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LITERATURE REVIEW

AND

COMPENDIUM OF RESEARCH

ON

PASTEURELLA PESTIS

Peter F. Olsen

Ecology and Epizoology Research
University of Utah

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Now = Yersinia pestis

PREFACE

This report is submitted to satisfy the contractual requirement for a review of the literature pertaining to Pasteurella pestis. Rather than being simply a literature review, it was deemed worthwhile to expand the scope of the report and make it a compendium of research done in Utah on this organism as well. It thus becomes a one-volume reference source to all work done by Ecology and Epizoology Research on the subject and summarizes all plague findings known from the State of Utah. Evidence of plague as recent as June 1969 is included.

The report is divided into ten tabbed sections comprising four main divisions. The first tab and first major division consists of a general literature review covering the following subjects: Definition; History and Distribution; Etiology; Transmission; Epizootiology; Signs, Pathogenesis and Pathology; Diagnosis; and Control. The major emphasis has been on sylvatic rather than human plague and geographically the western United States is stressed. Seventy-eight references are included. These have been carefully selected to guide readers to coverage of topics not covered fully here as well as to the most recent developments in such areas as diagnosis, epizootiology, control, etc.

The second tab and second major division ("Local Summary") is a compendium of research and disease survey findings conducted in the State of Utah. Chronological listing of all known evidence of plague in the state is included as well as lists of all known vertebrate hosts and fleas which have been found infected or indirectly associated with P. pestis in Utah.

The third main division including tabs 3-9, consists of the sections of the 1963-1968 Annual Summary Reviews which deal with plague and also the 1952-1962 Summary Status Report on Pasteurella pestis submitted by Ecology and Epizoology Research.

The fourth division, tab ten, consists of a copy of each of the five main journal articles published by members of this organization pertaining to plague.

Only sections dealing with Bryce Cyn included in this package

No

post-1968

PASTEURELLA PESTIS LITERATURE REVIEW

Definition

Plague is an acute infectious disease caused by Pasteurella pestis (Lehman and Neumann), is vectored by fleas, and affects primarily wild rodents and commensal rats (Rattus spp.) in many areas of the world. This zoonosis, listed as one of the six internationally quarantinable diseases, has tremendous public health importance when man becomes a victim of bubonic plague through intervention into the rodent-flea-rodent transmission cycle or by handling infected wild rodents.

History and Distribution

The causative organism of plague was discovered in 1894 by Yersin in Hong Kong, and in 1897 Ogata tentatively suggested that fleas may be involved in the transmission chain. Reports of the British Plague Research Commission (1905-1906, summarized in Lamb, 1908) on its work in India, did much to further knowledge about the disease, including the role played by the rat and the rat-flea. The actual means by which the bacteria multiply in the stomach of fleas, cause blockage of the proventriculus and are then regurgitated during a subsequent feeding was not worked out until 1914 by Bacot and Martin.

Although commensal rats had long been suspected to be somehow associated with plague, it was not until 1895 when infected tarabagans (Marmota siberica) were found in Mongolia and the transbaikalian region of Russia that it was confirmed that wild rodents were also host to the disease (Meyer, 1963). There are now more than 230 species or subspecies of wild rodents which have proven naturally plague-infected or are strongly incriminated from the western U.S., western Canada, Mexico, Argentina, Bolivia, Venezuela, Peru, Ecuador, China, Mongolia, Manchuria, U.S.S.R., South Africa, Kenya, Congo, Iran and India (Pollitzer, 1954; Pollitzer and Meyer, 1961; Meyer, 1963).

In the U.S., the first human case of plague was discovered in San Francisco in 1900, and the bacilli were isolated from commensal rats in 1902. It was not until 1908 that wild rodents, California Ground Squirrels (Citellus beecheyi), were found infected in Costa Contra County (Eskey and Haas, 1940; Link, 1955). By 1910 these squirrels had been found infected in nine California counties south of San Francisco Bay. This region remained the only known permanent focus of infection until 1934 when infected Belding's Ground Squirrels (C. beldingi) and Bushy-tailed Wood Rats (Neotoma cinerea) were discovered in Modoc County, California, 250 miles north of the nearest known plague focus and east of the Sierra Nevada Mountains (Wayson, 1947). In this year also, a human case of plague occurred in Oregon and became the first case outside of California attributable to association with wild animals. Intensive surveys were undertaken by both state and federal public health agencies which by 1950 extended through all the Rocky Mountain states to the Great Plains. Plague has now been detected among 57 wild rodent species or their ectoparasites in at least 140 counties of 15 western states as far east as the western

portions of Kansas, Oklahoma and Texas, as well as in Alberta, Saskatchewan and the state of Coahuila, Mexico (Link, 1955; Hubbert et al., 1966; Kartman et al., 1966; Stark et al., 1966). A map updated through 1968, taken from Stark et al. (1966), showing the distribution of P. pestis infection in wild rodents and fleas in the United States, is shown in the accompanying figure.

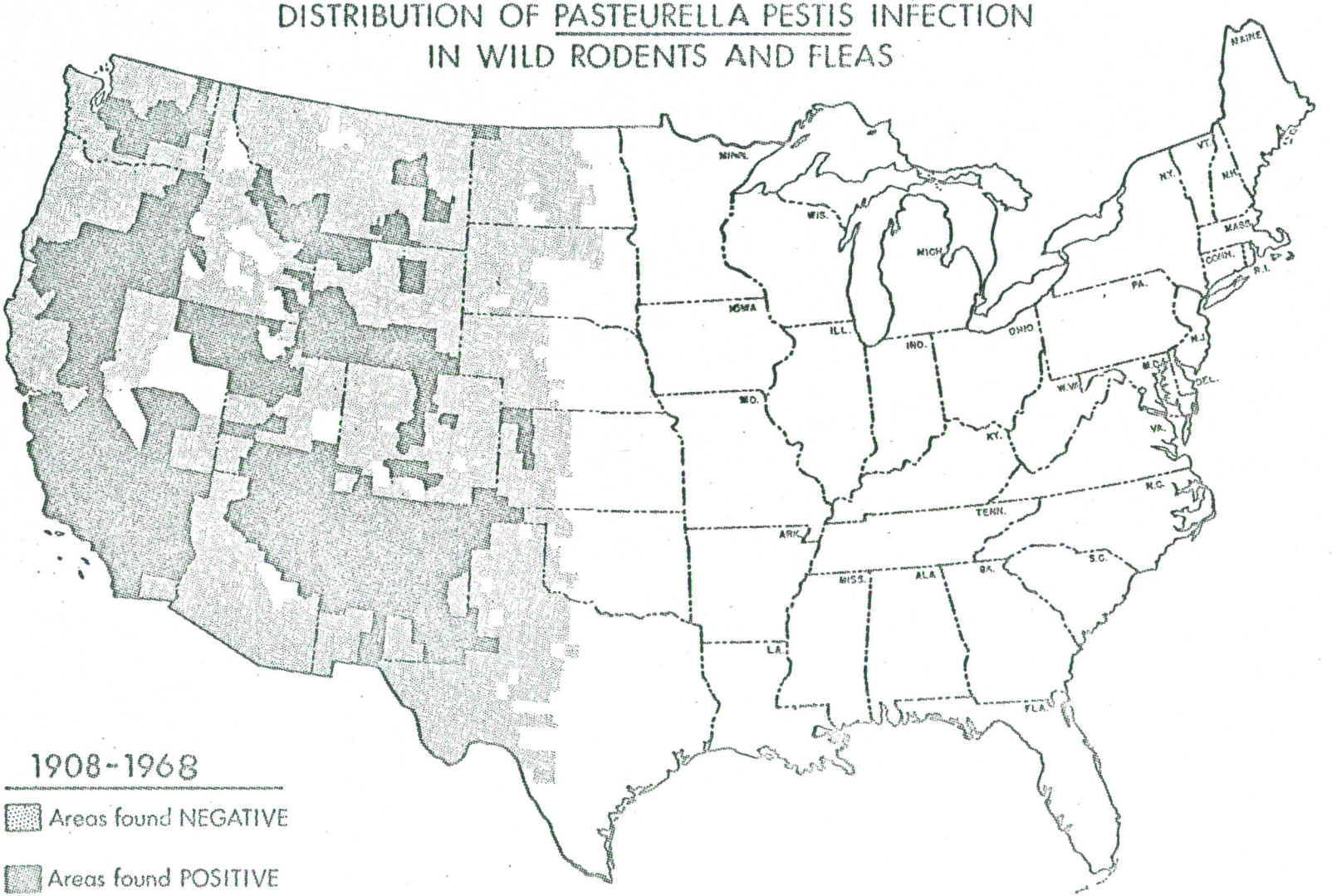
As intensively investigated as plague has been, new findings are continually being made which make changes in basic ideas regarding plague epidemiology necessary. A case in point was the discovery in July, 1968, of plague in the introduced fox squirrels (Sciurus niger) within the city limits of Denver, Colorado. Tree squirrels had not previously been implicated with plague in the United States, but, in epizootiological investigations following a human case derived from contact with these animals, P. pestis was diagnosed in more than 80 squirrels by isolation and fluorescent antibody techniques and also in the fleas (Orchopeas howardi) infesting them. Incidence rates were 15-20% among the several hundred animals captured or found dead during the summer and approximately 70% of the survivors were seropositive (U.S. Public Health Service, 1968: personal communication, A. M. Barnes, NCDC, Ft. Collins, Colo., July 1969). These findings point up the potential for plague to become established in the eastern United States where it has never been detected but where these tree squirrels are native and abundant.

Whereas it is generally felt that the original home of P. pestis was in central Asia, or in Africa, the question of how it arrived in North America and became established as an enzootic disease among wild rodents in the western U.S. is subject to some controversy. It appears from the chronology of the statistics of discovery in the various western states that after an original introduction into west coast seaports by plague-infected, ship-borne Rattus spp. and their fleas, an initial commensal rat phase eventually led to wild rodent infection followed by spread in an eastward direction (Eskey and Haas, 1940; Link, 1955). Other observers (Meyer, 1947) feel that it entered with wild rodents across the Siberian-Alaskan land bridge from central Asia and thus has been a naturally associated ecologic factor since the Pleistocene. Pollitzer (1954) discusses the merits and shortcomings of each theory but does not feel that a conclusion can be made.

That plague is still a significant disease of humans is revealed by the fact that in 1967 there were 5,574 suspect and bacteriologically confirmed cases in South Vietnam, these being due to contact with commensal rats and their fleas (WHO, 1967); authorities estimate the actual number of cases, however, to be closer to 25,000 (personal communication, Col. Ralph Singer, U.S. Army Chief Preventive Medicine Officer, July, 1969). Although in the U.S. a case of human plague acquired from commensal rats has not been recorded since 1924, from 1908 through 1967 there were 119 cases of plague, 66 of which were fatal, contracted from wild rodents or rabbits (Kartman et al., 1966; U.S. Public Health Service, 1966, 1967). This low case-rate belies the fact that there is still a potential danger to public health in this country since each bubonic plague victim runs the risk of developing the pneumonic form of the disease with the hazard of aerosol

SYLVATIC PLAGUE

DISTRIBUTION OF PASTEURELLA PESTIS INFECTION IN WILD RODENTS AND FLEAS



1908-1968

Areas found NEGATIVE

Areas found POSITIVE

spread to all of those with whom he comes in contact. This particular aspect of plague has recently been explored by Kartman et al. (1966) and Hubbert et al. (1966).

