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REVIEW OF TULAREMIA IN UTAH AND THE GREAT BASIN

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Abstract.— This is a compilation of tularemia research conducted in Utah, particularly at U.S. Army Dugway Proving Ground (DPG), Utah, and an evaluation of this information in relation to the current status of tularemia studies. A brief history of tularemia in Utah and a review of field and laboratory studies are included.

Human cases of tularemia occur throughout Utah during all seasons of the year. An analysis of recent human disease reveals a concentration of cases in rural areas, with a greater seasonal occurrence in late summer and early fall.

Research on tularemia as a zoonotic infection in and around the U.S. Army Dugway Proving Ground (DPG), Utah, has established the existence of natural foci of infection, cycles of activity, and probable reservoir hosts and vectors. In addition, studies have been directed toward determination of survival times of the organism as aerosols and as contaminants on surfaces in the laboratory and in nature under varying field conditions. Field and laboratory work also have been conducted at Brigham Young University and the University of Utah; several species of deer fly (*Chrysops* spp.) were found infected in nature.

Human tularemia is commonly a rural disease, probably with an eight-year cyclic tendency in Utah. It is transmissible to man through direct contact with the host, contamination of water and food, vectors, inhalation of dust as from tick feces while shearing sheep, and, uniquely in the Great Basin, by the bite of deer flies.

There have been several review articles on tularemia in recent years; Jellison and Parker (1945), Bell (1965), Olsuf'yev and Rodnev (1960), Hopla (1974), and Olsen (1975) are examples. In addition, several bibliographies have been compiled, e.g.: the U.S. Army Chemical Corps (1958), Hoogstraal et al. (1970–1972), and Pollitzer (1967). Cox (1964), at Brigham Young University, prepared a "Bibliography of Tularemia" with references arranged by subject matter, similar to the one published by the U.S. Army Chemical Corps. Jellison was author (1950) and coauthor (1945, 1951, 1956), of specific and general articles on tularemia (many of them on tularemia in Utah), and he prepared a current review and bibliography on tularemia (1974).

Much of the information given here is a review of large quantities of data from DPG reports and records not ordinarily available to the scientific community. Since the data are voluminous, not all can be analyzed; many DPG reports and articles are referenced for further analysis (if desired) by the reader. Other portions of this work constitute a literature survey.

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HISTORY

The etiologic agent of tularemia, *Francisella tularensis*, was not identified until this century (McCoy 1911, McCoy and Chapin 1912). However, tularemia may have appared earlier among humans in rural Utah. Pearse (1911), a Brigham City physician, studied six human cases of an unknown disease which occurred in August 1908 in the Brigham City-Tremonton area. It is believed to be the first clinical description of tularemia in the English language. Pearse left the disease unnamed. Later medical accounts reviewing epidemiologic and clinical aspects of the disease assumed deer fly bites were associated with it, although no infected insects were captured or identified.

Francis, another physician, first isolated *F. tularensis* from wild mammals and their ectoparasites in 1919 and conducted detailed studies near Holden in the Delta area of Millard County (Francis 1921, 1927). Before 1920 he referred to the disease as "Pahvant Valley plague" and "deer fly fever." Later (1921) he established and used the name tularemia for the disease. Simpson (1929) wrote a textbook on medical aspects of the disease, assembling knowledge to that time. He associated the cases in Utah largely with deer fly bites.

ETIOLOGIC AGENT

Francisella is distinctive and only distantly related to other bacterial organisms. Buchanan and Gibbons (1974) gave no hierarchical arrangement for it. The genus is placed with *Brucella*, to which it is not closely related,[2] in a group of genera of uncertain affiliation entitled "Gram-negative aerobic rods and cocci." There has been no general compilation of strains published to date, although there are significant differences in levels of virulence among strains of *F. tularensis*. Yet virulence alone does not provide a basis for classification, because under laboratory culture and storage it can change. Different laboratory hosts express different levels of resistance and display varying pathogenesis. Biochemical reactions (glycerine fermentation and the presence or absence of citrulline ureidase) have been related to virulence (Marchette and Nicholes 1961). Some strains resist streptomycin. Eigelsbach, Braun, and Herring (1951), Skrodsky (1966), and Dominowska (1967) observed a correlation between the colonial morphology and the pathogenicity and immunogenic properties of a given isolate.

Based on virulence, chemical reactions, morphology, geographic origin, epizootiology, epidemiology, vectors, reservoirs, association of different habitats, and modes of transmission, two basic subspecies of tularemia have gained recognition. These are commonly referred to as types A and B (Bell 1965). Subspecific designations also have been made referring to types A and B. The less virulent of the two is *palaearctica* (Type B) and is more frequently associated with agricultural areas and lotic waters, and may be maintained by chronic tularemia nephritis in muskrats, beavers, and voles. Voles may be the primary reservoir in some areas in western North America. Chronically infected vertebrates urinate onto watersheds, sometimes causing widespread and protracted human epidemics (Bell and Stewart 1975).

Human infection with *palaearctica* has occurred during threshing operations in the USSR. Possible similar occurrence of human tularemia in the Great Basin is discussed later under tularemia in soils. Another proposed name, *holarctica*, for Type B, implies that this type occurrs throughout all land masses of the Northern Hemisphere. Though *holarctica* is less restrictive in concept, *palaearctica* has taxonomic priority. *Francisella t. tularensis* (Type A, also designated *F. t. nearctica*) is more virulent and is frequently associated with infection in lagomorphs (hares and rabbits) and nonaquatic (xeric or mesic) rodents, more frequently involves human cases contracted during hunting, and is often associated with vectorborne transmission than is *palaearctica* (Bell 1965).

Besides the currently recognized sub-

[2]There is some serologic cross reaction between *F. tularensis* and *Brucella* (Hopla 1974, Quan 1978).

species, two additional nomenclatural designations have been proposed, *japonica* (Rodianova 1967) (for Japanese isolates) and *mediasiatica* (Aikimbaev 1966) (for a central Asian strain). Aikimbaev (1966) and Olsul'yev (1970) regard the latter as primitive. Aikimbaev proposed subspecific status for *mediasiatica*. Taxonomic status has not been evaluated for either of these two names.

The tularemia organism in nature is ubiquitous, but simultaneously demonstrates ubiety with regard to strain differentiation. Numerous strains have been recognized. These often have been designated with numbers or initials. At DPG, nine strains are maintained and studied: Jap 4, Ohara, Live Vaccine, S. C., Russ, Max, 38, 38A, and Schu 5. Similar groups have been kept at several educational institutions, the U.S. Public Health Service, Rocky Mountain Laboratory at Hamilton, Montana; Centers for Disease Control at Fort Collins, Colorado, and Atlanta, Georgia; and at several state health departments. Several strains may occur in one locality (e.g., Prince George County, Virginia, where several strains came from a single species of tick—*Haemaphysalis leporispalustris*). Karlsson et al. (1970) and Karlsson and Soderlind (1973) obtained 50 strains from a limited area in Sweden; most of these came from a single species of tick. Many publications list strains collected locally from nature or developed in the laboratory. In Stoenner et al. (1959) and Marchette and Nicholes (1961), the strains DPG-1,2,3,4,5,6, SKV-1,2,3, and 9-K-161 are reported as isolates from ticks (*Dermacentor parumpertus, Hemaphysalis leporispalustris,* and others), cottontails (*Sylvilagus audobonii*), and jackrabbits (*Lepus californicus*) around DPG. Marchette et al. (1961) listed 18 cultures kept at DPG and at the University of Utah, Salt Lake City. A staff report on tularemia at DPG (No. 88U; USA-DPG 1962b) listed 26 strains (18 from DPG) used in susceptibility and vector studies of transmission. There is no record of preservation of these isolates. Some strains are preserved in adjacent states. Dr. Thomas J. Quan of the Plague Branch of the Communicable Disease Center, Fort Collins, Colorado, has strains SKV-2 and DPG-1 as part of his *F. tularensis* collection. Mr. Scott Stewart, Rocky Mountain Laboratory, Hamilton, Montana, preserves numerous strains by lyophylization, but effort is not devoted to identification and cataloging; it is more convenient to obtain fresh material from nature for ongoing research.

