HISTORICAL REVIEW OF THE LITERATURE ON Q FEVER

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IDENTIFICATION AND EARLY STUDIES

"Q fever is an acute specific, often serious and occasionally fatal, rickettsial disease of man" (1). Investigation of an outbreak of fever of unknown origin among a large number of workers in a meat plant in Brisbane, Australia in 1935, by Dr. E. H. Derrick, Director of the Laboratory Section of the Queensland Health Department, led to the first knowledge of the clinical entity now known as "Q fever". In his first publication in 1937, Derrick (2) gave a clinical description of nine typical cases and reported on the nature of the causative agent, which he had isolated in guinea pigs from the blood of nine cases and the urine of three. Autopsied guinea pigs had enlarged spleens and livers, and emulsions of these organs were highly infective for new guinea pigs. In the same year Burnet and Freeman (3) demonstrated large numbers of rickettsial organisms in the liver and spleen of infected mice. Derrick (4) named this agent *Rickettsia burneti* after Burnet. He had called the clinical entity "Q fever", that is, a "query", and described it as characterized by headache, fever, myalgia, chilliness or rigor, mild respiratory symptoms, and a normal white blood cell count. Fever was of variable duration lasting from 9 to as many as 24 days.

In 1938 Davis and Cox (5) isolated a filter-passing agent from ticks of the species *Dermacentor andersoni*, which had been collected near Nine Mile Creek, about 32 miles west of Missoula, Montana. They first thought this to be the same or a similar agent to that isolated by Noguchi (6) from ticks in the Bitterroot Valley. They were able to infect guinea pigs by the intradermal, intraperitoneal, subcutaneous, intramuscular, intranasal, and intracerebral routes, with the production of febrile reactions and sometimes death with emaciation in two to three weeks. At necropsy infected pigs showed enlarged mesenteric and inguinal lymph nodes, engorged spleens, and icteric polar fat of the testes. Surviving guinea pigs were shown to be immune for as long as 116 days. The agent was maintained in guinea pigs by spleen passage. It was also shown to pass Berkefeld N and W filters, which are generally impermeable to rickettsiae. The agent was resistant to glycerol and to storage at 8 C up to 116 days. There was no cross immunity with the rickettsia of Rocky Mountain spotted fever or that of endemic typhus.

Parker and Davis (7), investigating the transmission of this filterable agent in *Dermacentor andersoni*, found it to survive in and be transmitted by nymphal and adult forms infected in the larval stage, and to survive through the eggs deposited by infected females, being transmitted to the progeny.

Cox (8) described the rickettsia-like morphology of this agent, a gram negative, pleomorphic, rickettsia-like organism, occurring both intra- and extracellularly in the tissues of infected guinea pigs. It would not grow in a leptospira-media, but was readily carried in a Maitland tissue culture of minced chicken embryo in human ascitic fluid or modified Baker's solution.

In 1939 Cox (9) published further data on his filter-passing agent, showing that it could not be cultivated and carried in serial passage in cell-free media, such as is commonly employed for the bartonellae, even though it would survive long periods in such media without transfer; and that it would pass filters that ordinarily retain bacteria and rickettsiae. He deemed it advisable to classify it tentatively with the rickettsiae and on the basis of its filter-passing ability suggested the name *Rickettsia diasporica*.

Cox (10) then found that his *Rickettsia diasporica* grew better in tissue cultures of minced yolk sac tissue than in minced chicken embryo, and obtained infective titers of 10^{-7} or 10^{-8}. No growth occurred under complete hydrogen tension. When yolk sac cultures were inoculated into guinea pigs, fever developed in 24 to 48 hours and death occurred in 7 to 12 days, though guinea pig spleen passage resulted in febrile reactions in 4 days and death in 2 to 3 weeks. However, the rickettsia grew even better in the yolk sac of the developing chick embryo, where

it produced 10 to 1000 times the infectivity of tissue cultures. Cox regularly obtained one billion infectious units per gram of tissue and titers as high as 10 to 100 billion infectious units were found. Cox (11) further studied the susceptibility of other laboratory animals and found white rats and mice were susceptible to infection, but had no signs of illness except enlarged spleens. Rabbits were also susceptible to inoculation but gave no definite febrile response. Rhesus monkeys gave no febrile reactions but could harbor the infective agent in the blood. Cox found that the feces and viscera of the adult *Dermacentor andersoni* contained extremely large numbers of rickettsiae, showing titers as high as chick yolk sac cultures. He then prepared vaccines from chick embryo tissues and from *Dermacentor andersoni* feces which he used to protect guinea pigs against infective doses of rickettsia as high as 10,000. Polyvalent vaccines for Q fever and Rocky Mountain spotted fever gave protection against both agents.

