir, or required the reintroduction of the infection from an outside source, but these explanations have not always been compatible with particular situations.

Furthermore, enzootic foci have been studied in which the percentage of infected fleas did not seem sufficient to account for the high percentage of wild rodents showing significant P. pestis hemagglutination titers. Assuming that the presence of P. pestis antibodies reflects infection with the plague organism, this suggests that a transmission mechanism in addition to that of the flea-vertebrate chain may be operative.

Recently, a series of reports by workers in France and Iran have appeared[39] which implicate the soil both as a source of the infection for animals, especially for burrowing animals such as Meriones spp., and as a means of preservation of the plague bacillus in interepizootic periods in a given area. The findings that

P. pestis can remain viable in soil for many months, and be transmitted to animals that come in contact with that soil, are of paramount importance in the study of plague in nature. Most certainly this would be an important factor in the ecology of the organism and in the pattern of the disease. Whether or not this is a universal phenomenon in enzootic plague foci and whether it is basic to the natural cycle of the infection remain to be determined.[40] The answer will depend upon intensive studies in the various world foci in which comparisons with the prevalence of flea transmission in the field will have to be accomplished, as well as laboratory comparisons of the vector efficiency to wild rodents of contaminated soil and infective fleas.

Selected Human Cases

The 20 cases of human plague that have occurred in this country since 1956 already have been discussed above. An item of interest, in addition to points already noted, is the column in Table 1 showing the original diagnosis made in each case. This is of significance to both the clinician and the public health worker. Of the 20 cases, six were first diagnosed as diseases other than plague. In at least two of these six cases plague was not suspected until the autopsy revealed suggestive pathology. Three of the 20 cases were diagnosed as plague retrospectively on the basis of serological evidence. The import of these histories to the clinician is obvious. In terms of public health, a wrong diagnosis may influence an epidemiologic investigation along erroneous lines, or it may preclude an investigation. Thus, in the 1959 case in Park County, Colorado (Table 1), no investigation was conducted until a year later when details of the case were noted and a suspicion of plague was formed. That the case actually was plague was determined in retrospect.[25]

Certain of the human cases have features that illustrate epidemiologic factors of some significance. Table 1 shows that rabbits were the source of infection in cases 5, 7, 8, and 12. In case 5 the family dog brought a rabbit from the field to the home of the victim. The dog showed positive serology for P. pestis. In cases 7, 8, and 12 the victims had hunted the rabbits for food, but in the first two of these cases rabbits represented a luxury food hunted as a sport by two Air Force officers, whereas in the latter case the rabbits represented a basic food source to a Navajo Indian sheepherder working during the winter. The chance nature of these human infections is emphasized by the fact that rabbits are not involved in permanent foci of plague in this country, but are occasional victims of the disease.

The speed of current air travel, and the promise of even faster travel in the near future, has resulted in what is sometimes called "jet-borne disease." Case 10 represents just such an instance. The victim acquired his infection near Santa Fe, New Mexico, and during the incubation period he flew to his home in Boston, Massachusetts, where he died. Plague was not suspected until an autopsy was performed.

In case 2 the victim also traveled during the incubation period from the infectious site in Colorado to her home in Texas where she died. Here again a diagnosis of plague was lacking until the autopsy. In case 4 travel was less extensive, from Yosemite National Park to the San Francisco Bay area. In these two cases travel was by automobile.

Cases 7 and 8 did not involve travel, but a definite potential existed. The two victims, officers in the Air Force, were members of a flight group flying fast jets to South America and England. Fortunately they were not on duty during the incubation period of their infections.

These cases underline the modern potential for a person to contract the infection in a sylvatic source, fly to another country—or half-way around the world for that matter—and succumb to clinical plague after arrival. The tendency, especially during travel, for plague to become pneumonic would pose a serious threat to medical personnel and other contacts of the patient in an area, perhaps, where plague is not even remotely considered in the diagnosis of febrile illness.

In 1965 an epidemic of plague occurred among Navajo Indians in the vicinity of Gallup, New Mexico (cases 13-19, Table 1). The epidemiology of this outbreak revealed unique features and it is of interest to reiterate briefly our discussion published elsewhere.[41]

The 1965 epidemic was the largest recorded in the United States in which each human case was associated with a separate infective source in wild rodents. All cases occurred in the same geographic region at a time when extensive epizootics in prairie dogs were noted. This episode contrasts sharply with the usual course in this country where an average of about two cases per year have occurred and where each case is isolated and unrelated to other cases both in time and space. In cases of plague involving non-Indians usually there is no common factor in the circumstances that lead each victim to contact the infectious source, a wild rodent or an infective flea. Such contact on the part of non-Indians is fortuitous and highly improbable because social and personal habits preclude a consistent or intimate contact of a large number of people with animals.

In the case of the Navajos there is a common factor that is lacking in the "outside" population. This is a social factor which is historically of long standing and undoubtedly antedates the invasion of North America by the white man. Indian society has been, and still is to a large extent, based upon intimate contact with nature. This is reflected in daily life, in religion, and in ceremonials.

The point of greatest significance is that the Navajo not only has lived, and continues to live, close to wild animals but that he has traditionally used many of these as food. The rabbit and the prairie dog have always been among the most favored of these wild animal sources of protein. The fatal Indian case in 1963 at Houck, Arizona, was associated with wild rabbits caught for food during winter sheepherding. The seven cases in New Mexico during 1965 were directly associated with prairie dog die-offs in the vicinity of the victims' homes. Furthermore, abundant evidence was obtained that Navajo children trap prairie dogs as a form of play.