Although there exists a vast literature dating back to 1500 B.C. on human plague infection, this phase has been largely ignored here and the major emphasis directed to the various manifestations of plague in wild rodents. Since sylvatic plague represents an independent epizootiologic entity from that affecting commensal rats, "classical" rat plague involving Rattus spp. and the rat-flea Xenopsylla cheopis was not discussed to any extent; this is quite thoroughly covered by Pollitzer's monograph (1954) and other standard references dealing with commensal rats such as U.S. Public Health Service (1949) and Calhoun (1963). Space limitations prevent more than a cursory examination even of those topics which are discussed in this account. The following are suggested as basic references for those commencing work on plague or who wish additional detail: Hirst (1953); Pollitzer (1954); Kartman et al. (1958); Pollitzer and Meyer (1961); Meyer (1963); Pan American Health Organization (1965); Kartman et al. (1966); and Stark et al. (1966). In each year's July issue of Tropical Diseases Bulletin is a summary of the previous year's abstracts of papers dealing with all aspects of plague.

Etiology

A vast amount of detail concerning the morphological and growth characteristics, biochemical properties, resistance, virulence, toxins and antigenic structure of P. pestis has been summarized by Pollitzer (1954, 1960) as well as by Meyer (1965). Here only certain aspects of the organism's characteristics which are basic or of special signigicance will be touched upon.

Plague bacilli are Gram-negative, non-motile, bipolar-staining, ovoid rods, 0.5-0.8 microns wide by 1.0-2.0 microns long in the parasitic stage but characterized by a wide variety of pleomorphic forms especially from tissues. These organisms grow readily but slowly on ordinary culture media, becoming visible in 24-48 hours at an optimum temperature of 28°C.

Particularly when cultured at 37°C, P. pestis is surrounded by an envelope which contains the non-toxic but highly antigenic Fraction I antigen which is believed to protect the cells against phagocytosis (Baker et al., 1952). Pesticin, V, W, and other antigens are elaborated under certain cultural conditions and also seem to be associated with prevention of phagocytosis or the ability to survive and multiply within phagocytic cells. The organism also produces an endotoxin; it is felt that liberation of this toxin from lysed cells is the ultimate cause of death in infected animals producing effects on the peripheral vascular system which cause hemoconcentration, shock, and parenchymal injury in the liver and kidneys (Rust et al., 1963). The highly variable virulence of wild strains of P. pestis is related, among other factors, to the ability to produce certain of these antigenic factors. To be fully virulent, a strain must be highly toxigenic,

capable of producing the V and W virulence antigens and the FI envelope antigen, able to synthesize purines, and form pigmented colonies on defined media containing hemin (Burrows and Bacon, 1956; Pollitzer, 1960; Meyer, 1965). Other biochemical factors which relate to virulence are discussed by Surgalla (1960) and Brubaker et al. (1965).

The plague bacillus is susceptible to streptomycin, tetracycline, chloramphenicol, and certain other antibiotics but is insensitive to penicillin. It is generally considered a fragile organism since it can be killed readily by exposure to moderate heat, a variety of chemical agents and sunlight. It is also readily killed by drying except when protected by organic material. In the latter case P. pestis has remained viable in dried sputum for three months, dry flea feces held at room temperature for five weeks, and, of potential epizootiological importance, in soil for at least eight weeks and in uninhabited deep rodent burrows for seven to eleven months in cold climates (Baltazard et al., 1963; Meyer, 1965; Goldenberg and Kartman, 1966).

The closely related P. pseudotuberculosis resembles P. pestis in many respects and has caused problems in diagnosis. Fully specific serologic tests are difficult due to the large number of antigens shared by the two organisms. Differentiation is made on the basis of growth rates in culture, motility, characteristic pathology in laboratory animals, phage lysis, biochemical tests, and fluorescent staining (Baltazard et al., 1956; Quan et al., 1965; Goldenberg, 1968), as is shown in the accompanying table taken from Stark et al. (1966).

Transmission

Although a variety of arthropods other than fleas have been found naturally infected with plague bacilli or have been shown to be susceptible to laboratory infection, none are thought to play a significant role as vectors (Pollitzer, 1954; Pollitzer and Meyer, 1961). On the other hand, the indispensibility of the flea as a vector in the basic sylvatic plague cycle has been universally acknowledged.

The classic biological transmitting mechanism is that involving the "blocking" phenomenon. Fleas feeding upon a septicemic host ingest P. pestis which then undergo multiplication within the stomach. After a variable length of time the proventriculus becomes plugged with a mass of the bacilli and the flea is said to be blocked. In such a state, since blood cannot pass to the ventriculus, the flea becomes starved and avidly seeks a blood meal. In its attempt to feed, blood filling the esophagus and containing bacteria dislodged from the blocking mass is forced back into the bloodstream of the host due to the elastic recoil of the esophagus walls. There are a number of variations from this general description characterizing different flea species and also a great deal of variability as to whether or not blockage occurs at all, length of time before blockage occurs, etc.

DIFFERENTIATION OF *PASTEURELLA PESTIS* AND *PASTEURELLA PSEUDOTUBERCULOSIS*

Reactions	*P. pestis*	*P. pseudotuberculosis*
1. Motility 20°C	–	+
35°-37°C	–	–
2. Capsule or envelope	+	–
3. Growth	Slow (24-48 hours)	Vigorous (24 hours)
4. Hemolysis on blood agar	–	–
5. Lysed by Phage * 25°C***	+	–
35°-37°C	+	+
6. Growth on desoxycholate agar – 48 hrs. at 35°-37°***	Small reddish, pinpoint, colonies, few in No.	Many yellow, large, opaque colonies
7. MacConkey's agar	+ Colonies round, pinpoint, clear to translucent (Good for isolation when gram negative and gram positive contaminants are present.)	+
8. Agglutinated with specific anti-plague serum ***	+	Cross reaction may occur if serum not carefully prepared and/or absorbed.
9. Stained with fluorescent antibody for *P. pestis.* ***	+	–
10. Pathogenicity ***	Mice, rats, guinea pigs, rabbits, etc.	White rats – Other rodents +
11. Biochemicals		
a. urea (Christensen) ***	– (but grows)	+
b. nitrates reduced to nitrites	+	+
c. indol	–	–
d. methyl red	+	+
e. rhamnose ***	–	A **
f. glucose	A **	A **
g. mannitol	A **	A **
h. dulcitol	–	–
i. melibiose ***	–	A **
j. sucrose	–	± A **
k. lactose	–	–
l. arabinose	A **	A **

* Samples of phage paper strips are available from San Francisco Field Station, CDC, USPHS, San Francisco, California 94118. Liquid phage preparation may be obtained from Laboratory Branch, Bacteriology Section, CDC, USPHS, Atlanta, Georgia 30333.

** A = acid only.

*** Indicates most useful differential diagnostic tests.

Prepared by : W. B. Cherry, Laboratory Branch, CDC, Atlanta, Georgia 30333

A great volume of literature exists which deals with fleas and flea-plague relationships. Important North American taxonomic works include Hubbard (1947), Jellison and Good (1942), Jellison et al. (1960),and Stark (1958). Lists of fleas which have been shown to be involved with plague naturally and through laboratory experimentation have been compiled by Wayson (1947), Link (1955), Pollitzer (1952, 1954), Machiavello (1954), and Pollitzer and Meyer (1961).

All fleas are not of equal significance in the role they play as vectors. Not only species, but also individuals within the same species exhibit profound differences in their potential and actual importance in plague epizootiology. These differences are based on what may be termed ecological and physiological factors. Some of the known ecological factors are: 1) Host range and specificity as related to whether these hosts are colonial, gregarious or solitary, are burrowing or surface-dwelling, and the degree of septicemia they exhibit following infection; 2) Geographic or distributional range of the flea; 3) Prevalence or density on hosts and seasonal occurrence in relation to periods when plague occurs; 4) Feeding habits and whether predominately a nest or body flea; 5) Resistance to adverse environmental factors including survival time in the absence of a host; 6) Climate and microclimate with their effects on survival, breeding, etc. Physiological factors which influence the ability of fleas to biologically transmit P. pestis include: 1) Proportion which become infected following a meal on a septicemic host; 2) Time between the infecting blood meal and blockage; 3) Whether blockage occurs or not, the proportion which exhibit it, and whether or not it is cleared; 4) Survival time following infection or blockage; 5) Inherent ability to transmit when blocked; 6) Presence of P. pestis antibodies in the blood meal (Kartman et al., 1958; Pollitzer and Meyer, 1961; Kartman et al, 1966; Stark et al., 1966).

Wheeler and Douglas (1945) devised a method which permits comparison of the relative ability of different flea species to transmit P. pestis. The method, as modified by Kartman (1957), combines the results of laboratory transmission experiments and field data into a single numerical value. This value, termed the "flea vector potential", is the product of the infection, blocking, transmission, and blocking-survival potentials, and the field infection and field prevalence indexes. The results of studies employing this technique and of others dealing with the relative plague-transmitting efficiency of wild rodent fleas are found in Eskey and Haas (1940), Wheeler and Douglas (1945), and Kartman et al. (1958).

Studies have shown that few wild rodent fleas are efficient as biological vectors. As opposed to X. cheopis, many such fleas take a much longer time (two or more months) to become infective and some never do block; others do not transmit even when blocked. Also, most wild rodent fleas survive for long periods after infection with some known to harbor P. pestis for over a year (Eskey and Haas, 1940; Pollitzer and Meyer, 1961; Kartman et al., 1966). These and other factors have led some observers to postulate that mechanical transmission may be more important in sylvatic plague epizootiology than previously thought. In this type of transmission, which probably requires the

mass attack of a number of fleas to be effective, fleas which have recently fed on a bacteremic rodent may mechanically transmit the organisms via their contaminated mouth parts. Kartman et al. (1958) suggest that "mechanical transmission by a highly prevalent flea may be the means by which epizootics among wild rodents flare up once they have been initiated by primary vectors that transmit biologically via the blockage mechanism".

The fact that wild rodent fleas are capable of carrying P. pestis for very long periods is a primary reason why most investigators maintain that fleas serve not only as vectors but also as one of the basic mechanisms for the perpetuation of sylvatic plague, especially when in association with microclimatic conditions particularly conducive to long survival such as in deep, cold, rodent burrows (Pollitzer and Meyer, 1961; Stark et al., 1966).

One factor which has been little studied, but may affect the ability of fleas to transmit biologically or have an effect on the virulence of strains is the presence of antibodies to P. pestis in blood meals taken by fleas. Bibikova and Gavryushina (1963) showed experimentally that 45 per cent of fleas fed on plague-immunized gerbils eliminated the infection from their gastrointestinal tract whereas none of those which fed on normal gerbils did. Fleas fed the immune blood meals also had a longer life span and there was some indication that a reduction in virulence of the organisms had taken place.