Storage and preservation or cultivation (especially in egg yolk) in the laboratory reduces virulence of the organism (Owen 1970). Green (1943) increased virulence of unnamed strains of *F. tularensis* by passage through cottontail rabbits and hares. On the other hand, he contended that passage through grouse reduced virulence. Owen et al. (1961) failed to enhance the virulence of *F. tularensis* by experimentally passing strains through hosts or ectoparasites. Some strains have considerable vitality for sustaining their characteristics. There are great variations of virulence in strains isolated in nature. Older literature on virulence refers to resistance, susceptibility, and mortality in human infections. No assignment of strains, even as far as types A or B, is possible for these old isolations. No classification or cataloging of *F. tularensis* strains appears possible at the present time. Buchanan and Gibbons (1974) suggested a nomenclature that has had partial acceptance at best. Thus, resolving the status of the number and identity of the strains of *F. tularensis* (other than the two principal types) remains an unresolved problem.

RESEARCH ON TULAREMIA IN UTAH AND THE GREAT BASIN, 1945–1975

Table 1 summarizes research on tularemia in nature in the Great Basin. These investigations are discussed in the following section. Krinsky (1976) devoted about half of his review of tularemia in tabanid flies (*Chrysops* spp.) to the historical occurrence of tularemia in nature in Utah and to research published by Utah-based authors. Krinsky's high regard for studies of tularemia in Utah prompted an expanded review.

DISTRIBUTION, RESERVOIRS, AND CYCLES IN NATURE.— The occurrence of tularemia in Utah differs from that in other parts of the world. Rodenwaldt et al. (1952) believed *F. tularensis* to be ubiquitous in the Holarctic Realm and to occur in permanent and well-defined epicenters where it is maintained, and from which it may spread. The area from

TABLE 1. Summary of basic research on tularemia in the Great Basin, 1945 to 1975.

Principal Investigators[1]	Date	Institution[2]	Subject of research
Jellison, Parker	1945	RML	Rodents, rabbits, and tularemia; *Sylvilagus* ssp.—basic reservoir and source of human tularemia
Jellison	1950	RML	Deer fly distribution
Jellison, Kohls, Philip	1951	RML	Tularemia in sheep
Jellison, Kohls	1956	RML	Tularemia in muskrats and humans around Utah Lake
Rodenwaldt	1952	U.S. Navy	Concept of epicenters
Woodbury, Parker	1953	U of U USA-DPG	Special report on tularemia
Woodbury	1954	U of U USA-DPG	Tularemia and biotic communities
U of U staff	1955	USA-DPG	Ecology of tularemia transmission
Philip, Bell, Larsen	1955	RML	Tularemia in jackrabbits in Nevada
Allred, Stagg, Lavender	1956	USA-DPG	Transmission by *Dermacentor parumapertus*
Stagg, Tanner, Lavender	1956	U of U USA-DPG	Experimental infection of native animals
Parker, Johnson	1957	U of U USA-DPG	Attempted transmission by fleas
Vest, Marchette	1958	U of U USA-DPG	Transmission from infected carcasses
Stoenner, Holdenried	1959	RML USA-DPG	Isolates of tularemia from Great Salt Lake Desert area
U of U staff	1961 thru 1969	U of U USA-DPG	Annual reports of surveillance
Parker, Olsen, Dolana	1970 thru 1972	EcoDynamics USA-DTC	Annual reports of surveillance
E&E staff	1973 to present	USA-DPG	Annual reports of surveillance
Lundgren, Marchette, Nicholes	1961	U of U USA-DPG	Immunity of host; virulence of pathogen
ditto	1962	U of U USA-DPG	Cutaneous allergic reaction
Gebhart, Thorpe	1962	U of U USA-DPG	Review of literature

Arkansas to southern Illinois constitutes one major epicenter in North America. Another well-defined epicenter exists in the western part of the continent, of which Utah (especially the Delta area) is a part. Later publications attach no particular significance to these epicenters of tularemia as defined by Rodenwaldt et al. Maximov (1960), however, regarded tularemia as an important natural regulator of rodent hosts and reported that it occurs in favorable foci in the USSR as related by the concept of "landscape epidemiology."

Jellison and Parker (1945) proposed that cottontails (*Sylvilagus* spp.) are basic reservoir hosts responsible for 90 percent of human tularemia in North America.

Several species of deer fly are the principal vectors to man from zoonotic sources (possibly infected hares) in Utah. Throughout the remainder of the world, ticks and sometimes mosquitoes (Rodenwaldt et al. 1952) are the principal vectors to man. Other sources of human tularemia infection include contact with the infected hosts, contaminated water, or aerosols.

Tularemia appears to occur widely in a variety of environments and hosts. Few areas are as ecologically diversified as Utah. Tularemia is widespread from the Great Salt Lake Desert to the Uinta Mountains. It has transmission cycles involving waterborne tularemia, as with muskrat trappers around Utah Lake (Jellison, Kohls, and Philip 1951); air-

Thorpe, Marcus, Sidwell	1962 thru 1967	U of U USA-DPG	Phagocytosis and other cellular factors relating to resistance
Cabelli et al.	1964	USA-DPG	Transmission by birds
Cox	1964	BYU	Bibliography of tularemia
Cox	1965	BYU	Tularemia in deer flies
Thorpe et al. (1965)	1951 thru 1964	U of U USA-DPG	Tularemia in wildlife and livestock in Great Salt Lake Desert
Thorne	1966	USA-DPG	Tularemia in soils at DPG
Johnson	1966	U of U USA-DPG	Ticks of DPG
Vest et al.	1965	U of U USA-DPG	Five-year review of tularemia field infections in western Utah
Knudsen, Rees, Collett	1968	U of U USA-DPG	Tularemia in deer flies in Salt Lake County; trapping tabanids
Klock, Fukushima, Olsen	1973	UDH USA-DTC	Tularemia epidemic: Delta, Grantsville
Olsen	1975	EcoDynamics USA-DTC	Review of tularemia

[1]See bibliography for complete citation.

[2]Institution abbreviations:

BYU = Brigham Young University, Provo, Utah
DPG = U.S. Army Dugway Proving Ground, Utah
DTC = Deseret Test Center, Fort Douglas, Utah
E&E = Epizoology and Ecology Branch prior to 1972; now Environmental and Ecology Branch, DPG
RML = Rocky Mountain Laboratory, Hamilton, Montana
UDH = Utah State Division of Health
USA = U.S. Army
U of U = University of Utah, Salt Lake City, Utah

borne tick feces as with sheep shearers (Jellison and Kohls 1956); direct contact, as with rabbit hunters; and deer fly bites as with 26 of 170 laborers at Locomotive Springs, Utah (Burnette 1936, Hillman and Morgan 1937). These latter authors reported that laborers removed their shirts while working, that sick jackrabbits were seen in the area, and 13 men were known to have killed jackrabbits or handled dead ones. The locations of initial ulcers of the shoulders and backs of the workmen suggested, however, that jackrabbits were not directly involved as a source of human tularemia.