During these latter investigations a staff member from the National Institutes of Health visited the Montana laboratory and assisted in making egg culture transfers of this agent. Fourteen days after his return to the National Institutes of Health he developed a febrile illness. Rickettsiae were isolated from his blood on the sixth day of illness. Cross immunity tests showed complete cross immunity between this isolated strain of *Rickettsia* and the Montana agent. Guinea pigs in the National Institutes of Health laboratory which had been immunized to a Q fever strain from Australia were, however, also immune to this agent. Therefore, Dyer (12) suggested the possibility that these two diseases were identical.

An exchange of rickettsial strains between the National Institutes of Health and the Walter and Eliza Hall Institute in Melbourne led to studies which proved that this was true. Dyer (13) reported on the similarity of the Australian and Montana strains, showing that they gave cross immunity in guinea pigs, as well as cross protection. Neither produced agglutinins for the *Proteus* organisms and both strains were agglutinated by the sera from the one patient from the National Institutes of Health known to have been infected by the Montana strain, and in whom the clinical disease appeared to have been similar to the Australian disease. However, there seemed to be some strain differences, as monkeys could be infected with the Australian Q fever strain but not with the Montana strain. The Australian agent produced a milder disease in guinea pigs and did not produce a local skin lesion at the point of inoculation as did the Montana strain. However, it was thought that the Australian agent may have been attenuated in transit. Because of the priority of Burnet's isolation, the organism now became universally known as *Rickettsia burneti*.

EPIDEMIOLOGY

Early Studies

Infections among laboratory personnel have been a striking feature in the development of knowledge concerning this disease. Such infections occurred in Derrick's laboratory in Brisbane (14), as well as in the laboratory of Burnet in Melbourne (15). No reports of naturally occurring cases had appeared in the United States, but in 1940 an outbreak of 15 cases of pneumonitis occurred among the employees of the National Institutes of Health. The causative agent was isolated from the blood of three patients and identified by cross immunity, cross protection, and cross vaccination tests as identical with *Rickettsia burneti* (16), which was being studied in the laboratory. There was no clear-cut evidence as to the method of transmission, and no secondary cases occurred. Clinical study of these cases by Hornibrook and Nelson (17) showed that roentgen-ray examination of the chest gave consistent evidence of pulmonary lesions. Aside from a short, hacking cough without sputum production and vague neuralgic-like chest pains in a few patients, no signs were observed that would particularly indicate pulmonary involvement nor were distinctive signs present on physical examination of the lungs. Nevertheless, soft, infiltrative lesions, sometimes single, but often multiple, were seen on the x-ray films. This discovery of an inapparent pneumonitis as a characteristic feature of Q fever in man marks the beginning of a new era in the clinical recognition of the disease entity.

Dyer, Topping, and Bengtson (16) suggest a similarity between the clinical finding in these cases and those of various reports in the literature during 1935 to 1940 of cases of "acute pneumonitis" and "atypical pneumonia". Bowen (18)

describes cases of what he calls "acute influenza pneumonitis" occurring among troops stationed in Hawaii. He was concerned with the frequency of unsuspected bronchopneumonia in the lung bases of patients clinically regarded as cases of acute or chronic bronchitis and comments that this finding appears to be more common in Hawaii than among troops stationed elsewhere. The eight cases of "atypical pneumonia" reported by Reimann (19) from the Jefferson Medical College and Hospital exhibited cyanosis and dyspnea, as well as pneumonic and neurologic symptoms that do not appear typical of Q fever. Reimann also describes the isolation from two patients of an infective agent which was weakly virulent for mice, producing pneumonitis and encephalitis in two weeks after inoculation. Smiley (20) reports 86 cases of "acute interstitial pneumonitis" among Cornell students, occurring between 1937 and 1939, characterized by cough, pain in the chest, and sore throat. His findings suggest that this was a contagious disease with the occurrence of secondary cases, a finding not compatible with available evidence on the epidemiology of Q fever.

The investigations of laboratory outbreaks failed to elucidate the mode of transmission of the infection. However, Derrick, Smith, Brown and Freeman studied the occurrence of the disease in animals in their natural state in Australia, and in 1939 published a report (21) involving the bandicoot, "a common small animal of the Australian bush," in the epidemiology of the disease. Bandicoots were shown to possess agglutinating antibodies to the rickettsia of Q fever and to be susceptible to the disease upon inoculation. A further paper by Derrick and Smith (22) in 1940 reported the isolation of three strains of *Rickettsia burneti* from the bandicoot. The next step was the search for a tick vector. Smith and Derrick (23) reported the isolation of six strains from the tick, *Haemaphysalis humerosa*, a common ecto-parasite of the bandicoot. Smith (24) showed that all stages of this tick could be infected and that the feces of such ticks were highly infectious for guinea pigs through the abraded or unabraded skin. However, history of tick bite has not been a feature of human infections so far reported.

Following these studies epidemiological surveys were made (25) utilizing the presence of serum agglutinins as an index of infection. The presence of agglutinins in the sera of abattoir workers who had no history of suspicious disease led the authors to conclude that Q fever may occur as an inapparent infection in the human. A further study (26) of the occupational and geographical distribution of Q fever patients in Australia showed that nearly all the patients living in the country were associated with cattle, and practically all the city patients worked at abattoirs. Agglutinins for Q fever were demonstrated in the sera of 12 of 879 dairy cows tested, but no rickettsiae were recovered from any of the cattle. There is no record that milk was tested at this time.