Epizootiology

Pollitzer and Meyer (1961) commenting on the complexity of plague epizootiology, noted "the infinite variety of manifestations of the disease resulting from the profound differences in hosts, vectors and environmental conditions in different areas". The attempt in this section will be to note some of the ecological factors which foster or inhibit plague, the concepts which have proved useful in clarifying its many manifestations, and the mechanisms now believed responsible for perpetuation of P. pestis.

A salient and apparently universal feature of sylvatic plague is a localized (focal) and discontinuous distribution; this in itself strongly suggests that an interaction of host and environment largely dictates where plague is found. The habitats in which it occurs and the animal species involved, however, vary tremendously. In the western U.S. alone, sylvatic plague is maintained in desert and grassland communities, mountain meadows, rock ledges, and fringes of cultivated areas (Eskey and Haas, 1940) and involves such diverse wildlife as ground squirrels, wood rats, prairie dogs, chipmunks, marmots, lagomorphs, deer-mice, and voles.

An attempt was made nearly thirty years ago to reduce this apparently bewildering complexity to a common denominator for plague and a number of other zoonoses by Pavlovsky (1966) in his concept of the "natural nidality" of disease. This proposes that plague has a natural focal localization within well-defined geographic areas where the pathogen, vectors and hosts form an ecological association in which,

because of certain factors favorable for long-term survival, the organism can circulate for an indefinite period of time. Here, although epizootics can occur, plague is usually present in a smoldering enzootic form. The interpretation of what constitutes a focus of plague varies with different authors (Stark et al., 1966), but it is probably best thought of as the specific ecological unit in an area where the true reservoiring mechanism perpetuates the organism during interepizootic periods and thus would not include the often much larger area in which plague might be active during an epizootic. In actuality, the term is often used much more broadly to include any area where plague evidence is detected due to the difficulty of delimiting actual boundaries which in themselves may be flexible with time.

In general, conditions favorable for an epizootic of plague are, in addition to the presence of P. pestis of sufficient virulence to cause infection, a dense population of susceptible rodents which, upon infection develop a bacteremia, combined with a high index and infestation rate of fleas which are efficient transmitters of the bacillus. But even when these requirements are fulfilled, the disease may not reach epizootic proportions because of the delicate balance between the enzootic and epizootic state. We are actually dealing with a complex interaction of host and parasite within the framework of the environment, creating a dynamic equilibrium wherein minor changes in any of a multitude of influencing factors can tip the balance one way or the other. Some of these factors have been mentioned during the discussion of transmission. Others known or suspected to be influential in plague epizootiology are: The species, subspecies or population of hosts involved, and the age and sex structure of same; the behavior characteristics of the hosts (degree of sociality, social status within the population, tendency toward and frequency of interspecific contacts); nutritional status with regard to both qualitative and quantitative aspects; movements, mobility or size of home range of hosts; breeding periods, number of young produced, rate of population turnover; fidelity or ubiquity in restriction or choice of habitats and the faunal richness or species diversity of the habitat.

While plague among commensal rats is invariably self-limiting (Pollitzer and Meyer, 1961), long-term persistence among wild rodents has been observed by workers all over the world. For instance, Meyer and Eddie (1938) recovered infected ground squirrel fleas from the same burrow systems where diseased ground squirrels were found 20 years prior and suggested that sylvatic plague probably persists indefinitely in an area once it has been invaded.

There seems to be consensus that four basic mechanisms are involved in the interepizootic survival and maintenance of P. pestis in natural enzootic foci: fleas, soil, hibernating rodents, and association of rodents with a spectrum of susceptibilities to infection. Not all may be operative in any one focus or are all of equal importance.

As was noted previously, in may situations fleas are thought to be very important reservoirs as well as vectors due to certain characteristics of wild rodent fleas, especially their ability to retain infection for long periods of time.

Relatively recent findings in France and Iran (Baltazard et al., 1963) as well as in the U.S. (Goldenberg and Kartman, 1966) indicate that, under the influence of certain microclimatic conditions, the soil itself may serve as a reservoir. It was found that the organism remained viable in soil within unoccupied burrows for many months and could be transmitted to animals coming into contact with this substrate. A hypothesis was forwarded that the remains of dead rodents and fleas and their feces provide the necessary organic material to allow survival of P. pestis in deep burrows. This mechanism needs much more investigation before its importance can be assessed, but it is probable that a good potential exists in limited areas where climatic conditions are particularly favorable.

That hibernating rodents may play a role in carrying infection over the winter season was long ago hypothesized and subject to investigation by workers in several countries (Pollitzer, 1954). In various marmots, susliks, and ground squirrels it has been found that if they were infected just before or during the period of torpidity, the infectious process was radically changed, with time to death much prolonged and resistance markedly increased. In many cases the hibernating rodents showed no signs of disease until four months later when emerging from hibernation, at which time they sickened and died of typical plague infections. Investigators in the USSR have demonstrated that resistance to plague infection increases in active rodents as the time for hibernation nears (Pavlovsky, 1966). While this mechanism is undoubtedly of significance in some plague foci, it is not necessarily essential since there are many areas of entrenched sylvatic plague where hibernating rodents are not part of the community.

Seemingly, the most universal of reservoiring mechanisms is that dependent upon the presence in a focus of individuals of varying susceptibility to plague and the circulation of the organism among them (Pollitzer and Meyer, 1961; Baltazard, 1960; Kartman et al., 1966). The majority of workers (e.g., Eskey and Haas, 1940) up until the 1950's believed that the primary reservoirs of plague were those species, such as prairie dogs and ground squirrels, which exhibited widespread epizootics and that the occasional finding of P. pestis in native mice represented side-links in the basic transmission chain. An epizootic among such species, however, often results in a rather complete die-off (Lechleitner et al., 1962) or decimates the population to the point where plague becomes quiescent or absent. Such is not the type of non-destructive, balanced host-parasite relationship which usually evolves between an organism and its maintenance hosts. Neither, however, is the relationship exhibited between plague and completely refractory hosts, since the organisms contacting such hosts meet a dead end because their defense mechanisms do not permit development of a bacteremia which is essential for transmission. Such species may only be indirectly involved in plague perpetuation by providing maintenance blood-meals for fleas or by serving as transporters of infected fleas to other susceptible rodents.

Some of the earlier workers in this and other countries had noted differences in the relative susceptibility to infection of different populations of the same species of rodents (McCoy, 1911; Meyer, 1942; Pollitzer, 1954). Relatively recent studies quantitatively assessing

the susceptibility of 32 species of native rodents from such widespread geographic areas as New Mexico, Washington, California and Utah have confirmed that such differences do exist (Holdenried and Quan, 1956; Bacon and Drake, 1958; Quan and Kartman, 1962; Marchette et al., 1962b). These and earlier qualitative studies, summarized in Marchette et al. (1962b), demonstrated not only species variations in susceptibility and differences with regard to sex, age, and season, but also differences in the same kind of animals depending upon whether they were from areas with or without a previous history of plague. The greater resistance of individuals from populations with previous plague exposure is not believed due to active immunity but rather to evolutionary change resulting from natural selection (Quan and Kartman, 1962). Another important result of these susceptibility studies was the typically heterogenic response noted among individuals of equivalent experimental groups of animals. Such variation was interpreted by Quan and Kartman (1962) to indicate that the relative susceptibility of populations cannot be applied to individuals and as a result, there will be many resistant individuals in a susceptible population and vice versa.

As a result of the foregoing, emphasis with regard to which rodents constitute vertebrate reservoirs has shifted to those which are resistant to the disease but susceptible to infection with P. pestis (Baltazard, 1960). In such animals an epizootic could and actually has been shown to sweep through a population without producing clinical disease or excessive mortality and would go completely undetected unless surveys were continually being made and serological methods used in the diagnosis (Kartman et al., 1962; Goldenberg et al., 1964). These animals, typified by some species of Peromyscus and Microtus in the U.S., while responding with an asymptomatic infection, usually have a transient bacteremia and thus could infect fleas even though their effectiveness in this regard would be less than in rodents dying with a teminal septicemia. Whereas persistence of P. pestis in the organs of these partially resistant animals for periods of up to five weeks after experimental infection and in the field during interepizootic periods has been demonstrated, the significance of this "latent" form of the disease in perpetuation of the organism or in transmission is not clear; only if the bacilli eventually escape the organs and invade the bloodstream would it have this potential importance (Meyer et al., 1943; Evans et al., 1943; Holdenried and Quan, 1956; Marchette et al., 1962b; Quan and Kartman, 1962).

It is noteworthy that Payne et al. (1955) as well as other investigators (cited in Pollitzer 1960) found a significant depression of resistance to infection by P. pestis in laboratory rats and mice following injection of cortisone or adrenocorticotropic hormone. Death or a generalized infection was observed even from P. pestis strains of very low virulence. These findings may have epizootiological significance in relation to stress induced in wild rodent populations either by adverse environmental factors or sociopsychologically by pathways described by Christian and Davis (1964).

Within a natural focus of plague, survival of P. pestis is now generally viewed to depend upon the commingling of rodent species of different susceptibilities and/or of individuals with heterogenic

responses withing a given species (Pollitzer and Meyer, 1961; Kartman et al., 1966). The more resistant individuals infect and maintain fleas and through ectoparasite exchange infect susceptible individuals or commensal species; the latter, even though they may succumb, continue the chain by adding to the infected flea population. When the density of susceptibles rises above a certain threshold and other influencing factors are favorable, an epizootic may occur and reduce their numbers; after it has terminated, the infection continues to smolder in the enzootic state in the resistant survivors. A rather clear-cut actual field situation in which this mechanism is illustrated by a close association of several animal species of variable susceptibilities with transfer of infected fleas from one to another in a mesquite community in southeast New Mexico is described by Kartman (1960).

Peromyscus maniculatus is a prime example of a rodent species which is capable of acting in this reservoir capacity (Marchette et al., 1962a). In addition to its partial resistance to plague, this species is characterized by a wide geographic distribution, is ubiquitous throughout many habitat types, and is commensal with a variety of other rodent species. Hudson and Kartman (1967) feel that from the consistency with which seropositives are found in this species from many areas, it could be used as an "indicator animal", but they also warn that negative serological results obtained during a one-month or one-season sampling period should not be considered evidence that P. pestis is absent.