Francisella novicida was isolated and described from Ogden Bay, on the eastern side of the Great Salt Lake (Owen 1974), and has never been reported elsewhere. Thus Utah differs from all other areas of the world by harboring all three recognized taxa of *Francisella.*

EPIZOOTIOLOGY OF TULAREMIA AT DPG.— In 1951 a program was begun to study and analyze plants and animals at DPG and adjacent areas (Woodbury 1956, 1964). Emphases were placed on enumerating enzootic pathogens as well as potential introduction of other pathogens to determine possible vectors and routes of natural dissemination. Most research on tularemia at DPG was conducted under contract. Reports entitled "A Study of the Ecology and Epizoology of the Native Fauna of the Great Salt Lake Desert" (Annual Summaries 1951–1969) were published by the University of Utah (USA-DPG 1951–1969). "Ecology Studies of Western Utah" 1971–1973 were prepared by EcoDynamics Incorporated (Desert Test Center USA-DTC 1971–1973). From 1969 through 1964, special summary reports on tularemia were published as DPG in-house reports. These voluminous reports contain much raw data in tables and graphs. Additional tabulation, study, and synthesis of data are not within the scope of this review. The following provides a cursory summary of some results.

From 1951 through 1979 evidence of tularemia existed in virtually all 46 areas of Utah in which specimens were collected and from 35 areas sampled routinely. Serologic evidence of the organism was found infrequently from rodents, usually in less than 1 percent of the specimens. In contrast, high rates were found for carnivores and livestock, usually greater than 11 percent, while moderate rates were recorded for deer and wild horses. Greater risk of exposure, longer lives, innate resistance, and persistence of antibodies may account for higher occurrence in these mammals as opposed to rodents. The incidence of antibodies was usually similar in widely different groups of hosts in the same year. For example, in 1965 22 percent of 651 cattle samples were positive, 42 percent of 1,579 sheep samples were positive, and 25 percent of 31 carnivore samples were positive. In 1968 the proportions of samples with antibodies to *F. tularensis* were small: 0.03 percent for rodents, 2 percent for livestock, and 3 percent for carnivores. In other years carnivores persisted with high rates, and rates in other animals were low. For example, in 1970 antibody rates were 4 percent in sheep, 0.4 percent in cattle, 0 percent for rodents, and 17 percent for carnivores. Antibody recoveries from rodents and jackrabbits remained consistently small however, suggesting that rodents play a minor role in maintenance. Also of little significance to the maintenance of *F. tularensis* in nature is the jackrabbit, which is very susceptible and succumbs promptly. This observation may explain why few jackrabbits in nature possess antibodies to tularemia.

A special summary report prepared by the Ecology and Epizoology research staff, University of Utah, summarized DPG studies on host relationships for ticks, lice, and fleas (USA-DPG 1962b). The report discussed experimental vector transmission studies that included immunization and susceptibility experiments using several strains of *F. tularensis* on laboratory mice, rabbits, guinea pigs, and deer mice. Isolations from wild mammals, birds, and livestock were tabulated. Ecological observations on biotic communities and population dynamics, particularly for the jackrabbit, were summarized. Serologic methods for detecting antibody activity, especially agglutinating, complement-fixing tests, and cutaneous responses were reviewed. Some of the information in this report has not appeared in published literature.

Stagg, Tanner, and Lavender (1956) produced experimental infection of *F. tularensis*

in jackrabbits, seven species of rodents, and coyotes (*Canis latrans*). They found that coyote pups were less susceptible to tularemia than rodents. Infection of rodents via contaminated food was difficult. When infection of rodents and jackrabbits was successful (as from aerosols), the disease usually progressed rapidly to death (3–5 days).

Gebhardt and Thorpe (1962) presented a tabular review of worldwide vectors and hosts. The pathogen, vectors, hosts, epidemiology, epizootiology, and control were given a generalized interpretation. Thorpe et al. (1965) reported on tularemia studies from their inception at DPG (1951 through 1964). Areas of study included the Bonneville Basin of western Utah and adjacent portions of Nevada, where 35 areas were sampled semiannually or quarterly. During the 13-year period 52 isolations of *F. tularensis* were made, approximately half from wild mammal tissues and half from ectoparasites. The authors also tabulated information on human tularemia from 1941 through 1964. This information, updated with data from the Utah State Division of Health, is presented in this article as Figure 1 and is discussed later in the section: "Distribution of Recent Cases of Tularemia in Utah." Isolation data with respect to livestock, wild mammals, birds, and their ectoparasites and collections of positive sera were also tabulated. Six local epizootics were observed during the 13-year period. Tissue isolates were made from jackrabbits, which were collected in great abundance, one cottontail, and four rodents. Serum agglutinins were found in birds, wild mammals (including deer), and livestock (roughly 25 to 30 percent of the serum samples tested). Most isolates possessed maximal virulence; however, two isolates from the cottontail and a Great Basin pocket mouse (*Perognathus parvus*) were of low virulence. Thorpe et al. indicated that strains from North American nonaquatic hosts and ectoparasites are sometimes of lower virulence.

Vest et al. (1965), in a five-year study of enzootic diseases in Utah, reported that 10 strains of *F. tularensis* were isolated from lagomorphs and rodents. All strains were of maximum virulence. One viable organism sufficed for a lethal dose in laboratory rabbits, mice, hamsters, and guinea pigs. Olsen and Dolana ([EcoDynamics, Inc.] USA-DTC 1971–1973) provided additional support to Stagg, Tanner, and Lavender (1956), Marchette et al. (1961), and Thorpe et al. (1965).

Olsen and Dolana found that (1) *F. tularensis* isolated from most hosts near DPG usually had maximal virulence, but occasional isolations had little virulence; (2) carnivores were readily infected but recovered and did not demonstrate a carrier state; (3) cottontails were susceptible to infection; and (4) jackrabbits were more susceptible than cottontails. Klock, Olsen, and Fukushima (1972) obtained eight isolations of *F. tularensis* from *Chrysops discalis, Dermacentor parumapertus, H. leporispalustris,* and jackrabbits from four areas near DPG (Delta,[3] Iosepa, Callao, and Gold Hill). Tests of virulence showed all eight to be typical Type A (*nearctica*), which is virulent for laboratory mice and rabbits. EcoDynamics personnel ([Olsen and Dolana] Desert Test Center 1971 Annual Report [USA-DTC 1972]) were mystified by the large numbers of seropositive cottontails near Delta because tularemia is uniformly fatal to cottontails. They hypothesized that (1) Delta cottontails were somewhat resistant to *F. tularensis* as a result of selection pressure, or (2) the detection of the antibody was a nonspecific reaction, or (3) an avirulent strain of *F. tularensis* (present in the area) was responsible for the antibody titers. They found support evidence that there probably were specific and protective antibodies for cottontail rabbits in the Delta area. Selected details of these supportive data are given later under "Hosts." On the basis of their findings, the EcoDynamics staff (1972) questioned the validity of the generally accepted concept (based primarily on virulence) of types A and B for *F. tularensis*. Olsen and Dolana conjectured further that neither type is limited to specific habitat types nor to specific animal groups. They stated that types A and B allow synthesizing the bewildering array of strains into an epizootiological pattern. No alternative

[3]Delta, 97 air km (60 air miles) from Dugway, is not physically near, but is environmentally similar with few barriers between the two areas.

method for organization or cataloging was offered.