In a discussion of the epidemiological findings on 176 cases diagnosed in Queensland, Derrick (27) in 1944 suggested a mode of transmission involving the bandicoot, cattle, and four species of ticks. He thought infection in the bandicoot might be maintained by the ticks *Haemaphysalis humerosa* and *Ixodes holocyclus*. Infection in cattle might be maintained by the ear tick *Haemaphysalis bispinosa*, and transmitted from cattle to man, such as the dairy farmer, by either the bite of *Haemaphysalis bispinosa* or *Boophilus annulatus microplus*. The source of meat workers' infection might be tick feces in infected dust, although the cases occurred in the meat workers in a curiously haphazard and spasmodic fashion, so that it seemed the source of infection did not persist in the environment.

The first naturally occurring case of Q fever in the United States was reported in 1941 by Hesdorfer and Duffaloe (28) and was observed in a 20-year-old male from Missoula, Montana. This patient had an onset with fever, leukocytosis, and abdominal symptoms, but pneumonic lesions were demonstrated by roentgen-ray examination. Although his acute sera produced no symptoms in guinea pigs, at three weeks after onset, his sera had an agglutinating titer of 1:80 against Q fever rickettsiae, and at six weeks a titer of 1:160. This man had been working in the woods at Christmas time felling trees but gave no history of tick bite. The mode of infection was not determined.

Q Fever in the Mediterranean Area

Until 1944 Q fever had been recognized as a disease occurring chiefly in Australia; interest in the United States and other parts of the world was confined to those interested in research on

rickettsial diseases. But in the winter of 1944 and the spring of 1945 eight outbreaks of a disease resembling primary atypical pneumonia occurred among United States Army troops stationed in the Mediterranean area. Robbins *et al.* reported on the clinical features, epidemiology, and the etiological agent concerned. Isolation and identification of rickettsia from the blood of these patients established the outbreak as Q fever.

The disease (29) was manifested by a sudden but not severe onset, with chilly sensations, sweats, malaise, weakness, muscle aches, frontal headaches, and anorexia. Uncommonly chest pain and mild gastrointestinal symptoms occurred. In some cases a "two-hump" phenomenon was seen, with mild symptoms lasting two or three days followed by recession for as much as a week. Return of symptoms resulted in more severe illness. The course of the illness was characterized by severe frontal headache, malaise, chills, retro-orbital pain, anorexia, hacking cough, and chest pain. On physical examination there was fever, usually between 103 and 105 F, a slight bradycardia, a few crepitant rales and dullness in localized areas in the chest, and splenomegaly. In a few cases slight stiffness of the neck appeared, and some patients had a generalized adenopathy. The roentgenological findings were particularly characteristic. There was pneumonic consolidation in patchy areas, having a homogenous, ground-glass appearance. The majority of the cases had single lesions involving part of a lobe, most frequently the lower lobes. There seemed to be no correlation between the extent of the pneumonic involvement and the severity of the clinical disease. White blood cell counts and urine examinations were normal. Blood cultures for bacteria and febrile agglutination tests were negative. Sedimentation rates were elevated during the acute stage of the disease, with values of 20 to 50 mm per hour, and returned to normal during convalescence. No cold agglutinins were demonstrated, nor were antibodies for influenza or psittacosis viruses. Bed rest was the principal means of treatment, sulfonamide and penicillin therapy being tried without success. In general, no complications ensued, and once the temperature returned to normal, the patient was left with no residual symptoms except moderate weakness, which varied with the severity of the acute illness. A weight loss of 15 to 20 pounds during the illness was the rule.

This disease was differentiated from primary atypical pneumonia of unknown etiology by its acute onset, lack of upper respiratory symptoms, rapid convalescence, and the absence of cold agglutinins in the blood. The differential diagnosis included a number of other diseases producing pneumonia, both viral and bacterial, as well as mycotic, but since no bacteria or fungi could be isolated, and no viral antibodies demonstrated, these appeared to be eliminated.

The diagnosis was confirmed by the isolation of the rickettsia of Q fever (30), 16 strains being recovered from patients' blood by the intraperitoneal inoculation of guinea pigs.

The description of these eight military outbreaks is the first report of Q fever in the Mediterranean area (31). Most of the outbreaks occurred in the North Apennine region between Florence and Bologna, but one was in Corsica and one had its origin in Greece. This seems to indicate a widespread distribution of the disease, and the demonstration of complement-fixing antibodies in the adult civilians of the town of Pagliana is evidence suggesting that the disease is endemic there.