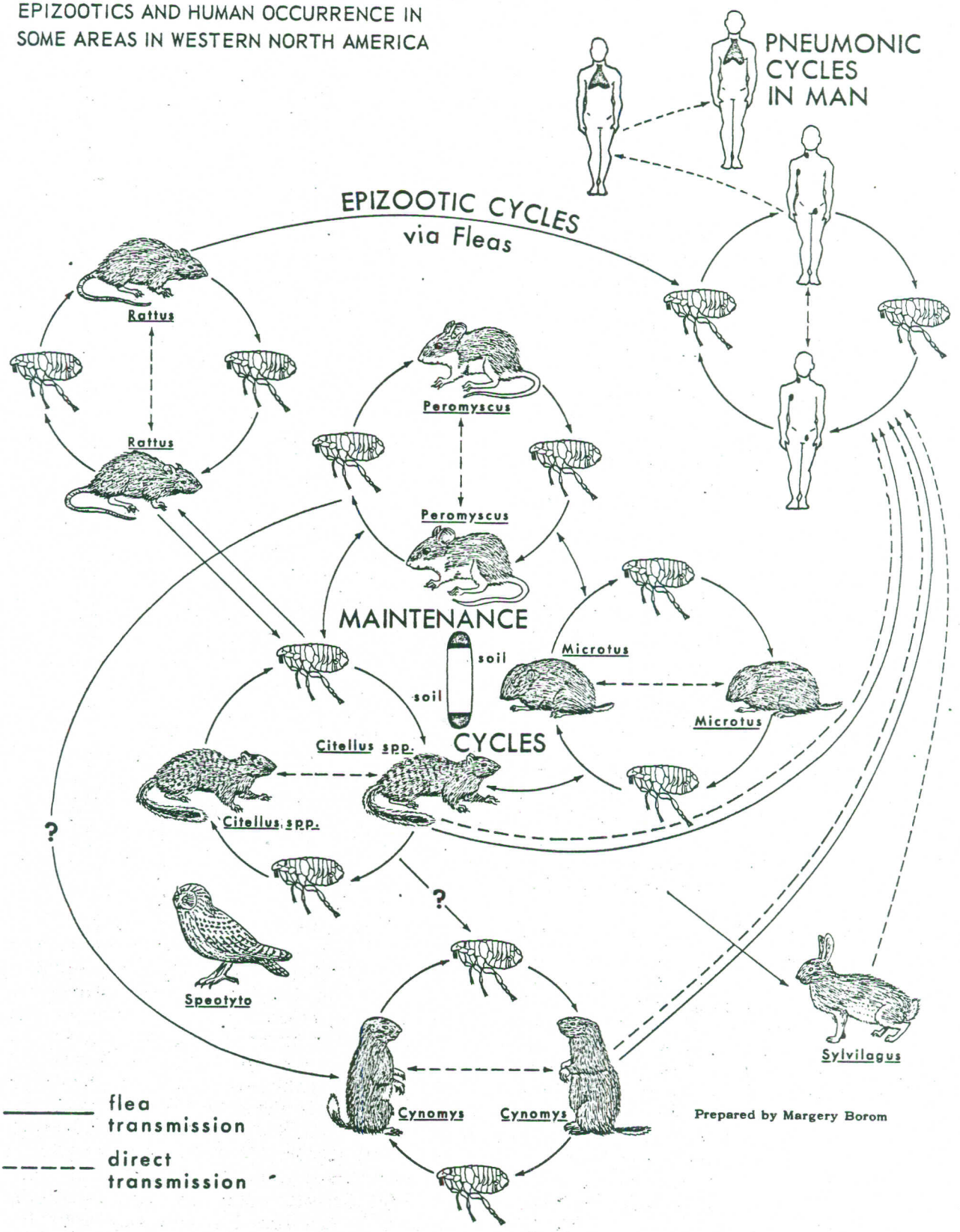
Kartman (1960) aptly sums up the situation concerning which of the reservoiring mechanisms may be operative or more important in a given focus as follows: "In sylvatic plague, mechanisms observed in epizootics cannot be generalized since each focus of the disease constitutes an independent phenomenon and must be investigated as a relatively unique situation...Besides variations in the basic factors,... significant differences may occur in the mechanics of sylvatic foci which influence the survival and transmission of the disease in modes peculiar to the given locality at a particular time."

Stark et al.(1966) have attempted to summarize the primary factors involved in plague epizootiology in some areas of the western United States and show the relation between maintenance cycles, epizootics, and human occurrence in the illustration which is reproduced here.

Signs, Pathogenesis and Pathology

Relatively few descriptions of the pathological changes which take place in wild rodents infected with plague have been published. Pollitzer (1960) summarizes the available information for the Asian tarabagans, susliks and gerbils and certain of the South American and South African rodents as well as giving detail of the findings in commensal rats and laboratory animals. Pseudotuberculosis and tularemia are two rodent diseases which might be most readily confused with plague. The gross pathology resulting from both natural and experimentally induced cases in what may be considered a "typical" species of highly susceptible North American rodent, Citellus beecheyi, has been described by McCoy (1911).

RELATION BETWEEN MAINTENANCE CYCLES, EPIZOOTICS AND HUMAN OCCURRENCE IN SOME AREAS IN WESTERN NORTH AMERICA



Prepared by Margery Borom

McCoy classified the gross pathology observed upon necropsy into three categories: 1) Acute plague - squirrels dying in from three to five days with one or more hemorrhagic buboes and an enlarged spleen but no macroscopic lesions in the internal organs; 2) Subacute plague - animals in which death occurred at six days or later with caseous buboes without evidence of surrounding hemorrhage and usually with pinpoint, nodular necrotic foci of the spleen, liver or lungs; 3) Residual (resolving) plague - ground squirrels killed two to three weeks following infection in non-lethal cases typically had one or more enlarged lymph glands containing yellow purulent foci. McCoy called attention to the fact that the lesions of plague are generally quite constant in laboratory animals, but, in contrast, there is marked diversity, especially in the subacute and resolving form, in the pathology observed among the ground squirrels.

McCoy felt that the variations in pathology reflected variations in the resistance of individual animals and of populations. This has since been confirmed and workers throughout the world have reported finding an "inapparent" or "latent" form of plague in a variety of species of naturally infected wild rodents characterized by the absence of gross lesions, negative results of direct bacteriological examination, but positive experimental results with the organs of these animals (Pollitzer 1954). Such asymptomatic infections are now believed to be far more common than perviously thought, especially among resistant populations of normally susceptible species or among individuals of species which are typically resistant.

Microtus californicus has been especially well studied in this respect. This species is susceptible to invasion of the organism and its establishment in tissues but usually does not sicken or succumb either in nature or to the experimental inoculation of large numbers of plague bacilli. Although serological positives may approach 100 per cent in a population, few isolations by either culture or animal inoculation techniques may be made (Goldenberg et al., 1964; Hudson et al., 1964; Hudson and Kartman, 1967). It is known that the bacilli persist in Microtus for short periods and may resolve into inapparent infections, a situation which has also been noted in other rodent species as well; in some of these species, however, tissue persistence is quite prolonged (Meyer et al., 1943; Evans et al., 1943; Holdenried and Quan, 1956). Goldenberg et al.(1964) state that the bacilli, after introduction by flea bite, are taken up by the lymphatics, carried to the regional lymph nodes and then to the viscera; after multiplication in these organs the bacteria appear in the blood. Their isolations of P. pestis from the blood and blood-filtering organs in Microtus indicate that there is a period of bacteremia. Thus, even in animals with asymptomatic infections, a sporadic or transient bacteremia may provide an opportunity for fleas to become infected (Quan and Kartman, 1962). It has been found, however, that some species of resistant rodents, e.g., Peromyscus maniculatus from Utah, often die without a detectable bacteremia (Ecology and Epizoology Research, 1963).

Diagnosis

Until 1935, laboratory diagnosis of plague in wild rodents generally consisted of necropsy with confirmation of gross lesions by microscopic and cultural methods and by inoculation of tissues into guinea pigs. It was not until 1936 that triturated fleas collected from survey animals were routinely inoculated into laboratory animals (Eskey and Haas, 1940; Link, 1955).

It is impossible to go into all the many facets of plague diagnosis. For additional detail consult: Baltazard et al., (1956), Pollitzer (1954, 1960), American Public Health Association (1963), Stark et al. (1966), and Goldenberg (1968). A flow diagram for the isolation and identification of the plague bacillus from animal specimens taken from Stark et al. (1966) is illustrated in the accompanying figure.

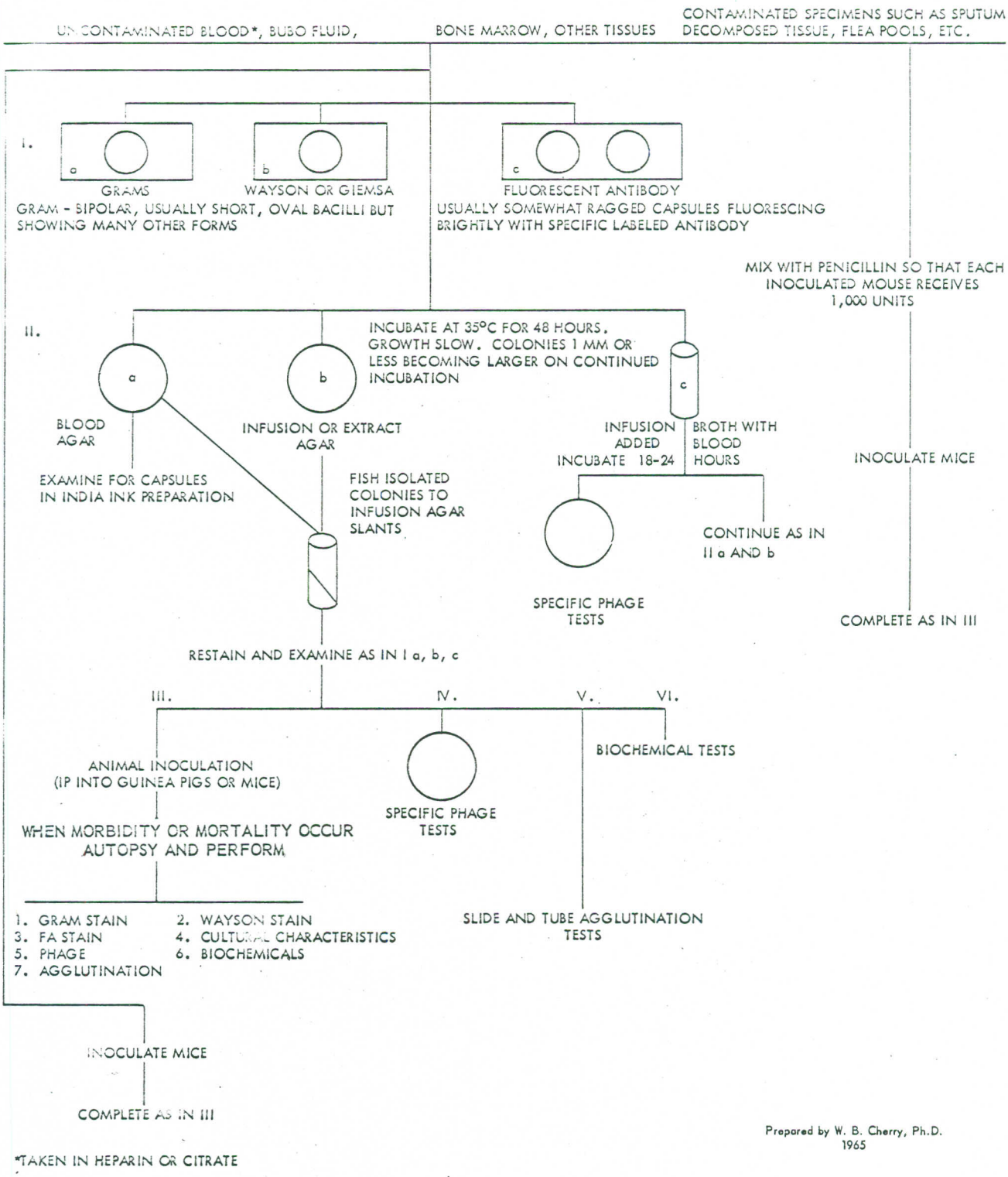
General diagnostic methods include: culturing of suspect tissue at 25-30°C on blood agar at pH 7.2 or in infusion broth at pH 7.4, microscopic examination of isolated organisms using Gram's and Wayson's stains, biochemical tests (carbohydrates, urea, desoxycholate-citrate, hydrogen sulfide and indole production, methyl red and methylene blue reduction), specific phage lysis at 25°C, motility tests at 20°C, staining of heat-fixed smears by fluorescent antibody anti-*pestis* globulin, and subcutaneous inoculation of tissues into white mice and guinea pigs.