House dogs or sheep dogs also were noted to be a possible factor. Rabbits and prairie dogs make up a portion of their diet and it has been noted that they will occasionally bring these mammals back to the home area. It is known that dogs have been associated with human plague cases and these Indian dogs have been shown to have significant P. pestis hemagglutination titers. Thus dogs on the Navajo reservation may possibly act as a bridge for infected mammals and/or their fleas.

The epidemic in New Mexico suggests that the problem of plague in the Navajo reservation, and possibly in other reservations and areas where Indians live, has unique epidemiologic characteristics in comparison with the general problem of sylvatic plague in the United States. There seems little doubt, on theoretical grounds, that Indians have been subjected to plague during their long history since it is the present consensus that wild rodent plague has been entrenched in western North America and Mexico from prehistoric times. In the present instance, the plague cases were community-oriented on the basis of

socioeconomic factors and, although they were not familial in character, they can be described as a community cluster.

Role of the Public Health Worker

We have presented a few of the facts concerning plague epidemiology in the United States since many public health and medical workers view the disease as an historic curiosity of little more than passing academic interest. The magnitude of the potential for human plague and the danger of a pneumonic outbreak are not clearly appreciated. In the medical profession there has been some evidence of change, since in 1962 the American Medical Association established a Department of Environmental Health in the Division of Environmental Medicine to deal with zoonoses among other problems. A new emphasis was placed upon such diseases as typhoid, yellow fever, smallpox, and plague.[42] Public health workers in health departments of certain states and counties located within the vast western enzootic plague focus have been cognizant of the problem and have contributed to our understanding and to the control of the disease.

In terms of a zoonosis, all professionals working in the field of health are actually dealing with the public health. Thus a private physician attending a patient suffering an acute febrile infection with lymphadenopathy, in an area where plague is enzootic, must obtain a history of his patient's activities along lines of clinical epidemiology. In plague, speed of treatment is essential, and treatment should begin before a final diagnosis is made. At the beginning, a searching appraisal of the patient's history combined with observed clinical features will result in the necessary presumptive diagnosis underlying the start of treatment. Thus in case 11 (see Table 1) the patient survived primarily because the physician immediately presumed plague precisely on the basis of the above factors.

The public health worker is fundamentally concerned with zoonoses as disease potentials residing in the natural or man-made environments that threaten human populations. When plague occurs in man, the public health scientist employs epidemiologic and ecologic principles in defining the infectious locus, its current status as a hazard, and recommendations for its control. The inquiry must reach beyond that level, however, since in public health the main avenue of defense against disease is prevention. Accordingly, the public health worker will, depending on the circumstances, employ such measures as quarantine, mass immunization, chemoprophylaxis, environmental modification, chemical control, and education.

In wild rodent plague, the public health worker must be aware of specialized laboratories that can determine unequivocally the presence of Pasteurella pestis in specimens. This problem recently was emphasized when "plague" was mistakenly reported from Alaska.[35] The areas of greatest risk must be recognized since each year more and more thousands of tourists, campers, hunters, etc., are spending their vacation time in national and state parks, hunting and fishing areas, and a host of other places where contact is made with natural habitats and their mammalian fauna. Rodents and fleas infected with P. pestis have been found in such areas as Yosemite National Park, Lava Beds National Monument, Yellowstone National Park, Bryce Canyon National Park, the Lake Tahoe area, and many other places attractive to our highly mobile population.

Wild rodent plague in the United States will remain a "permanent" enzootic focus for a long time. Public health workers, including the medical profession, can do much to reduce the

hazard by requesting the aid of the United States Public Health Service in apprehending human cases, detecting outbreaks in wild mammals, and in educating the public to the dangers involved.

Summary

Bubonic plague continues to assert itself in epidemic form in a number of countries and the disease undoubtedly will remain under international quarantine for many years. Due to various factors, both natural and man-made, there has been a sharp decline in "classical," rat-borne plague throughout the world. In the United States the transmission of the infection to man from commensal rats appears virtually unknown at present. In contrast, the western part of the United States, approximately from the 100th meridian, contains a permanent focus of sylvatic (or wild rodent) plague in which the organism Pasteurella pestis continues to circulate in associations of various rodent and flea species living within diverse ecosystems.

In current studies of sylvatic plague much of the work has been concerned with factors responsible for the maintenance of the infection cycles in natural foci. Not only do different species of rodents commingle, but they show significant differences in susceptibility to plague. Species of Peromyscus and Microtus can be subjected to epidemics of infection (asymptomatic) and serologic studies have indicated the extent of infection both in space and time. Hibernating rodents can maintain the infection through the winter. Fleas also show varying efficiency as vectors, different host preferences, and they transfer among hosts and are capable of harboring infection for a year or more in deep rodent burrow systems.

In the United States from 1908-1965 there have been 111 human infections contracted from wild rodents and other mammals or their fleas, resulting in 64 deaths. In recent years, human cases of plague, with a history of association with wild rodents, have occurred in New Mexico, Arizona, Colorado, and California.

During 1965, seven cases of plague among Navajo Indians occurred in McKinley County, New Mexico. This was the largest plague epidemic in the United States in which each human case was associated with a separate infective source in wild rodents. All cases occurred in the same geographic region at a time when extensive epizootics in prairie dogs were noted.

Although human plague contracted in sylvatic foci has averaged less than two cases per year, each case represents a potential threat to public health. This is illustrated by cases that have gone undiagnosed, have been mistakenly diagnosed, or have traveled thousands of miles during the incubation period. Thus the physician as well as the public health worker can play a unique role in the detection, diagnosis, and prevention of plague epidemics.

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