The attack rate was between 20 and 30 per cent of the strength of the military units involved. The disease showed a distinct tendency to remain localized and affect only the units occupying certain billets. This gave rise to the hypothesis that Q fever is a "place infection." The majority of the epidemics were associated with the presence of animal life, such as pigeons, rats, mice and cattle. There was striking association also with accumulations of dust, either in attics or on hay and straw. Although some of the outbreaks were explosive in character, pointing to a common source of infection, in no instance was food or water incriminated. Transmission by insect bite seemed unlikely, as there was a universal failure of patients to report any bites. The epidemological evidence did not indicate the likelihood of person to person spread, and no cases occurred among hospital personnel caring for patients, or among other patients hospitalized in the same wards with cases, in spite of the fact that no isolation precautions were taken. Although the authors hypothesize that the disease was transmitted by the inhalation of dust infected with animal or insect excreta, it was not

possible to determine definitely the source or mode of transmission of the disease. However, the evidence concerning the interval between infection and onset of symptoms was clear-cut and consistent. The incubation period was found to be from 14 to 26 days, with a mean of 19 to 20 days.

The studies on the etiological agent involved in these outbreaks had been carried out by the Virus Section of the 15th Medical General Laboratory, and in the summer of 1945 20 cases of Q fever occurred among the laboratory personnel (32). The most likely mode of transmission appeared to be the inhalation of infected air, the rickettsiae having become suspended in the air of the virus laboratory. The beginning of the outbreak coincided with the growing of the rickettsia in chick embryos, for the agent had been previously maintained in guinea pigs for two and one-half months without evidence of human infection.

At the same time that these investigations were being carried on in the Mediterranean area, Major C. J. D. Zarafonetis learned from Dr. J. Caminopetros of an outbreak resembling influenza which had occurred in Athens and its suburbs during the winter of 1944–45 (33). The disease appeared to differ from ordinary influenza in that specific lesions of the lungs were evident on x-ray examination. Though apparently endemic in Greece, it had affected the Germans there severely and they had termed it the "Balkan Grippe". Dr. Caminopetros had established in guinea pigs a readily transmissible febrile infection from the blood of one of these patients. Guinea pig tissue specimens were forwarded to the Respiratory Diseases Commission Laboratory, and from these an agent was isolated in chick embryos and identified as a strain of Q fever rickettsia, then termed the "Balkan Grippe" strain.

This strain was used in agglutination tests to identify an outbreak of acute febrile illness occurring among troops returning from Italy in May of 1945. These troops debarked at Newport News, Virginia after a nine-day voyage from Italy and were transferred to Camp Patrick Henry, Virginia. Of 379 troops, a total of 143 patients were hospitalized, of which 128 showed pulmonary infiltration. These cases showed the same general syndrome of symptoms as those of the study in the Mediterranean area. This outbreak appeared to have more mild and asymptomatic cases, but this could be explained by the intensive case-finding procedures employed, since roentgenographic surveys were made of the entire exposed group (34). This infection was clearly acquired at the Grottaglie Air Base (35), since simultaneous epidemics occurred among troops from this air base en route to Boston as well as to Newport News, but no cases occurred among troops from other bases in transit with Grottaglie Base troops. As judged by the day of sailing, the mean incubation period was 13 days, with a range of 5 to 24 days. The duration of the epidemic was approximately three weeks, with 50 per cent of the onsets within a period of six days. Such a sharply defined outbreak suggests a relatively heavy exposure during a short period of time. In fact, the epidemic curves resemble those of water-borne typhoid fever resulting from a single exposure. However, no evidence pointed to the incrimination of water or food as a common source. In fact, in spite of intensive questioning, little evidence of any kind was uncovered to point to the source of the infection or the mode of transmission. There appeared to be no association with particular buildings or billets, nor with straw, hay, accumulation of dust, or biting insects.

The identification of this epidemic as Q fever rests upon the results of agglutination tests with the "Balkan Grippe" strain of rickettsia as an antigen (36). Fourfold or greater rises in titer were found in convalescent sera of 50 patients with clinical and roentgenological findings compatible with a diagnosis of Q fever. Maximum titers of 1:8 or above were obtained in 109 sera from a group which included both patients and associated well soldiers. The results of agglutination tests were substantiated by complement-fixation tests using the Australian strain antigen which in 6 out of 28 tests gave titers of 1:32 or greater.

Two laboratory outbreaks occurred among personnel of laboratories studying the "Balkan Grippe" and the Italian strains. In the Laboratory of the Respiratory Disease Commission 15 of 49 employees and 1 visitor developed cases of clinically typical Q fever, confirmed by rises in agglutinating titer (37). Infection appeared to be from inhalation of air-borne droplets or droplet nuclei. There was ample opportunity for contamination of the air, since infected yolk sacs

were ordinarily ground in open mortars and sedimented by centrifugation. Two of nine employees regularly working in the egg room wore double face masks and did not develop any disease, while the other seven did.