Although equally susceptible, these two laboratory animals differ in their responses to the endotoxin of the plague bacillus and thus react differently. The mouse, being much more susceptible to the toxin, dies rapidly with large numbers of organism in the tissues but little or no gross pathology. The guinea pig, however, will survive several days longer after being inoculated with the same dose which would kill a mouse overnight; during this time interval pathognomonic changes develop which are characteristic: marked infiltration at the site of inoculation, edematous and hemorrhagic buboes in regional lymph nodes, enlargement of the spleen and liver with both organs often having yellowish, pinpoint, necrotic nodules, and lungs with congestion or areas of consolidation. Death ordinarily occurs in 3-7 days. Smears and impression films made from the heart-blood, spleen, liver and buboes of inoculated guinea pigs usually show great numbers of plague bacilli. The isolation of strains of *P. pestis* which are avirulent for guinea pigs but fully virulent for certain of the native local rodent species (Ecology and Epizoology Research, 1963; Marchette, 1963) suggests that the latter may be of value as laboratory animals for the isolation of such strains which may be overlooked in a routine survey when only guinea pigs are employed.

The decayed or mummified carcasses of animals found during field investigations can be tested for the presence of *P. pestis* by use of a modified Ascoli (precipitin) test (Larson et al., 1951) or fluorescent antibody staining techniques (Hudson et al., 1962; Stark et al., 1966). Bone marrow is a useful source of material in such cases.

Goldenberg et al. (1964) have shown that animal inoculation is approximately three times more efficient than bacterial culture in

FLOW DIAGRAM FOR ISOLATION AND IDENTIFICATION OF PLAGUE BACILLUS FROM ANIMAL SPECIMENS



Prepared by W. B. Cherry, Ph.D.
1965

obtaining isolations from Microtus tissue and found that approximately 25,000 viable organisms per gram of tissue was the minimum concentration detectable by cultural methods. A similar superiority of animal inoculation techniques has also been shown in detecting plague bacilli in fleas (Quan et al., 1958).

It has only been within the last five to ten years that highly sensitive and specific serological methods have been employed with confidence in the retrospective diagnosis of P. pestis infection in wild rodents and in detecting natural foci of plague activity. These methods have taken on added importance in view of the difficulty of organism isolation from the relatively resistant rodents now believed to be of primary importance in the maintenance of P. pestis. Recent investigators have had considerable success employing the complement fixation and passive hemagglutination tests (Cavanaugh et al., 1965; Hudson and Kartman, 1967). Both of these tests employ the Fraction I envelope antigen, recently evaluated by Chen (1966), prepared according to the method of Baker et al. (1952) and have been adapted to microserological techniques so that as little as 0.05 ml or less of serum is required. The majority of investigators feel that the hemagglutination test is superior to the complement fixation test on the basis of sensitivity, ease of performance, and the fact that the frequent occurrence of anti-complementary activity in wild rodent sera often presents difficulties in the complement fixation test. It also has an advantage in detecting enzootic areas since the antibodies detected are more persistent than those determined by complement fixation; the latter appear earlier and disappear more quickly and are thus more indicative of recent infections (Cavanaugh et al., 1965; Hudson and Kartman, 1967; Hudson et al., 1964).

Hudson et al. (1964) using the passive hemagglutination test, found positive reactors in from 65 to 100 per cent of the Microtus californicus trapped during successive plague epizootics on a California study area and present data on average titers, antibody persistence, seasonal incidence and serological histories of individual animals. Although this test is quite specific, it is not absolutely specific since antigens of certain P. pseudotuberculosis strains may give cross reactions (Quan et al., 1965). Hudson and Kartman (1967) caution that it is necessary "to examine serological results in the light of known background information concerning the susceptibility of the animal species involved, the previous history of a given area with respect to the occurrence of plague, and concurrent isolation of P. pestis from host and vector populations".

It was previously noted that Peromyscus maniculatus might serve as a sentinel or indicator animal for the presence of plague in an area. Dogs and other carnivores, considered highly resistant to plague, may serve this same function. During the 1965 plague outbreak among prairie dogs on the Navajo Indian Reservation in New Mexico, 13 of 27 dogs tested gave positive results with the passive hemagglutination test; seropositive dogs were associated with four of the human cases in this outbreak (Kartman et al., 1967). The only evidence of plague activity in connection with a fatal human case in southeast Utah during 1966 was the finding of positive titers in two of the family dogs (Ecology and Epizoology Research, unpublished data, 1966).

Hudson and Kartman (1967) note that three of four dogs associated with a human case in Arizona during 1963 had positive titers as did dogs from their California plague study area where Microtus were primarily involved.

Control

With enzootic plague firmly entrenched in wild rodents over vast areas, control measures are ordinarily undertaken only as emergency steps with limited objectives in those situations where a high potential exists for transfer of P. pestis from sylvatic sources to humans or where a sentinel human case has occurred. In such instances a program combining medical surveillance, publicity and education, flea control, and rodent suppression is most likely to achieve the desired results.

Control measures have almost invariably been directed at the conspicuous, highly susceptible epizootic hosts of the disease such as ground squirrels, marmots, chipmunks, etc. Such efforts, even if successful, do not lead to elimination of plague from the area, since these animals are not the ones involved in the maintenance function. These efforts can, however, lead to a reduction in the potential for human infection since it is these epizootic hosts rather than the enzootic reservoir mice which have been the principal sylvatic sources of human infections (Murray, 1964).

In general, measures taken to reduce the human plague potential in an area should be directed against the flea vectors as well as against the vertebrate hosts; flea control itself has become an important technique in combatting plague by interfering with or breaking the normal rodent-flea-rodent transmission chain. If rodent control alone is practiced, the situation may be made worse since large numbers of hungry fleas may remain which potentially could shift from their normal hosts to man or which would attack new rodent hosts as soon as they immigrated into the area; under conditions of high population pressure this might be an immediate influx.

In relatively small areas of high human exposure such as campgrounds and National Parks, the insecticide-bait-box method (Barnes and Kartman, 1960) of reducing flea infestations on rodents has been effectively employed. The bait-box consists of a board, heavily covered with 10 per cent DDT dust or 5 per cent malathion dust, baited with a pan of rolled oats or other attractants in the center, and covered with a tin roof for protection from the weather. Rodents can enter from either end, become dusted with the insecticide and carry some back to their burrows, thereby reducing both body and nest fleas.

For larger areas, 5 per cent malathion at 0.5 pounds per acre, 10 per cent DDT, or other residuals such as dieldrin, aldrin, heptachlor or benzene hexachloride may be applied by direct dusting of burrows with hand dusters or area application of the insecticides from aircraft or vehicle-mounted power dusters may be effective (Ryckman et al., 1953, 1954; Miles and Wilcomb, 1953). Rodent control, when deemed necessary, preferably immediately following or concurrent with flea

control, can be achieved by a variety of methods including fumigation of individual burrows with carbon bisulfide or hydrocyanic gas or burrow or area application of bait containing sodium fluoroacetate ("Compound 1080") or other poisons.

The published accounts of the tremendous efforts put forth to eliminate or control sylvatic plague over vast areas in the USSR by exterminating rodents and fleas in zones where natural foci exist have recently been compiled and reviewed by Pollitzer (1966). The unsuccessful attempts in the early 1900's to eliminate plague by eradication of ground squirrels in California are described by Link (1955). Murray (1964) has reviewed the current philosophy of plague suppression in California which embodies a flexible program of rodent and/or flea control based upon zoning of the state according to degrees of epizootic hazard. Tirador et al. (1967) have described the considerations and the methods used to reduce the plague potential during a 1965 outbreak among prairie dogs associated with six human cases on the Navajo Indian Reservation in New Mexico.

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SUMMARY OF UTAH PLAGUE INVESTIGATIONS

1969 (?)

The first evidence of plague in Utah came to light as the result of a human case acquired in July, 1936, from contact with a ground squirrel about 10 miles north of Beaver City in the south-central portion of the state. U.S. Public Health Service survey teams isolated Pasteurella pestis from Spermophilus variegatus, Marmota flaviventris and their fleas from this area. A State of Utah field survey unit traveled over the state in 1937 sending fleas to the U.S. Public Health Service Plague Laboratory in San Francisco. Intermittant surveys were conducted in Utah by Public Health Service survey teams until 1949 when field surveys for locating plague were abandoned in favor of ecological studies of plague (Stark, 1958). Implicated in these surveys were primarily those rodents lethally susceptible to plague such as S. variegatus, S. armatus, M. flaviventris, Cynomys sp., and Neotoma lepida as well as their associated fleas. This work was summarized in a paper by Allred (1952) in which he also studied the distribution of some fleas known to be capable and potential vectors of plague in the State.

In June, 1948, the Vector Control Branch of the U.S. Public Health Service Communicable Disease Center initiated a rodent control and plague investigation project in Salt Lake City. This work, which consisted essentially of rat control based on sanitation, inspection, vent-stoppage, etc., continued in north-central Utah for almost two years. Exploratory surveys were made to determine whether or not plague was present in the area, the nature of the infection and probable danger to humans. A great deal of information was gathered regarding host-flea records and plague was demonstrated to exist close to human habitation centers just outside of Salt Lake City. Some evidence was found of intermingling between rat and ground squirrel populations in certain localities. This work was summarized in an unpublished manuscript by Myklebust et al. (1950).

In 1950, a Public Health Service grant was made available to Dr. D. Elden Beck, Brigham Young University, for a study to determine distribution, life histories, host preferences, etc., of plague vectors in Utah. This resulted in a publication (Beck, 1955) reviewing the plague situation and containing many charts and distribution maps of fleas.

Stark (1958) published the most comprehensive treatise on plague in Utah, dealing not only with the taxonomy, distribution and host relationships of fleas, but reviewing all previous work pertaining to fleas and plague in the state, and discussing the medical importance, ecology and epizootiology of plague as well. On the basis of the data collected to that time, Stark speculated that since isolations of P. pestis in Utah were confined to the main north-south mountain ranges at 6000 feet elevation and above, this distribution might be indicative of some of the ecological requirements for the existence of plague in the state.