Olsen (1975) reviewed some of the Great Basin surveys by DPG abstracted in the preceding paragraphs. He noted that the majority of isolations of *F. tularensis* came from jackrabbits and its primary tick parasite (*D. parumapertus*), but agglutinins were detected in 22 percent of blood samples from cattle and sheep. Of interest is the decline in rate of recovery of evidence of the tularemia organism in nature from 1954 to 1970. The majority of isolations were made earlier with comparatively little change in field collecting effort. This suggests wide and long-term variation in the amount of pathogen circulating in native reservoir hosts and vectors of the area.

EPIDEMIOLOGY OF TULAREMIA AROUND DPG.— Klock, Olsen, and Fukushima (1973), who described an outbreak of tularemia in 1971 near Delta and Grantsville, Utah, studied the epidemiology of 39 human cases with investigations of vectors, hosts, and incidence of isolations from specimens collected. Nineteen of these human cases suffered deer fly bites, and another nine reported insect bites by unknown species. The pathogen was isolated from hosts and vectors in both areas and adjacent areas such as Skull Valley, Utah. Also, there was an epizootic among lagomorphs. *F. tularensis* was isolated from tissue of jackrabbits and cottontails. Because of unusually large numbers of midges (*Leptoconops* spp. and *Culicoides* spp.) observed in 1971, the authors suggested that these might have played a role in the human outbreak.

VECTORS.— Cox (1965), in a study on *F. tularensis* and deer flies in the environs of Utah Lake, isolated the organism from *Chrysops* spp. in nature for the first time. Experimental transmissions by *C. discalis* was demonstrated by Francis and Mayne (1921). Cox's isolation of *F. tularensis* from *C. fulvaster* and *C. aestuans* demonstrated that species other than *C. discalis* (this common species was only suspect before that time) are vectors. Knudsen, Rees, and Collett (1968) isolated *F. tularensis* from *C. discalis*, thus associating the bite of *C. discalis* with a human case. Other isolations of *F. tularensis* from deer flies from near the Great Salt Lake, made by the University of Utah Ecology and Epidemiology group, suggested a potential health hazard from *Chrysops* spp. Krinsky (1976) pointed out that isolations from deer flies in Utah in 1965, 1968, and 1969 provided evidence of the potential importance of these tabanids in the dissemination of *F. tularensis*, even though they are regarded as short-term mechanical vectors. After these isolations, EcoDynamics researchers made net collections of tabanids and later suggested epidemiologic associations with human cases (Deseret Test Center Annual Reports, USA-DTC 1971–1973). Klock, Olsen, and Fukushima (1973) suggested the same associations (discussed later in this review). Philip (1968) found that another tabanid (*Tabanus punctifer*, may have been associated with a human case reported near Battle Mountain, Nevada.

Parker (1957) and Parker and Johnson (1957) attempted the transmission of *F. tularensis* by fleas in the laboratory. In one attempt, three species of fleas were infected, but none of them transmitted *F. tularensis* to a susceptible host. In another attempt, *Orchopeas leucopus* transmitted *F. tularensis* to a specimen of *Peromyscus treui*. Extensive studies on transmission of tularemia by ticks, overwintering, and transovarial passage of the pathogen have been conducted at Rocky Mountain Laboratory in Hamilton, Montana (Jellison 1974). Vector studies of tick transmission are reported in the University of Utah Ecology and Epidemiology Annual Report (USA-DPG 1962b). *Otobius lagophilus*, removed from a dead jackrabbit, transmitted *F. tularensis* to cottontails and to a domestic white rabbit (*Oryctolagus* spp.), the first known transmission by this tick. Twenty-two species of ticks were recorded from DPG and environs, of which five species (*Dermacentor andersoni, D. parumpertus, Ixodes kingi, Haemaphysalis leporispalustris*, and *Otobius lagophilus*) were infected with *F. tularensis* (Johnson 1966, Thorpe et al. 1965, and Annual Reports USA-DPG 1962–1969). It is conceivable that, in the Great Basin, the tick and jackrabbit (*D. parumapertus* and *L. californicus*, respectively) constitute a polyhostal reservoir (Hopla 1974:47).

HOSTS.— Marchette et al. (1961) demonstrated the susceptibility of locally captured

wild mammals to tularemia. Eleven species of wild rodents and cottontails were very susceptible. Some species of wild rodents (*Onychomys leucogaster, Peromyscus maniculatus,* and *Neotoma* sp.) were very susceptible to virulent strains but were resistant to the avirulent "38" strain. Carnivores (*Taxidea taxus, Vulpes macrotis,* and *Canis latrans*) were readily infected orally; the infection soon was no longer demonstrable, and the animals did not become carriers. The authors concluded that tularemia in the Bonneville Basin is a disease primarily of jackrabbits, with the cycle in nature maintained by that host and the vector (*Dermacentor parumapertus*). The authors also concluded that *Lepus* spp. were more susceptible than *Sylvilagus* or *Oryctolagus.* The published conclusions of these authors differ from the general concept throughout the Annual Reports (USA-DPG 1964–1969) that jackrabbits are so susceptible that they play a minor role in maintenance. The snowshoe hare (*L. americanus*; European counterpart—*L. timidus*) is less susceptible than jackrabbits or Minnesota *Sylvilagus* spp. to infection with *F. tularensis* (Green 1943, Green, Larsen, and Bell 1939). Marchette et al. (1961) noted that *L. c. deserticola* was more susceptible than *L. c. texianus.*

About half of 19 cottontails (*S. audobonii*) captured near Delta showed no demonstrable levels of antibody to *F. tularensis* (EcoDynamics Inc. USA-DTC 1972). However, 9 survived the challenge inoculation of 83 cells of *F. tularensis*; they had developed high levels of antibodies. Subsequently, an isolate from cottontails from Delta was tested on other cottontails collected from Delta and Gold Hill. All of the experimental hosts from Gold Hill died, suggesting that some of the Delta cottontails were naturally "immunized" with an avirulent strain of *F. tularensis.* This natural avirulent strain may have been responsible for previously observed seropositive cottontails (31 percent of 62 specimens) collected near Delta in 1972 (USA-DTC 1972). EcoDynamics concluded that Delta cottontails may possess some innate resistance to certain strains of *F. tularensis.* However, much more work needs to be done to clarify the relation, if any, between lethality of various strains and the response of partially resistant hosts (such as laboratory rats and cottontails).

The EcoDynamics group (USA-DTC 1972) reported that 54 carnivores (41 percent) had significant levels of hemagglutinins for *F. tularensis.* This group of carnivores included 52 bobcats (*Lynx rufus*), 19 badgers (*Taxidea taxus*), 8 skunks (*Mephitis mephitis*), 19 coyotes (*Canis latrans*), 30 kit foxes (*Vulpes macrotis*), and 2 domestic cats (*Felis domesticus*). The positive specimens came from the 13 collecting areas around DPG. A more sensitive hemagglutination technique was developed in the early 1970s. Therefore, the higher percentage of serum samples with agglutinins found from 1970 to 1972 (11 percent), may be expected to have higher (though not significantly higher) values when compared to those calculated from tube agglutination testing from 1960 to 1969 (roughly 8 percent). The two tests (tube agglutination, later replaced by microagglutination, and hemagglutination) are discussed later under "Methodology."