Work at the National Institutes of Health was also followed by a laboratory outbreak, with 45 cases occurring between February and May of 1946. Thirteen cases showed clinical or x-ray evidence of pneumonitis, and 32 cases were found without such evidence. In reporting on the clinical features, Spicknall *et al.* (38) felt that without serological evidence the cases would have been difficult to distinguish from influenza, although they exhibited much the same symptoms as previously noted in the military outbreaks of Q fever. Both the Italian and American strains were used in complement-fixation tests to confirm the diagnoses. The Italian strain again appeared more sensitive, giving titers of 1:16 to 1:1096, with convalescent sera, while American strain titers varied from 1:4 to 1:512. Four sera failed to react with the American strain at all. There was no correlation between the height of titer and the severity of the infection. Penicillin, sulfadiazine, and immune blood injections failed to alter the course of the disease.

Q Fever in the United States (Figure 1)

The first naturally occurring outbreak of a febrile illness identified as Q fever in the United States came in March of 1946 among stock handlers and slaughterhouse workers in Amarillo, Texas (39). There were 55 cases among 136 employees associated with the handling of livestock, an attack rate of 40 per cent. The cases showed a wide range of severity, varying from mild influenza-like disease to two deaths (40). The Montana Nine Mile strain was used in complement-fixation tests on sera drawn one and three weeks after onset. Rises in titer served to confirm the diagnoses, and the results of the tests could be duplicated without much variation in titer (41). The rickettsial agent was isolated from the blood of two patients by intraperitoneal injection of dilute brown agouti mice. No clinical

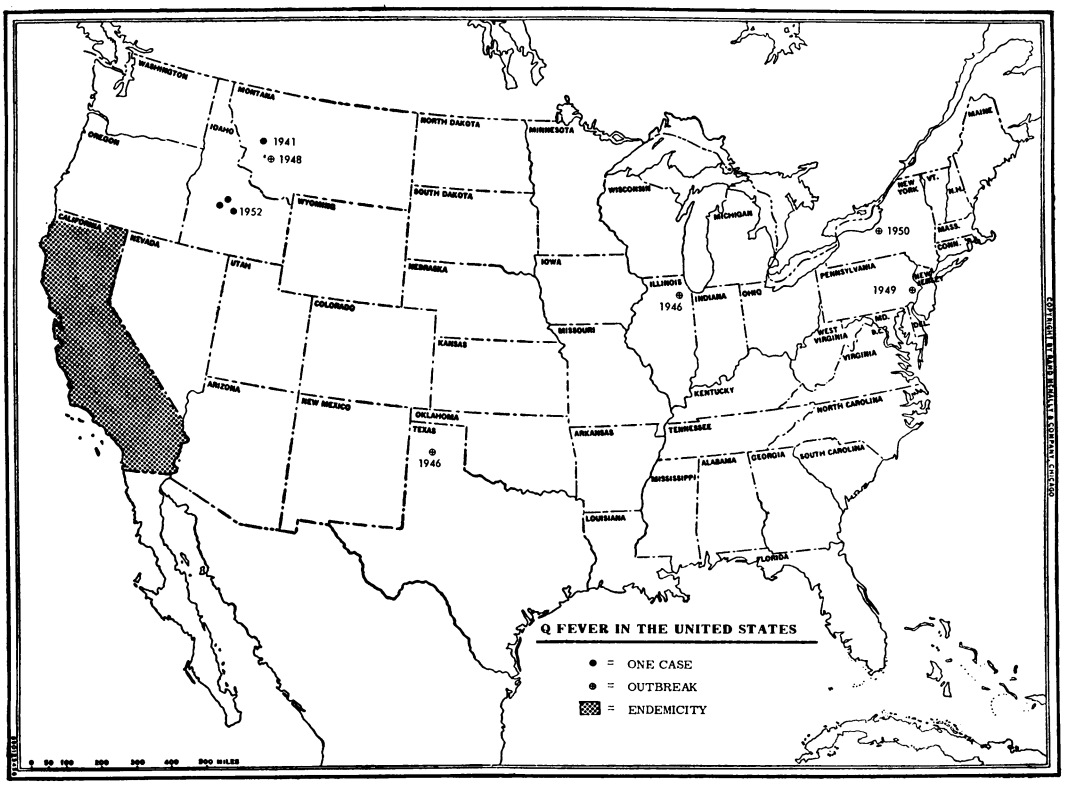

Figure 1. Q fever in the United States.

symptoms appeared in the mice, but complement-fixing antibodies appeared in their blood and spleen passage was readily accomplished (42). A few months later a second such explosive outbreak occurred in a packing plant in Chicago (43). Twenty-three workers from the sheep- and calf-killing department of the plant became ill. Neither sheep nor calves could be incriminated as a source to the exclusion of the other, but the infections definitely took place during a single week in July—the only time all those affected worked together. Evidently the source of infection remained on the killing floor only a short period of time. The same seems to be true of the Amarillo outbreak, in which a single lot of cattle appear to be implicated. Nothing unusual was found in the history of those particular cattle, which were yearlings from Portales and Clovis, New Mexico, and Wheeler, Texas. No history of illness nor of infestation with ticks was found. In neither outbreak did the epidemiological evidence indicate conclusively the mode of transmission, but inhalation of infected dust or droplets appeared the most likely explanation. In both epidemics the attack rates were much higher (68–79 per cent) among those workers actually engaged in the killing of animals and the handling of carcasses, especially where the work involved splatter, *i.e.*, washing, opening the belly and handling of viscera and offal.