In 1951, the U.S. Army Chemical Corps, Medical Investigation Division, Wildlife Branch, initiated a study of diseases of the fauna native to the area on and around Dugway Proving Ground in the Great Salt Lake Desert region of western Utah. The University of Utah, Ecology and Epizoology

Research, became involved as a contractor in 1952. The first years of this study were primarily concerned with basic ecology; some disease survey work was done with tissues and ectoparasites being tested for P. pestis by the San Francisco Plague Laboratory of the U.S. Public Health Service. The year 1954 marked the beginning of a comprehensive survey of the wildlife of the area for a number of zoonoses including plague. From 1954-57, the University sent all specimens to the U.S. Public Health Service Rocky Mountain Laboratory, Hamilton, Montana, for diagnosis; the results of this study, which included an isolation of P. pestis from the tissues of P. maniculatus and another from fleas of this rodent species collected in May, 1957, from Indian Farm Canyon in the Deep Creek Mountains, were summarized by Stoenner et al. (1959).

From September, 1957, to the present, Ecology and Epizoology Research has performed its own diagnostic assays. Serological tests for plague were first instituted in 1961; during this year and 1962 a standard tube agglutination test was run. Starting in 1963 the complement fixation test employing P. pestis Fraction I antigen was routinely employed and has been in use ever since. This year also marked the beginning of a much more systematic plan of sampling the wildlife in the various geographic sub-areas in adequate numbers. Special diagnostic procedures including the use of highly susceptible native rodents to isolate native strains of low virulence, confirmatory serological testing by the passive hemagglutination test, fluorescent antibody testing, individual plating of fleas, etc., have been employed in special study situations.

After the U.S. Public Health Service investigations terminated in 1950, there was little or no effort made by any group to test for evidence of plague in Utah until the U.S. Army-sponsored Ecology and Epizoology Research studies began in 1954. The last isolate made by the former group was in May, 1949, and it was not until May, 1957, that the next evidence of plague was obtained. Since 1954, this project has tested approximately 51,000 mammals plus their ectoparasites for evidence of P. pestis. Of these, the 29,000 mammals collected since 1963 have been tested serologically as well. A total of 89 isolations of the organism, (59 from fleas and 37 from tissues) has been made and 164 positive serological reactors have been detected. No evidence of plague was detected in nearly 4,000 birds tested. All evidence of the occurrence of plague in Utah since 1950, with the exception of the isolate from the 1966 human case in Oljato and the serological evidence from the two dogs associated with this case, have resulted from the efforts of this group.

In addition to surveillance efforts, experimental susceptibility studies of native animals, investigations of the vector-efficiency, ecology and host relationships of fleas, and studies on the basic epizootiology of plague, especially in regard to reservoir species in enzootic areas, have been conducted by Ecology and Epizoology Research. These studies are reported in the following publications: Howell, 1957; Parker, 1958; Parker and Howell, 1959; Marchette et al., 1962a, b; Marchette, 1963; Thorpe et al., 1963; Ecology and Epizoology Research, 1964a, b, 1965, 1966, 1967, 1968, 1969; Cavanaugh et al., 1965; Egoscue, 1966; Olsen, 1967; Johnson et al., 1968; Parker, 1969; and Olsen, 1969.

Although the majority of animals tested by Ecology and Epizoology Research have come from the West Desert region of Tooele and Juab counties, many additional areas have provided animals on a sporadic basis. Among these might be mentioned the Wasatch Front or Salt Lake City area, Curlew Valley in the northwest corner of the state, Bryce Canyon, Oljato, the Logan area, and areas in eastern Nevada and southern Idaho. These samples are ordinarily obtained to provide comparative data on disease incidence rates with our primary study area.

There are certain areas where evidence of plague has been found on many occasions and which have been designated "foci" of plague. The best such example is the Deep Creek Mountains focus in the western part of Juab and Tooele counties. Since 1956 approximately 3000 animals have been sampled from this area and a total of 26 tissue isolations, 48 isolations from fleas and 151 serological reactors have been detected in nine separate locations on both sides of the mountain range in the foothills, canyons and near the peaks at elevations ranging from 5200-8200 feet. The primary species involved are three species of Peromyscus, Microtus longicaudus, Neotoma lepida, and Eutamias dorsalis as well as the fleas Malaraeus sinomus and Opisodasys keeni keeni. Detailed reports on the findings and epizootiology of plague in this area will be found in Marchette et al. (1962b) and in each Annual Summary Review from 1964 through 1968.

Another plague focus is located in Bryce Canyon National Park in the high plateau country of Garfield and Kane counties at 8000-9000 feet elevation. Evidence of plague in Bryce Canyon was first obtained in 1965 and has been found every year since, including 1969, from animals obtained on a one-week trip each September. Here, involvement has been limited almost exclusively to two species of chipmunks, Eutamias umbrinus and E. minimus and their primary flea Monopsylla eumolpi. The significant factor in this focus is that there is a high potential for human involvement in the sylvatic cycle because of the biting habits of this flea and the close association between chipmunks and tourists; the evidence of plague has been from animals and fleas collected at tourist campsites and viewpoints. Detail of the Bryce Canyon investigations will be found in the Annual Summary Reviews for the years 1965 through 1968.

A third area from which several indications of P. pestis activity have been obtained is in Curlew Valley, Boxelder County, in the northwestern corner of the state. Here the involved species were jack-rabbits, Lepus californicus, and P. maniculatus and the flea Epitedia stanfordi. The intriguing aspect of plague ecology here is that the positive animals came from the valley floor communities consisting of shadscale and sagebrush flats at 4750 feet elevation, ecologically typical of many valleys in Utah and five miles from the nearest foothills or mountains. Additional detail of this focus are discussed in the Annual Summary Review for the years 1965, 1966 and 1967.

The 1966 fatal human case of plague occurred near Oljato, San Juan County, on the Navajo Indian Reservation in the Canyonlands country of the southeast corner of Utah under an entirely different set of ecological conditions. This area consists of hummocky, red sandstone desert flatland

at 4850 feet elevation with vegetation consisting primarily of ephedra, greasewood, mesquite, cacti and grasses. No evidence of plague was found in the limited number of wild animals collected here although two of the dogs belonging to the victim's family did possess antibodies. In the 1966 Annual Summary Review there is a detailed discussion of the findings and probable ecology of plague in this area.

Single isolates from tissues or fleas or serological reactors have been found at a number of other sites in Utah by Ecology and Epizoology Research, sometimes from areas which have been surveyed time and again; follow-up investigations have usually not turned up additional evidence. This should, perhaps, not be unexpected, in view of the statement of Quan and Kartman (1962) that, "A population of rodents...in the Western United States, would have to be closely observed for a decade or longer before one could conclude that plague was or was not present". Even when employing sensitive serological tests Hudson and Kartman (1967) caution that "...it is apparent that negative serologic results obtained during one month or season of the year cannot in themselves be used to ascertain whether an area is free from plague".

In the accompanying four tables and two maps, an attempt has been made to compile all the data known relating to plague incidence in Utah.

The first table is a chronological listing of all known flea isolates, tissue isolates and serological reactors and gives information pertaining to the species of vertebrate host, species of flea when involved, and the month, year and location the evidence was obtained. Included is data on 166 serological reactors, 45 isolations of P. pestis from tissues and 64 isolations from fleas.

The next table lists those species of mammals which have been involved with plague in Utah and the number of isolations and serological reactors associated with each species. Involvement has been shown for 24 species including man. Isolations have been made from the tissues of 11 species, positive serological reactors found in 18 species, and 10 are known to have hosted infected fleas. Most of the evidence has been from the three species of Peromyscus, especially P. maniculatus, N. lepida, S. variegatus and E. dorsalis.

The third table lists those flea species from which isolations of P. pestis have been made and includes the host relationship of the infected fleas. At least 11 and possibly as many as 13 species have been found infected with the majority of isolates being from Malaraeus sinomus and Opisodasys keeni keeni infesting Peromyscus.

The final table lists the counties in Utah from which evidence of P. pestis activity has been recorded together with the vertebrate involved, the kind of evidence and the year of initial and most recent evidence. To date, plague activity has been demonstrated in 13 of Utah's 29 counties.

The maps show for the state as a whole and for the primary Ecology and Epizoology Research study area in more detail, the geographic location of plague activity. The lack of evidence in the eastern portion of the

state is felt to reflect lack of investigation rather than any ecological barriers which exclude sylvatic plague from this area. Although this portion of the state was surveyed during the mid-1930's by U.S. Public Health Service teams, the methods in use at that time were relatively insensitive, no serology was run, and the emphasis was on the collection of highly susceptible rather than reservoir species of mammals.

The primary conclusions which can be drawn from the insight into plague ecology which has been gained since 1936 and especially in the last 15 years, is that plague can and does exist in a wide variety of ecological situations and can be supported or maintained by several combinations of rodent-flea complexes. It is not, as was formerly thought, confined to mountainous areas at higher elevations, having been found in sparsely vegetated desert valley floors at elevations as low as 4300 feet as well as through foothill and conifer and deciduous forest communities up to 9000 feet elevation. With regard to the variety of ecological conditions with which sylvatic plague has been associated, Kartman (1960) aptly sums up the situation as follows:

> "In sylvatic plague, mechanisms observed in epizootics cannot be generalized since each focus of the disease constitutes an independent phenomenon and must be investigated as a relatively unique situation...Besides variations in the basic factors...significant differences may occur in the mechanics of sylvatic foci which influence the survival and transmission of the disease in modes peculiar to the given locality at a particular time."

It is our considered opinion that in Utah the distribution of sylvatic plague is much more widespread than has been demonstrated, that its presence cannot be closely associated with a given landscape, and that there are very few areas where plague could not be demonstrated if rodent sampling of sufficient intensity and duration were conducted.

CHRONOLOGICAL LISTING OF ALL KNOWN EVIDENCE OF PLAGUE IN UTAH

Flea Isolate	Tissue Isolate	Positive Serology	Vertebrate Host	Flea Species	Month	County	Elev.	Location
			1936					
	X		Human		July	Beaver	-	10 N.Beaver, Indian Ck. Cyn.
X			Spermophilus variegatus	undet.	July	Beaver	6500	5 E.Beaver, Beaver Cyn.
	X		S. variegatus		"	"	"	14 NE.Beaver, Indian Ck. Cyn.
X			S. variegatus	undet.	"	"	"	" "
X			S. variegatus	undet.	"	Sevier	6700	13 NE.Cove Fort, Clear Ck. Cyn.
	X		Marmota flaviventris		"	Beaver	7000	15 NE.Beaver, Indian Ck. Cyn.
	X		Cyanomys sp.		Aug.	Garfield	6600	5 NE.Panguitch, Marshall Ranch
X			Cyanomys sp.	undet.	Aug.	Garfield	7000	2 E.Hatch
			1937					
X			S. variegatus	undet.	July	Morgan	-	1/2 E. Morgan
	X		Spermophilus armatus		Aug.	Wasatch	-	21 SE. Heber, W.Strawberry Res.
			1938					
X			Neotoma lepida	undet.	May	Kane	5500	11-14 NW Kanab
	X		S. armatus		June	Wasatch	-	S.Strawberry Res.
X			S. armatus	undet.	July	Rich	6440	3 SE. Woodruff
X			S. armatus	undet.	"	"	"	1 W. Woodruff
			1948					
X			S. variegatus	undet.	Sept.	SaltLake	4600	2 S.Heughs Cyn.Wasatch Blvd.
X			Peromyscus maniculatus	Megabothris abantis	"	"	6000	MillCk.Cyn. E.Evergreen Picnic Grnd.
			1949					
X			S. variegatus	Diamanus montanus	March	SaltLake	5200	Heughs Cyn. Gravel Pit
X			S. armatus	Neopsylla inopina Thrassis francisi Opisocrostis tuberculatus	May	Sevier	8600	33 E.Richfield, Fish Lake Rd.