The phenomenon of carnivorism among rodents is well known in literature for both dissemination and maintenance of plague and tularemia. Vest and Marchette (1958) fed carcasses of 119 rodents (*Peromyscus* spp.) infected with *F. tularensis* to 11 species of rodents (squirrels, heteromyids, and cricetids). In all cases, every rodent that ingested infective flesh contracted tularemia. Some species (mostly heteromyids) were reluctant to feed on flesh, but did so when starved. The extent to which wild rodents supplement their natural diet with flesh was not determined.

Cabelli, Ferguson, and McElmury (1964) and Cabelli et al. (1964) reported that the mourning dove (*Zenaidura macruora*) is relatively resistant to *F. tularensis,* but the authors speculated that fecal transmission could be significant in dissemination of tularemia to susceptible birds. It is of interest that, when a Schu strain of *F. tularensis* was administered to several species of oceanic birds by several routes, few transmissions from infected to susceptible birds were observed. *Francisella tularensis,* however, was found in the bird excreta although no other evidence of disease (bacteremia) was noted. The brown noddy (*Anous stolidus*), whitecap noddy (*A. min-*

utus), white tern (*Gygis alba*), and sooty tern (*Sterna fuscata*) were susceptible to infection. Infection in these birds was achieved by respiratory or cutaneous pathways, rarely by the oral route.

HOST IMMUNE SYSTEM.— Thorpe and Marcus (1962, 1964a,b, 1965a,b,c, 1966, 1967) and Thorpe, Sidwell, and Marcus (1964) reported on the implication of phagocytosis in *F. tularensis* infections. They determined that the phagocytic system of the immune mechanism functions as importantly as the antibody system for resisting and overcoming infections.

STUDIES OF *F. TULARENSIS* IN SOILS AND ON FOMITES.— At DPG research and testing was conducted on *F. tularensis* to characterize its aerosol stability and persistence in soils and on fomites. Many observations and experiments were conducted by DPG Life Science Division that were apart from studies by contractor groups to DPG such as the University of Utah and EcoDynamics, Inc. and in-house field work by the Environmental and Ecology Branch. Most specific studies on *F. tularensis* were highly specialized and printed as numbered reports (other than USA-DPG 1951–1969, USA-DTC 1971–1973, USA-DPG 1976, 1978, and University of Utah contract reports). The primary purpose of field-related work (referenced above) was to study the nature and geographic distribution of tularemia occurring naturally in the DPG area. An additional purpose was to monitor the potential for intrusion or establishment of tularemia relative to test activities. Both laboratory and field studies of aerosols were conducted from the early 1950s through the late 1960s. Many facts were reported concerning *F. tularensis* in nature. Unfortunately, this information was not readily available to the scientific community at large. Many of these documents are now available through interlibrary loan.

An experiment by Thorne (1966) is pertinent to this presentation. Three predominant soils of the DPG area (sand dune, clay flat, and salt flat) were inoculated with *F. tularensis*. The pH of the three soil types varied but little (7.5–7.9). In general, sand dunes were the least favorable for preservation of *F. tularensis*, probably because this soil dried out faster than the other two. High moisture in the soils at the time of inoculation was the single most important factor for survival. Survival of the organism was better below the surface. Subsequent wetting increased survival. Exposure to sunlight was deleterious. The maximum times after inoculation that tularemia organisms could be recovered from the soil were 90 days in winter and 35 days in summer. When conditions were adverse (as in summer heat), survival was as short as a few hours.

An interesting problem has been reported from USSR by Olsuf'yev and Rodnev (1960). Tularemia infection of humans is acquired by the pulmonary route while harvesting cereal crops. Crops were apparently contaminated by infected *F. t. palearctica*, and human infection resulted from inhalation of dust raised into the air from contaminated straw and grain. These conditions are reported to have caused mass infections in people processing the harvest (Spendlove 1974). Popek et al. (1969) reported that washing sugar beets contaminated by infected rodents in a sugar beet works in South Moravia created aerosols that infected 237 people over four harvesting seasons. To date, similar events have not taken place in the Great Basin. Waterborne tularemia did infect human beings in Oregon during a meadow mouse population explosion (Jellison, Bell, and Owen 1959). A potential for airborne infection of tularemia exists throughout the Great Basin whenever threshing or harvesting operations occur.

METHODOLOGY

SEROLOGY.— With the basic technique of Alexander, Wright, and Baldwin (1950), the staff of EcoDynamics and their predecessors developed a highly sensitive hemagglutination (HA) test. Dr. Bruce Hudson at the Public Health Service, Center for Disease Control, Fort Collins, Colorado, assisted in preparing lipopolysaccharide extract of *F. tularensis* for sensitizing sheep cells. This method is currently used at DPG. Tube agglutination (TA) was replaced by microagglutination (MA) in 1977. Hemagglutination (HA) was first tried by EcoDynamics in 1970, and this test replaced TA in 1972.

Duplicate samples were tested in 1973 and 1978. According to the 1973 Annual Report

(USA-DPG 1976:89–94 and Table 44), testing by untanned sensitized sheep erythrocytes was more sensitive to the presence of antibodies to *F. tularensis* than was testing by agglutination of a stained antigen (MA) by antibodies in unknown samples. The polysaccharide sensitized sheep cells are more likely to yield false positive tests. Today the more sensitive HA test is used as a screen and second confirmation, and the less sensitive MA test is used as a final confirmatory test. In all replicates MA and TA tests gave similar results and TA has been discontinued.

RECOVERY OF PATHOGEN FROM INFECTED ARTHROPODS.— Improvements in techniques are presented in the 1973 Annual Report (USA-DPG 1976). Though the passive HA micro-test became firmly established, discussions of other methods in earlier Annual Reports (USA-DTC 1971–1973) merely allude to more recently developed methods. One of these is the hemolymph test (Burgdorfer 1970), in which the distal end of a tick leg is cut and the hemolymph collected on a slide, stained with immunofluorescent or other dye, and examined. This method was discussed in some detail in the 1971 Annual Report (Deseret Test Center USA-DTC 1972). However the test has not been used at DPG.

SKIN TEST FOR EVIDENCE OF TULAREMIA.— Cutaneous allergic reactions have been developed for the diagnosis of tularemia in rodents and rabbits (Lundgren, Marchette, and Nicholes 1961, 1962). Cutaneous sensitivity was elicited by inoculating as few as 10 *F. tularensis* cells; sensitivity was demonstrable for 25 to 53 weeks, depending on species. This diagnostic test aids in establishing previous infection with tularemia for wildlife species. Buchanan, Brooks, and Brachman (1971) reviewed the use of skin tests for human clinical identification of tularemia and epidemiologic studies. Human reactors may remain hypersensitive for as long as 40 years. Antigen prepared for a human skin test (but suitable for use on hosts such as jackrabbits) is available at the Center for Health and Environmental Studies at Brigham Young University.