The first evidence that Q fever was endemic in this country was contributed by Dr. F. W. Young, a practicing physician in Artesia, California (44). He noted outbreaks of fever in his patients following the "Santa Ana" windstorms in an area where dairying is the principal industry. Dr. Young sent sera to the National Institutes of Health and obtained positive evidence of Q fever infection in eight of his cases. The United States Public Health Service then made a rapid survey of the area, from which they concluded that the disease was endemic in southern California. Cases reported by private physicians as "virus pneumonia" were investigated, and 17 patients with typical clinical histories and positive complement-fixation tests for Q fever were found (45). Titers varied from 1:64 to 1:512. Rickettsiae were isolated from the blood of four cases. In 15 cases the patient had visited or lived near dairies. Sera from dairy cattle were then tested and 16.2 per cent were found to have complement-fixing antibodies for Q fever. There were positive findings in some cattle from all nine of the dairies tested. Titers of 1:8 appeared to be significant in cattle sera. Most of the cattle tested were from the San Joaquin and Sacramento Valleys, but others were from Oregon, Washington, Idaho, Utah, and Colorado. Sera from Texas beef cattle and Maryland milk cows tested at the same time were found negative. The agglutination test was considered unreliable for cattle testing, since it gave 60 per cent positives in 500 to 600 bovine sera. There was no evidence to indicate when Q fever appeared in the area, and few if any ticks were found on cattle in the milk shed.

A field laboratory for the study of the epidemiology of Q fever was established at Hondo, on the property of the Rancho Los Amigos, as a joint project of the National Institutes of Health, the California State Department of Public Health, the Los Angeles City and County Health Departments, and the California State Department of Agriculture (46). Since the serological and epidemiological findings of the survey in Los Angeles County pointed to the dairy industry, Huebner *et al.* (47) then investigated the cow as a reservoir of infection. No rickettsiae were isolated from whole blood, blood clots, urine, or feces of dairy cattle, but they were recovered with relative ease from the raw milk of the four dairies studied. Febrile episodes typical of Q fever were produced in guinea pigs upon the subcutaneous or intraperitoneal inoculation of 3–5 ml of raw milk, and eight strains of rickettsia were established in yolk sac culture from infected guinea pig tissues. These strains were positively identified by cross immunity tests with the Nine Mile strain. Infected raw milk was used for the preparation of butter which was found to remain infectious on storage for 41 days after preparation (48).

About this time a change was made in the name of the Q fever agent. Because of the striking differences which separate these rickettsiae from those of other rickettsial diseases, Bengtson, Steinhaus, and then Philip (49) proposed that the organism be placed in a new genus, to be known as *Coxiella* in honor of Dr. H. R. Cox, the genotype to remain the same. This change appeared justified on the basis that the Q fever agent varies from the type organism, *Rickettsia prowazeki*, in that the former is filterable, is much more resistant to physical and chemical agents,

does not produce agglutinins to the *Proteus* organisms, and does not typically produce the rash seen in other rickettsial diseases. This change in name has been accepted and the organism is now known as *Coxiella burneti* (Derrick) and is so listed in the 1948 edition of Bergey's *Manual of Determinative Bacteriology*.

Since *C. burneti* was known to be a more resistant organism than other rickettsiae, it was now most important to investigate the efficacy of pasteurization in destroying the organism in milk. Four closely observed tests of the holding vat and high temperature fast time (HTFT) techniques of pasteurization as employed in five Los Angeles area dairies were made (50). So far as could be determined, milk pasteurized in the HTFT equipment was rendered free of infection, when the same milk in the raw state was highly infectious. In three of four vat pasteurization experiments, *C. burneti* was apparently eliminated from the milk. But milk from one vat pasteurizer produced antibodies against Q fever in guinea pigs. Similarly 3 of 32 bottles of vat-pasteurized market milk and one of four specimens of vat-pasteurized market cream produced antibodies in guinea pigs. Lennette *et al.* (51), testing dairies in northern California, also found that 1 of 35 tests on vat holding pasteurization and in 2 of 42 tests on HTFT equipment *C. burneti* apparently survived in the pasteurized milk. Ransom and Huebner (52) observed the thermal death point of *C. burneti* in a constant temperature water bath for 30 minutes to be between 63 and 65 C. Survival of some rickettsiae at 63 C (145.4 F) may explain the failure of some pasteurizing techniques to eliminate the organism from the milk.

Once it was established that Q fever was prevalent among the cattle of the Los Angeles area, a search was made for a tick vector. But conditions in this area are not favorable for the *Ixodid* ticks common in the United States, and none were found on the dairy cattle examined. However, the spinoza ear tick, *Otobius megnini*, is indigenous to the southwestern states and when these ticks were collected and examined, *C. burneti* was isolated from 10 of 246 lots tested (53). This finding adds another species to the growing list of ticks known to harbor this infection. But *Otobius megnini* has rarely been recorded as feeding on man, and its role in the transmission of Q fever, even among cattle, is not yet clear.