(cont.) Chronological Listing...

Flea Isolate	Tissue Isolate	Positive Serology	Vertebrate Host	Flea Species	Month	County	Elev.	Location
			1957					
X			P. maniculatus	undet.	May	Juab	6200	IndianFarm Cyn. 7SW Callao
	X		P. maniculatus		"	"	"	" "
			1959					
	X		Dipodomys ordii		May	Tooele	4500	Redding Spgs. 7N Callao
			1961					
X			Peromyscus crinitus(4)	Malaraeus sinomus(14)	March-Dec.	Juab	6200	DeepCk.Mtns; IndianFarm Cyn. 7SW Callao
X			Peromyscus truei(3)	" " (9)	"	"	"	" "
X			P. maniculatus(6)	" " (7)	"	"	"	" "
X			P. truei	Opisodasys keeni keeni	"	"	"	" "
X			P. maniculatus(3)	" " " (7)	"	"	"	" "
X			Reithrodontomys megalotis	" " "	"	"	"	" "
X			P. maniculatus	Orchopeas leucopus	"	"	"	" "
X			P. maniculatus	Monopsyllus wagneri	"	"	"	" "
X			P. maniculatus(2)	Histrichopsylla linsdalei(2)	"	"	"	" "
	X		P. truei(3)		"	"	"	" "
	X		P. maniculatus		"	"	"	" "
		X	P. maniculatus(12)		"	"	"	" "
		X	P. truei(5)		"	"	"	" "
		X	P. crinitus(3)		"	"	"	" "
		X	Eutamias dorsalis(6)		"	"	"	" "
		X	N. lepida(4)		"	"	"	" "
		X	Dipodomys microps		"	"	"	" "
		X	Perognathus parvus		"	"	"	" "
		X	Sylvilagus nuttallii		"	"	"	" "
			1962					
X			P. maniculatus	O. k. keeni	Feb.	Juab	6200	IndianFarm Cyn. 7SW Callao
		X	P. maniculatus(43)		Jan.-Nov.	"	"	" "
		X	P. truei(4)		"	"	"	" "

(cont.) Chronological Listing...

Flea Isolate	Tissue Isolate	Positive Serology	Vertebrate Host	Flea Species	Month	County	Elev.	Location
			1962					
		X		P. crinitus	Jan.-Nov.	Juab	6200	IndianFarm Cyn. 7 SW Callao
		X		E. dorsalis(2)	"	"	"	" "
		X		P. parvus	"	"	"	" "
		X		N. lepida(4)	"	"	"	" "
		X		N. cinerea	"	"	"	" "
		X		S. variegatus(3)	"	"	"	" "
			1963					
	X			P. maniculatus(5)	Jan.-May,	Juab	6200	IndianFarm Cyn.
	X			P. crinitus	&" Nov.	"	"	"
		X		P. maniculatus(13)	Nov.-Dec.	"	"	"
		X		P. truei(2)	"	"	"	"
		X		P. crinitus	"	"	"	"
		X		N. lepida(3)	"	"	"	"
		X		P. maniculatus	March	Tooele	5800	Benmore;LookoutPass, 6WNW Vernon
		X		P. maniculatus	"	"	5400	Stansbury; 3N Clover
		X		Ondatra zibethicus	"	Utah	4500	3S American Fork
		X		Lepus californicus	May	Boxelder	4900	Montello; 3NE Tecoma Siding
	X			P. maniculatus	August	SaltLake	5100	Mouth of Mill Ck. Cyn.
			1964					
		X		E. dorsalis	Jan.	Juab	6200	Indian Farm Cyn.
		X		P. maniculatus(2)	Jan.-Feb.	"	"	"
	X			D. ordii	April	Tooele	4400	N.Tip DugMtn. 29SW Easy, DPG
		X		Ammospermophilus leucurus	May	Juab	5000	N.Tip Fish Spgs. Range
	X			P. maniculatus(2)	December	Juab	6300	DeepCk.Mtns;Tom'sCk.Cyn. 6SW Callao
	X			P. truei	"	"	"	" "
		X		P. maniculatus(12)	"	"	"	" "
	X			P. maniculatus(4)	"	"	5600	DeepCk.Mtns; RedCedarCyn.8SW Callao
	X			P. truei	"	"	"	" "
		X		P. maniculatus(9)	"	"	"	" "
		X		P. truei(3)	"	"	"	" "

(cont.) Chronological Listing

Flea Isolate	Tissue Isolate	Positive Serology	Vertebrate Host	Flea Species	Month	County	Elev.	Location
			1965					
		X	P. maniculatus(3)		Jan.	Juab	7000	DeepCk.Mtns;MiddleCyn. 6W Cal' o
		X	P. maniculatus(2)		Feb.	"	5900	DeepCk.Mtns;FalkenbergCyn 10S. al.
		X	P. maniculatus		"	"	6200	IndianFarm Cyn.
		X	P. truei		"	"	"	"
		X	E. dorsalis		"	"	"	"
	X		P. maniculatus		"	"	"	"
	X		P. truei		"	"	"	"
		X	L. californicus		June	Boxelder	4750	CurlewValley; 20W Snowville
		X	L. californicus		July	"	4700	" "
	X		Eutamias umbrinus(2)		Sept.	Garfield	8000	Bryce Canyon Natl. Park
X			E. umbrinus	Monopsyllus eumolpi	"	"	"	"
	X		P. maniculatus		"	Tooele	5200	Wside DeepCk.Mtns; 3N Ibapah
X			P. maniculatus	Epitedia stanfordi	Nov.	Boxelder	4700	CurlewValley; 20W Snowville
	X		P. maniculatus(3)		"	"	"	" "
			1966					
	X		Human		May	SanJuan	4850	MonumentValley; 3NW Oljato
		X	Canis familiaris(2)		"	"	"	" "
	X		E. umbrinus		Sept.	Garfield	8000	Bryce Canyon Natl. Park
X			E. umbrinus	M. eumolpi	"	"	"	"
		X	P. maniculatus		Nov.	Juab	8200	DeepCk.Mtns;Upper Tom's Ck. Cyn. 9WSW Callao
			1967					
X			P. maniculatus(2)	O. k. keeni	July	Juab	8200	Upper Tom's Ck. Cyn.
	X		Microtus longicaudus(2)		"	"	"	"
	X		Eutamias minimus		Sept.	Garfield	8000	Bryce Canyon Natl. Park
			1968					
	X		E. minimus		Feb.	Tooele	4300	Old Lincoln Hwy; 23W Easy, DPG
		X	P. maniculatus		June	Juab	6200	Indian Farm Cyn.
X			M. longicaudus	Malaraeus telchinum	July	"	8200	Upper Tom's Ck. Cyn.

(cont.) Chronological Listing...

Flea Isolate	Tissue Isolate	Positive Serology	Vertebrate Host	Flea Species	Month	County	Elev.	Location
			1968					
	X		M. longicaudus		July	Juab	8200	Upper Tom's Ck. Cyn.
		X	M. longicaudus		"	"	"	"
X			E. umbrinus	M. eumolpi	Sept.	Kane	8700	Bryce Canyon Natl. Park
		X	E. minimus(3)		"	Garfield	8000	"
		X	E. umbrinus		"	Kane	9000	"
			1969					
		X	Vulpes macrotis		Jan.	Tooele	4300	Government Ck. 8WSW Easy, DPG
	X	X	P. maniculatus		May	Tooele	5800	Stansbury; 3W Clover
		X	P. maniculatus(2)		June	"	7800	W.side DeepCk.Mtns;RockSpgs.Cyn. 8SE Ibapah
	X		P. maniculatus		"	Garfield	8000	Bryce Canyon Natl. Park
X			M. longicaudus	Unident. (Monop. sp. possibly exilis)	"	Tooele	8200	E. side Dog Crk. Mtns. Goshute Cyn
X	X		M. longicaudus	O. kearni	Sept.	Juab	7900	E. side Dog Crk. Mtns, Granite Creek Cyn.
	X		1970 P. maniculatus		March	Juab	4800	N.E. end of Fish Springs range

VERTEBRATES INVOLVED WITH PLAGUE IN UTAH THROUGH ~~JUNE~~ 1969

Species	Isolations of *P. pestis* from tissues	Positive Serological Reactors	Host to *P. pestis*-infected fleas
Sylvilagus nuttallii		1	
Lepus californicus		3	
Eutamias minimus	2	3	
E. dorsalis		10	
E. umbrinus	3	1	3
Marmota flaviventris	1		
Ammospermophilus leucurus		1	
Spermophilus armatus	2		3
S. variegatus	1	3	6
Cynomys sp.	1		1
Perognathus parvus		2	
Dipodomys ordii	2		
D. microps		1	
Reithrodontomys megalotis			1
Peromyscus crinitus	1	5	4
P. maniculatus	~~21~~ 32	104	19
P. truei	6	15	4
Neotoma lepida		11	1
N. cinerea		1	
Microtus longicaudus	~~34~~	1	~~23~~
Ondatra zibethicus		1	
Canis familiaris		2	
Vulpes macrotis		1	
Human	2		
TOTALS	~~45~~ ~~46~~ 47	166	~~44~~ 45

FLEAS FROM WHICH ISOLATIONS OF *PASTEURELLA PESTIS* HAVE BEEN MADE IN UTAH THROUGH ~~JUNE~~ 1969 TOGETHER WITH ASSOCIATED HOSTS

Diamanus montanus	(1)	*Spermophilus variegatus*
Epitedia stanfordi	(1)	*Peromyscus maniculatus*
Histrichopsylla linsdalei	(2)	*P. maniculatus*
Malaraeus sinomus	(13)[a]	*Peromyscus crinitus* (4)[b] *Peromyscus truei* (3)[c] *P. maniculatus* (6)[d]
Malaraeus telchinum	(1)	*Microtus longicaudus*
Megabothris abantis	(1)	*P. maniculatus*
Monopsyllus eumolpi	(3)	*Eutamias umbrinus*
Monopsyllus wagneri wagneri	(1)	*P. maniculatus*
Neopsylla inopina *Opisocrostis tuberculatus* *Thrassis francisi*	(1)	*Spermophilus armatus*
Opisodasys keeni keeni	(~~8~~ 9)[e]	*M. longicaudus* (1) *P. truei* (1) *P. maniculatus* (6)[f] *Reithrodontomys megalotis* (1)
Orchopeas leucopus	(1)	*P. maniculatus*
Undetermined	(~~10~~ 11)	*Cynomys* sp. (1) *S. armatus* (2) *S. variegatus* (5) *Neotoma lepida* (1) *P. maniculatus* (1) *M. longicaudus* (1) (*Monygilla* sp.) (ex[illegible])