IMMUNOFLUORESCENCE.— Karlsson et al. (1970) and Karlsson and Soderlind (1973) reviewed the use of immunofluorescent (IF) technique in identifying 54 strains, 4 from man and 50 from natural hosts (mostly hares and ticks) in Sweden. They found that once techniques have been established in a given laboratory, histopathologic examination was simplified, and the hazard of laboratory-acquired infection was reduced. The IF method was successful for identifying tularemia in decomposed material. Cutaneous allergic reactions and IF techniques are two promising methods for identifying current tularemia activity in human and other mammal populations around DPG.

A TECHNIQUE FOR SAMPLING TABANIDS FOR F. TULARENSIS.— Knudsen, Rees, and Collett (1968) described a trap designed to obtain large numbers of deer flies and other tabanids for surveys for the tularemia organism. The trap is pyramidal, about 1 m high and 1 m across the base. About midway up the triangle face on either side is a rectangular flapped opening for flies to enter. Once inside, the flies can enter a funnel (20 cm diameter) against the tip of the pyramid. The top of the funnel is closed but has small openings around the perimeter. Some of the flies inside the funnel may fall through the narrow end, through a plastic tube into a styrofoam box beneath containing 4 to 8 kg of dry ice, which freezes the flies. The sublimation of carbon dioxide also serves as an attractant and is the only bait used. During one season (1968), Knudsen, Rees, and Collett trapped 1,248 deer flies (*C. discalis*) from marshes bordering the southeastern shore of the Great Salt Lake. Isolates of *F. tularensis* were obtained from flies trapped in this manner.

RECENT AND CURRENT PROJECTS

During 1974 and 1975 personnel at DPG further improved the hemagglutination test, which had proved valuable for the staff of EcoDynamics. Lipopolysaccharide antigen was prepared for serologic examination of wildlife and livestock serum specimens collected around DPG. The macroagglutination test has been replaced by a microagglutination test in accordance with Massey and Mangiafico (1974). Owen (1974) described morphology and characteristics of *F. tularensis* and provided information useful in growing and identifying isolates.

With these recently improved techniques it has been reconfirmed that low levels of antibody occur in serum samples taken from rodents and lagomorphs and a higher incidence occurs in serum samples from carnivores. As presented in preceding annual reports (USA-DPG 1951–1969), sera from a few wild horses at DPG were nearly all positive, but generally antibody response in livestock varied. A greater percentage of sheep seem to possess tularemia agglutinins after a stay on a distant summer range than sheep bled during the winter around DPG. Curiously, specimens of deer serum contributed by hunters in 1973 possessed no demonstrable antibody, though response in deer had been high during some previous years.

Incidence of tularemia in wildlife around DPG will be reviewed in future publications. The first will deal with jackrabbit population changes and tularemia. There has long been an assumption that population reduction of jackrabbits is somehow associated with outbreaks of tularemia in nature. During the last 13 years quantitative data have been collected around DPG which support the general observation that the jackrabbit is subject to large changes of a cyclic nature. While dying jackrabbits infected with *F. tularensis* have been found, the organism or the disease it produces has not been proved responsible for a widespread decline in jackrabbits. For example, Philip, Bell, and Larsen (1955) recorded infected *Dermacentor parumapertus* from infected jackrabbits during a peak in the population cycle of these lagomorphs in Nevada. Firm evidence that tularemia was responsible for eventual decline of the population was not demonstrable. There appears to be simultaneous association of pathogen activity (e.g., evidence of antibodies) from cattle, sheep, carnivores, cottontail rabbits, jackrabbits, and rodents. There also seems to be an inverse correlation with jackrabbit density, particularly the marked decline of jackrabbits in the DPG area (definitely evident in 1973). At that time there was an apparent increase in tularemia activity. This event followed rather closely the increase of activity of *F. tularensis* in all indicator species during the early 1970s.

Epizootiologic and epidemiologic studies were conducted in California (outside the Great Basin) by Lane and Emmons (1977). They concluded that human cases have gradually decreased since 1927, and they theorize that the cause was urbanization and selective pressures that have resulted in a decreased virulence of organisms maintained by reservoir species. A gradual decrease is not evident from data on human tularemia collected from Utah, but urbanization correlates with a decrease of incidence of tularemia as in California. There is a periodic resurgence in time that may be more marked in Utah than in California.

Distribution of Recent Human Cases

The Communicable Disease Section of the Utah State Division of Health has kept records of reportable diseases, including tularemia, for many years. With their permission, recent records representing current conditions have been tabulated and are presented as part of Figure 1. Thorpe et al. (1965) and Jellison (1974) have assembled records of tularemia cases through 1964. Jellison's format has been used here with additional detailed information included.

In Figure 1 the number in each county on the upper right is 1 percent of the human population in 1977. The number on the upper left is the total cases of tularemia reported from 1941 through 1977 (37 years). The larger figure in the center of the county is the number of tularemia cases per 100,000 persons per annum, averaged for 37 years. The ratio between the total number of cases in each county and the 1977 population of each county was analyzed with a posteriori test by simultaneous testing of the homogeneity of sets of replicates for goodness of fit (G-Statistic, Sokal and Rohlf 1969). Ten sets of samples (under "maximum nonsignificant ranges" in Table 1) were homogeneous; that is, no ratio within each of these sets was significantly different at the 5 percent level of confidence. The counties which are indicated as significantly higher under "exclusive ranges of homogeneous ranges" overlap with no ratio included in the low group. Ratios in Table 2 are expressed as average cases per 100,000 per annum on the map. Three rural counties, Daggett, Millard, and Rich, had values above 15 per 100,000. Seven more rural