Stoenner (54) investigated the role of the milking process in the intraherd transmission of Q fever and concluded that it was unlikely that natural infection in cattle was acquired by entrance of rickettsiae through the teat canal, since repeated applications of infected milk to the teats failed to result in any infection in the cow.

Since little clinical evidence of infection was evident in cows known to be shedding *C. burneti* in the milk and having antibodies in their blood, the California investigators felt it desirable to autopsy an infected cow in order to observe the extent of the infection in the tissues. A mature dairy cow known to have had a positive complement-fixation test and to have been shedding organisms for at least two months was killed and autopsied (55). The few lesions found were nonspecific and could not be attributed definitely to Q fever. *C. burneti* was demonstrated in the milk and udder tissues of all four quarters and in the supramammary lymph nodes proximal to the udder. No rickettsiae were isolated from any other fluids or tissues of the cow or of its five-month-old fetus.

A biochemical study (56) of the milk from a cow with an experimental infection of Q fever showed increases in the concentration of butterfat and nonfat solids. These changes disappeared in eight days. No change in the blood hemoglobin occurred.

In spite of the finding of rickettsiae in raw milk, it did not appear from epidemiological evidence that the spread of infection could adequately be attributed to drinking of raw milk. Huebner and his group (57) studied 300 cases of Q fever with three deaths, in Los Angeles and vicinity. Cases occurred throughout the area at all seasons over several years, and were observed in both sexes, in various races, and at ages varying from 3 to 75 years. The age, sex, and race distribution suggests that industrial occupation may be an important source or mode of spread of the disease; 79 per cent of the cases were in males and 91 per cent of the cases fell in the 20- to 59-year age group. However, occupational contact with livestock could account for only 38 per cent of the known cases, as 60 different occupations were represented. Forty-five per cent of the patients lived in close association with livestock yards or dairies, and 32 per cent of the households of patients used raw milk. If these three factors are considered as

possible modes of spread of the disease, and combined, 79 to 100 per cent, or all but 64 of the 300 cases, are accounted for. No common factor was found for the other 21 per cent of the cases. Investigators in northern California (58) also found most patients to be exposed to domestic livestock by occupation or residence. Serological studies were made on some 10,000 persons in selected groups in the southern area (59). The criterion for past infection was a definite 3– or 4–plus complement fixation at a serum dilution of 1:8, or higher, with Henzerling antigen in the Bengtson warm water bath, 37 C technique. This test was believed to be of high specificity, but low sensitivity, and therefore to reflect only part of the total past infection which had occurred. Of the general population group of Los Angeles and environs only 1.36 per cent were positive. Those persons in occupations associated with livestock had positive percentages ranging from 3.9 per cent in employees of meat packing plants handling few dairy cattle to 23 per cent in dairy workers. Six factors were found associated with positive serologic findings: (a) residence less than one-quarter mile from a dairy or livestock yard, (b) occupational contact with livestock or its raw product, (c) the use of raw milk, (d) beginning residence in Los Angeles prior to January 1, 1947, (e) age in years above 39, and (f) a history of illness diagnosed as pneumonia, influenza or fever of unknown origin.

The first human cases of Q fever recognized in northern California were uncovered through serologic surveys early in 1948 (60). Field studies indicated these cases were associated not with dairy cattle but with sheep and goats. When the animals associated with human cases were tested for complement-fixing antibodies, 37.9 per cent of the sheep and 43.6 per cent of the goats, but only 2.6 per cent of the cattle sera were positive (61). Rickettsiae were isolated from the milk of both sheep and goats (62). A serologic survey (63) of 16,045 animal sera from northern and southern California showed that in commercially slaughtered animals in general only 2.1 per cent of the cattle and 3.5 per cent of the sheep had positive findings. But when animals associated with human cases were studied, cattle were found to be the species giving most evidence of infection in southern California, and sheep in the northern area. Goats appeared to be involved in both areas, as 15.4 per cent of the goats tested in the northern area were positive and 11.3 per cent in the southern.

Since contact with livestock seemed so important in the spread of the disease, air samplers were used to try to obtain some direct evidence of environmental contamination by infected animals. When air samples were taken in endemic areas, *Coxiella burneti* was isolated from dust-laden air samples collected in a beef broth fluid from a feeding and holding pen of a dairy in southern California and from the barn of a sheep ranch in northern California (64). Both places were known to be associated with human cases of Q fever. Following this, rickettsiae were also isolated from the air of a shed of a commercial goatery, using a capillary-impinger type of air sampler with sterile skimmed milk as a collecting fluid (65).