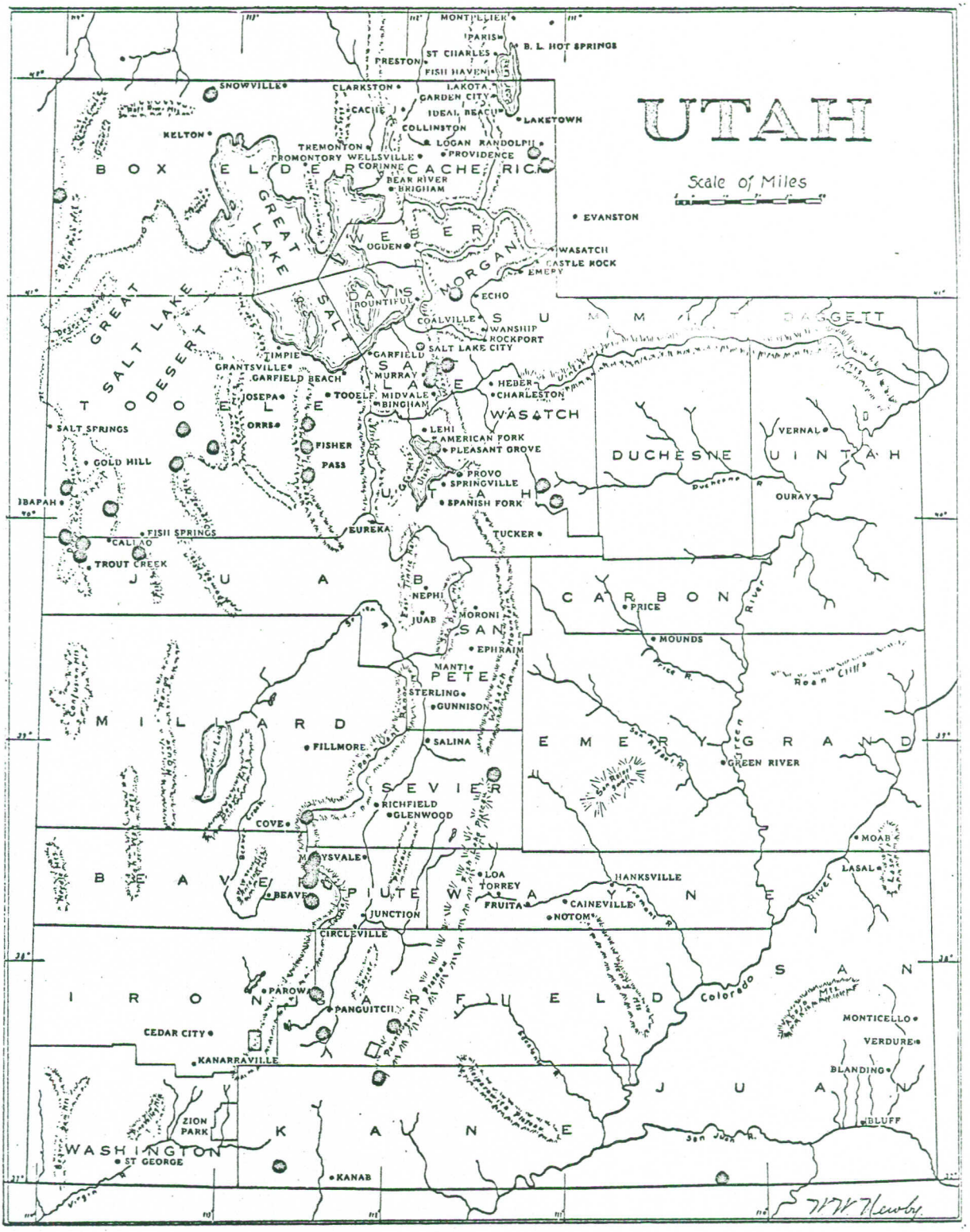
Note: Numbers in parentheses are the number of occasions positive fleas of indicated species have been found on host. Does not include time when individual fleas were tested and more than one flea from a given host was positive. Total flea isolations are indicated by superscripts: a = 30, b = 14, c = 9, d = 7, e = 12, f = 10.

Counties in Utah Yielding Evidence of *Pasteurella pestis* Activity Including Type of Evidence, Species Involved and Year of Initial and Most Recent Evidence

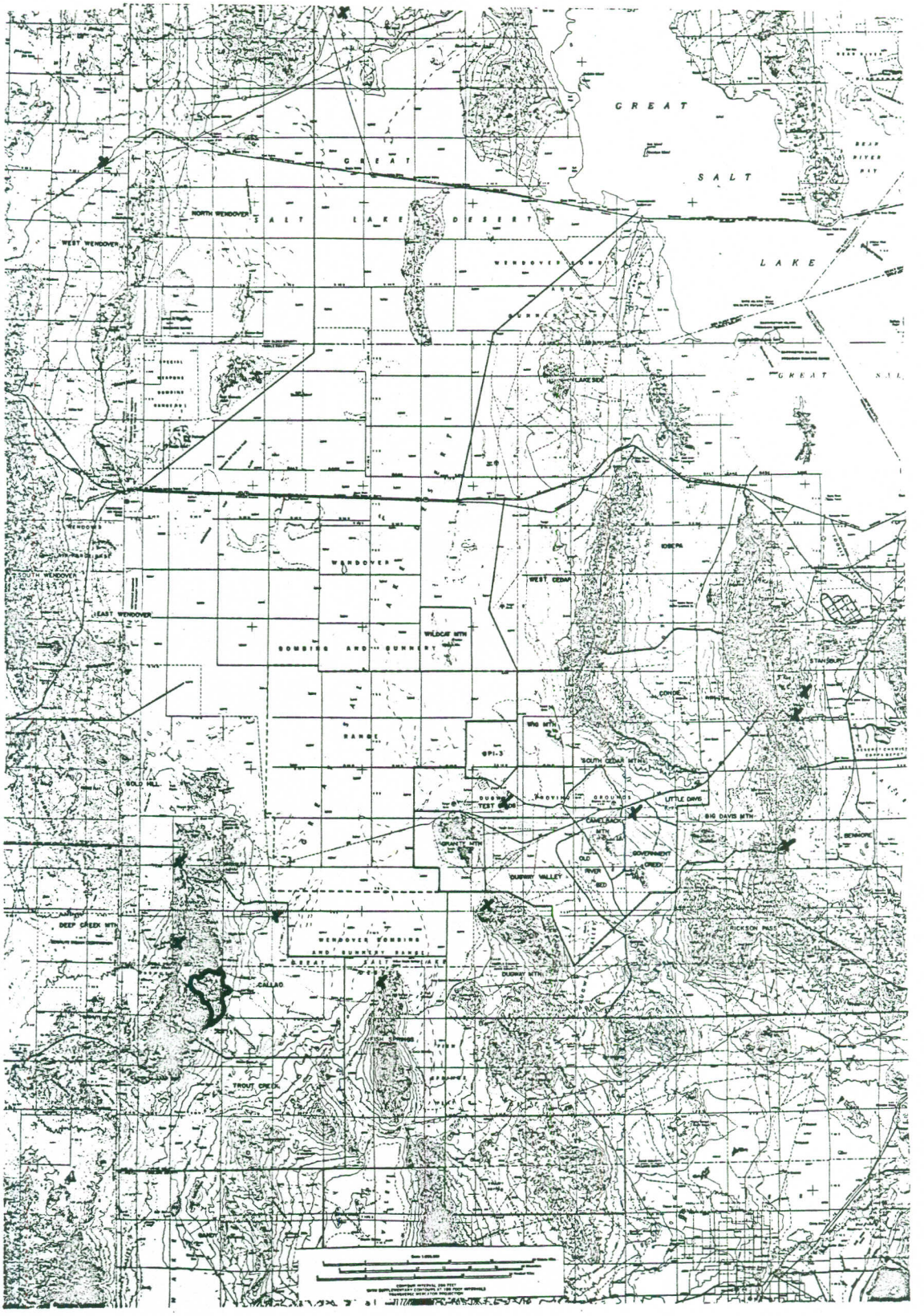
County	Vertebrate Involved	Tissue Isolate	Positive Serology	Host to Infected fleas	Year of initial evidence	Year of most recent evidence
Beaver	Human	X			1936	1936
	Spermophilus variegatus	X		X		
	Marmota flaviventris	X				
Sevier	*S. variegatus*			X	1936	1949
	Spermophilus armatus			X		
Garfield	*Cynomys* sp.	X		X	1936	1969
	Eutamias umbrinus	X		X		
	Eutamias minimus	X	X			
	Peromyscus maniculatus	X				
Morgan	*S. variegatus*			X	1937	1937
	S. armatus			X		
Wasatch	*S. armatus*	X			1937	1938
Kane	*Neotoma lepida*			X	1938	1968
	E. umbrinus		X	X		
Rich	*S. armatus*			X	1938	1938
Salt Lake	*S. variegatus*			X	1948	1963
	P. maniculatus	X		X		
Juab	*P. maniculatus*	X	X	X	1957	~~1968~~ 1970
	Peromyscus crinitus	X	X	X		
	Peromyscus truei	X	X	X		
	Reithrodontomys megalotis			X		
	Eutamias dorsalis		X			
	N. lepida		X			
	Dipodomys microps		X			
	Perognathus parvus		X			
	Sylvilagus nuttallii		X			
	S. variegatus		X			
	Neotoma cinerea		X			
	Ammospermophilus leucurus		X			
	Microtus longicaudus	X	X	X		
Tooele	*D. ordii*	X			1959	1969
	P. maniculatus	X	X			
	E. minimus	X				
	Vulpes macrotis		X			
	M. longicaudus			X		

(Cont.) Counties in Utah Yielding Evidence of *Pasteurella pestis* Activity...

County	Vertebrate Involved	Tissue Isolate	Positive Serology	Host to Infected fleas	Year of initial evidence	Year of most recent evidence
Utah	*Ondatra zibethicus*		X		1963	1963
Boxelder	*Lepus californicus*		X		1963	1965
	P. maniculatus	X	X	X		
San Juan	Human	X			1966	1966
	Canis familiaris		X			



MAP SHOWING LOCATIONS WHERE EVIDENCE OF PASTEURELLA PESTIS HAS BEEN FOUND IN UTAH THROUGH JUNE 1969



MAP SHOWING LOCATIONS WHERE EVIDENCE OF PASTEURELLA PESTIS HAS BEEN FOUND IN PRIMARY ECOLOGY AND EPIZOOLOGY RESEARCH STUDY AREA THROUGH JUNE, 1969

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