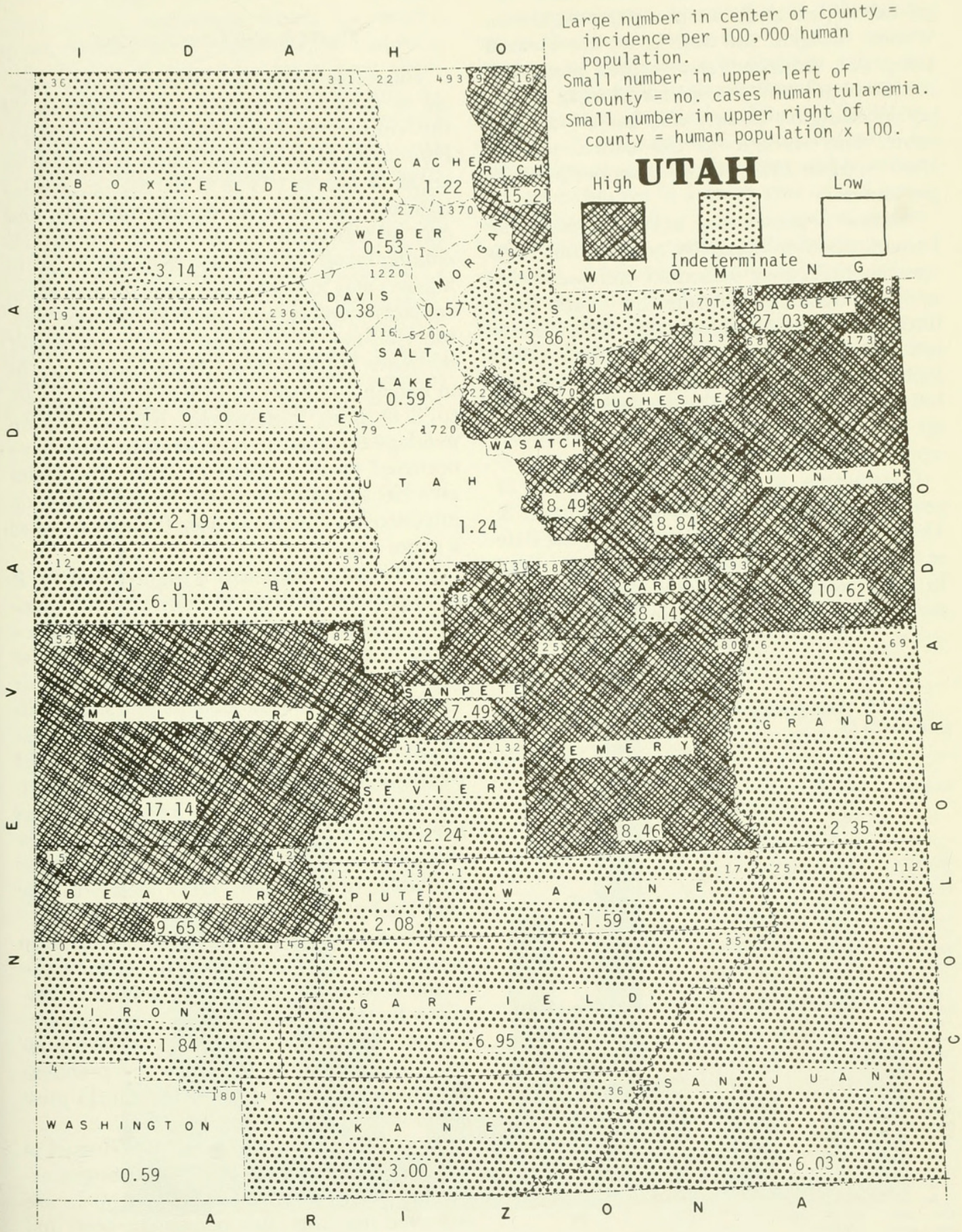

Fig. 1. Incidence of human tularemia, 1941 through 1977.

counties, Beaver, Carbon, Duchesne, Emery, Sanpete, Uintah, and Wasatch, had values above 7 per 100,000. Counties with the lowest values (less than one per 100,000), Davis, Weber, Morgan, and Salt Lake, are located along the Wasatch Front, which has dense human population (except for Morgan County). Washington County also has a very low value. The average for the entire state of Utah (1941 to 1977) is 1.66 cases per 100,000 per annum.

Figure 2 shows the actual number of known cases in Utah by year from 1960 through 1977. Two periods of increase above average occurred during the years 1961 through 1964 and 1969 through 1971. Values less than 10 were experienced from 1965 through 1968, and the high of 1971 was followed by a series of values which were lowest for the longest departure from the average for 1972 through 1977.

Distribution of cases by month for the 17 years preceding 1978 is shown in Figure 3. These cases represent date of report, not date of onset or contact with sources of infection. In most cases contact would occur about a month earlier, making the lowest three months January through March, and highest three months July through September.

TABLE 2. Homogeneity of sets of replicates tested for goodness of fit.

County	Ratio: Cases / Pop.	Maximum Nonsignificant Ranges	Exclusive Ranges of Homogeneous Ratios
Daggett	.01000		
Millard	.00634		
Rich	.00562		
Uintah	.00393		
Beaver	.00357		
Duchesne	.00327		High
Wasatch	.00314		
Emory	.00312		
Carbon	.00301		
Sanpete	.00277		
Garfield	.00257		
Juab	.00226		
San Juan	.00223		
Summit	.00143		
Box Elder	.00116		
Kane	.00111		
Grand	.00087		Indeterminate
Sevier	.00083		
Tooele	.00081		
Piute	.00077		
Iron	.00068		
Wayne	.00059		
Utah	.00046		
Cache	.00045		
Salt Lake	.00022		
Washington	.00022		Low
Morgan	.00021		
Weber	.00020		
Davis	.00014		

REVIEW AND CONCLUSIONS

Tularemia organisms were probably present in nature and in man around the turn of the century in Utah and perhaps earlier. *Francisella tularensis* in Utah is ubiquitous in terms of habitat. Type B (*F. t. palaearctica*) typically occurs as an aquatic infection and may be transmitted from natural sources (including water and aquatic mammal hosts) to humans and to nonaquatic hosts by ingestion, contact, aerosols, and several arthropod vectors (Jellison, 1974). Type A (*F. t. tularensis*), the more virulent form, which usually occurs in nonaquatic hosts and their arthropod vectors, is more widespread; its distribution overlaps the aquatic type. Human cases have occurred in all counties of Utah. The Delta area has sustained repeated human tularemia infections in which the deer fly has served as a major vector.

Although *F. tularensis* is highly invasive, it is fragile and difficult to cultivate and maintain. Strains of greater and lesser virulence occur in nature, apparently simultaneously at the same site and even in the same host or vector. Despite well-documented strain differentiation, only two subspecific designations are accepted currently. Classification of tularemia organisms is a complicated subject. No coordinated effort by researchers has been made to keep all of the strains, and few attempts have been made to verify strains available. In Utah only DPG maintains any identified strains.

Although numerous variant strains occur in nature, workers have agreed to accept types A and B (or their counterpart names in references to this disease). While these concepts are not necessarily germane to current studies, it is necessary to recognize the problems that numerous strains, which are always present in nature, pose in everyday studies.

Recent contributions made by personnel at DPG include evidence that the pathogen exists in virtually all areas where specimens are collected regularly, that nonaquatic hosts and their vectors seem to harbor the more virulent Type A (*F. t. tularensis*), and that rodent hosts seem involved superficially. The role of

jackrabbits in maintenance and transfer of tularemia is poorly understood. Serum specimens with high titers are most frequently found among carnivores, which apparently do not develop overt symptoms but maintain antibodies to *F. tularensis* for a long time, and livestock that are exposed to vectors. As with jackrabbits, the part that carnivores and livestock have in epizootiology of tularemia is unclear. Although some birds are susceptible, the pathogen passes from birds with difficulty. They probably play no role in epizootiology in the Great Basin. Levels of serum agglutinins among various species of mammals correspond well both geographically and in time. As the antibody levels rise slightly in rodents and lagomorphs, a concomitant increase is found in serum samples of carnivores and livestock. Tests by the former Plague Laboratory in San Francisco and at DPG indicate that fleas are probably not vectors.

To improve our knowledge of epizootiology of the disease, one needs a clearer understanding of the role of jackrabbits in transmitting tularemia and whether tremendous fluctuations in population density affect frequency of transmission. Also needed is a knowledge of strain differences and whether virulence changes in a given area over a period of time. Finally, a determination should be made of the regression and subsequent occurrence of tularemia during apparent interepizootic times with regard to geographic sites, ecologic niches, and primary hosts and vectors. Because of the variety of conditions under which the disease occurs, Utah appears to be a prime area for study.

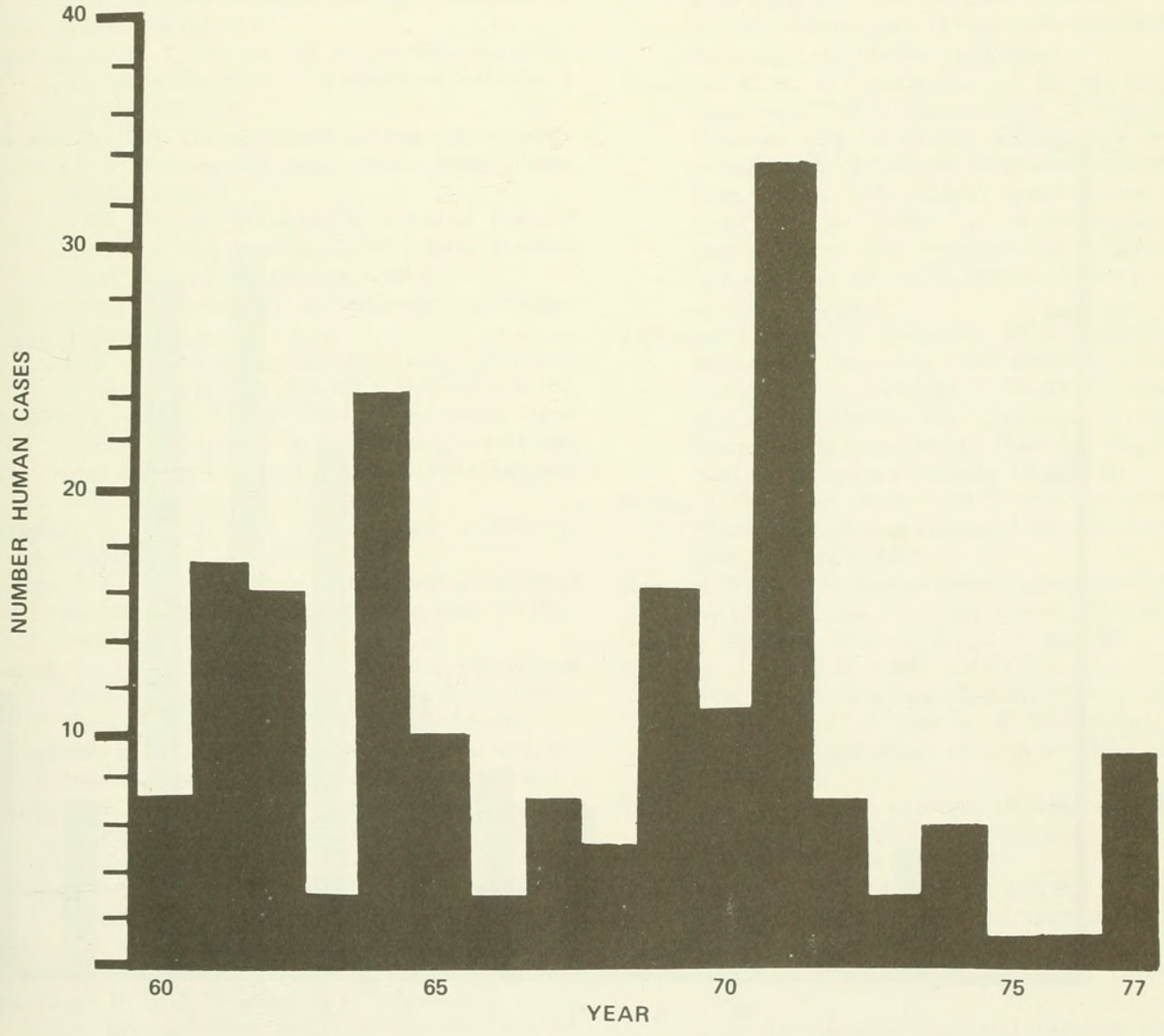

Fig. 2. Annual occurrence of tularemia in humans in Utah, 1960–1977.

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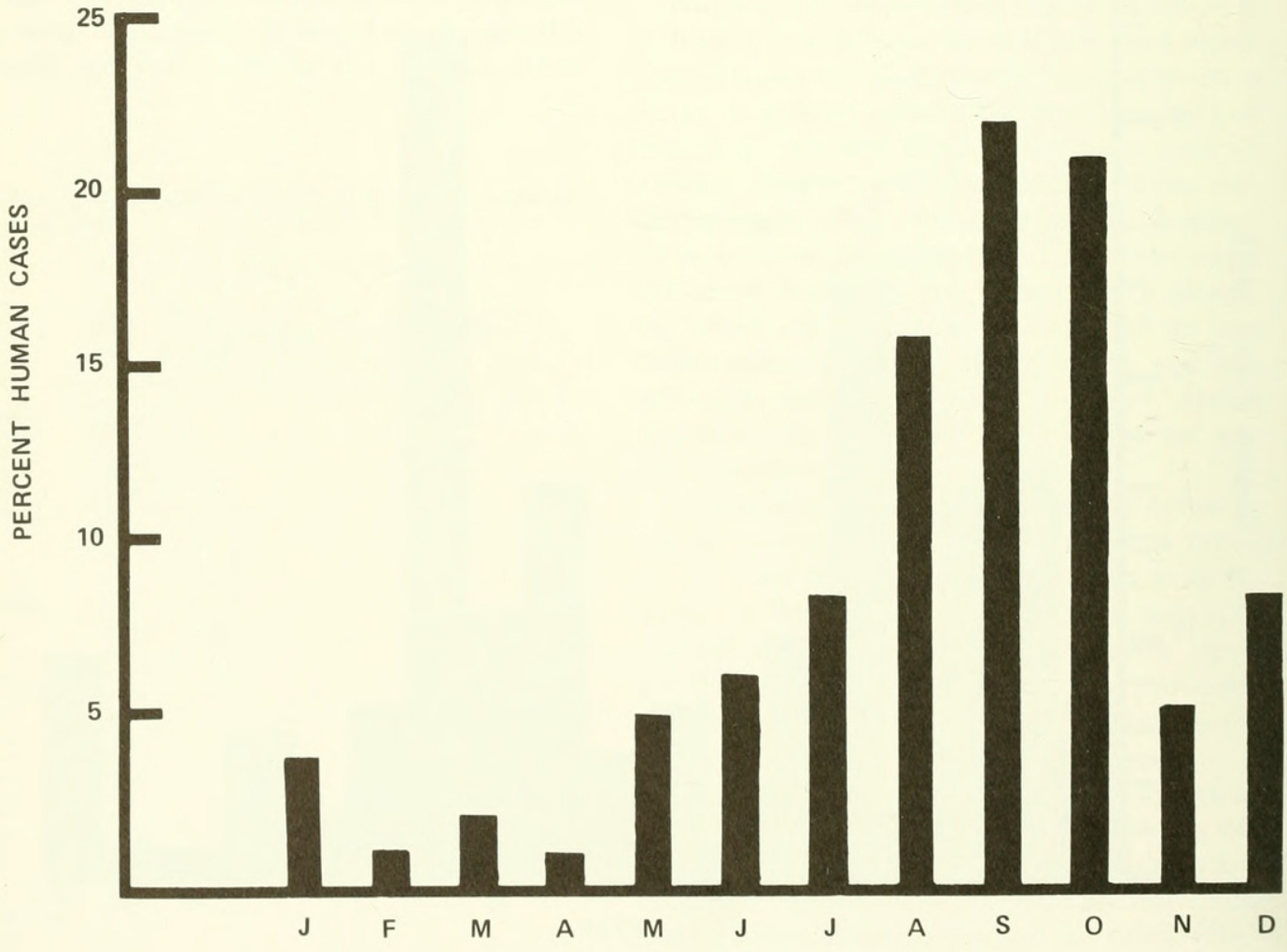

Fig. 3. Monthly occurrence of tularemia in Utah, 1961–1977.

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