Outbreaks of Q fever occurred among the students of an agricultural college (66) where the sheep were found to harbor the infection and aboard a ship transporting goats (67). Epidemiological studies of these outbreaks, and one in a small rural community (68), as well as a general summary of the 350 cases which occurred in northern California during 1948–1949 (69), pointed to a dissemination of the causal agent through the means of contamination of the environment and the atmosphere.

The infection in sheep was studied by means of experimental inoculations by the intravenous route. No signs of clinical disease except fever were observed. Rickettsemia of variable duration was detected, and persistence of rickettsiae in the tissues for at least 43 days suggested that Q fever in sheep is a long-continued latent infection (70). Since Luoto and Huebner (71) had demonstrated *C. burneti* in parturient placentas of cows, the northern California workers (72) investigated sheep placentas. *C. burneti* was found in placentas from 21 of the 72 sheep examined, and positive isolations were obtained from placentas from serologically negative as well as positive animals. It appears that negative serologic findings do not necessarily indicate absence of infection in sheep. The high titers found in placental tissues indicate that this organ constitutes a rich source of infective material for the contamination of the environment. Experiments with intratracheal inoculation of sheep (73) showed that no organisms could be recovered from the inoculated animal until parturition occurred; then rickettsiae suddenly appeared

in the dejecta and secretions of the sheep as well as in the lamb and pen-mates of the inoculated animal. Epidemiological studies (69) showed that Q fever cases in northern California had a seasonal distribution distinctly different from those in the south of the state. Nearly 70 per cent of the northern cases occurred during March, April, and May. Since in northern California lambing takes place only in the winter and early spring months, opportunity for placental contamination of the environment correlates well with the seasonal occurrence of cases. By contrast, in the dairying industry in southern California, parturition with opportunity for environmental contamination occurs the year around, and those cases of Q fever observed exhibited little or no seasonal variation.

Clark *et al.* (74) made a clinical study of 180 cases of Q fever in northern California and concluded that Q fever as seen there was a systemic disease of variable severity, and that clinical or roentgenological evidence of pulmonary involvement was not essential for diagnosis of the disease. He found hepatomegaly and liver tenderness rather common and thought that evidence of liver damage should not be considered inconsistent with a diagnosis of Q fever. Nausea and vomiting were also common in the more severely ill, and 74 per cent of the patients complained of true shaking rigors on one or more occasions. Febrile illness of more than three weeks' duration was not uncommon, especially in older age groups. Most patients had sudden onset and extremely severe headache, with fever which characteristically showed daily remission toward normal. One-fourth of the patients had a dry, nonproductive cough. Diagnosis of these cases as Q fever rested upon either: (a) demonstration of *C. burneti* in the blood during the acute phase, (b) demonstration of a fourfold or greater rise in complement-fixing or agglutinating titer on convalescent sera, or (c) a titer of 1:32 or above in a single serum specimen with a history of illness clinically compatible with Q fever within the previous two months.

Since the discovery that Q fever is endemic in California, a few cases have been reported from other sections of the country. Bondi and Sigel (75) in 1949 described a case of serologically authenticated Q fever naturally acquired in Pennsylvania, the first to be reported from the eastern United States. In 1952 Anderson (76) reported three cases among workers on a sheep ranch near Gooding, Idaho. These cases occurred during lambing season. Three occupational epidemics of Q fever were reported in the United States in 1949 and 1950. The first was an outbreak among laundry workers (77) who handled soiled laundry from a laboratory engaged in Q fever studies. Three clinical cases and three serologically positive cases of subclinical infection were found. Seven workers in the same laundry, whose work did not involve the handling of soiled linen before laundering, showed no evidence of infection. In 1950 an outbreak of Q fever occurred among the employees of a rendering plant in Syracuse, New York (78), which had received infected guinea pig carcasses from a research institution. Nine patients were hospitalized and serologic titers to Q fever were found in 35 additional workers. Sigel *et al.* (79) reported on an epidemic among workers in a wool and hair processing plant. Sixty-seven of 152 employees had titers to the Nine Mile strain varying from 1:2 to 1:2048. Raw and scoured wool were imported by this company from many countries, and operations in the plant produced great amounts of dust.

International Aspects (Figure 2)

In August of 1945 (80) a case of Q fever was encountered in Panama during a study on the etiology of atypical pneumonia. This case, the first described in Central America, was identified as Q fever by serological and immunological tests with the American Q fever strain, and a "Panamanian" strain of rickettsia was isolated from the patient. Since this time, two more cases among permanent Panamanian residents have been described (81). A second Panamanian strain of rickettsiae, strain "JD" was isolated from one of these patients.

Since 1948 Q fever has been reported from many other parts of the world. Herzberg (82) reports an epidemic of 175 cases in Stuttgart, Germany in 1950. In Turkey, Payzin (83) found antibodies to Q fever in man, sheep, goats, and cows, as well as evidence of many human cases. Clavera (84) reported four cases of laboratory-acquired infection in Madrid, and Simovic (85) and others (86) have reported epidemics of proved Q fever in Bosnia.

Further work in Italy, where Q fever has been known since World War II, has shown that

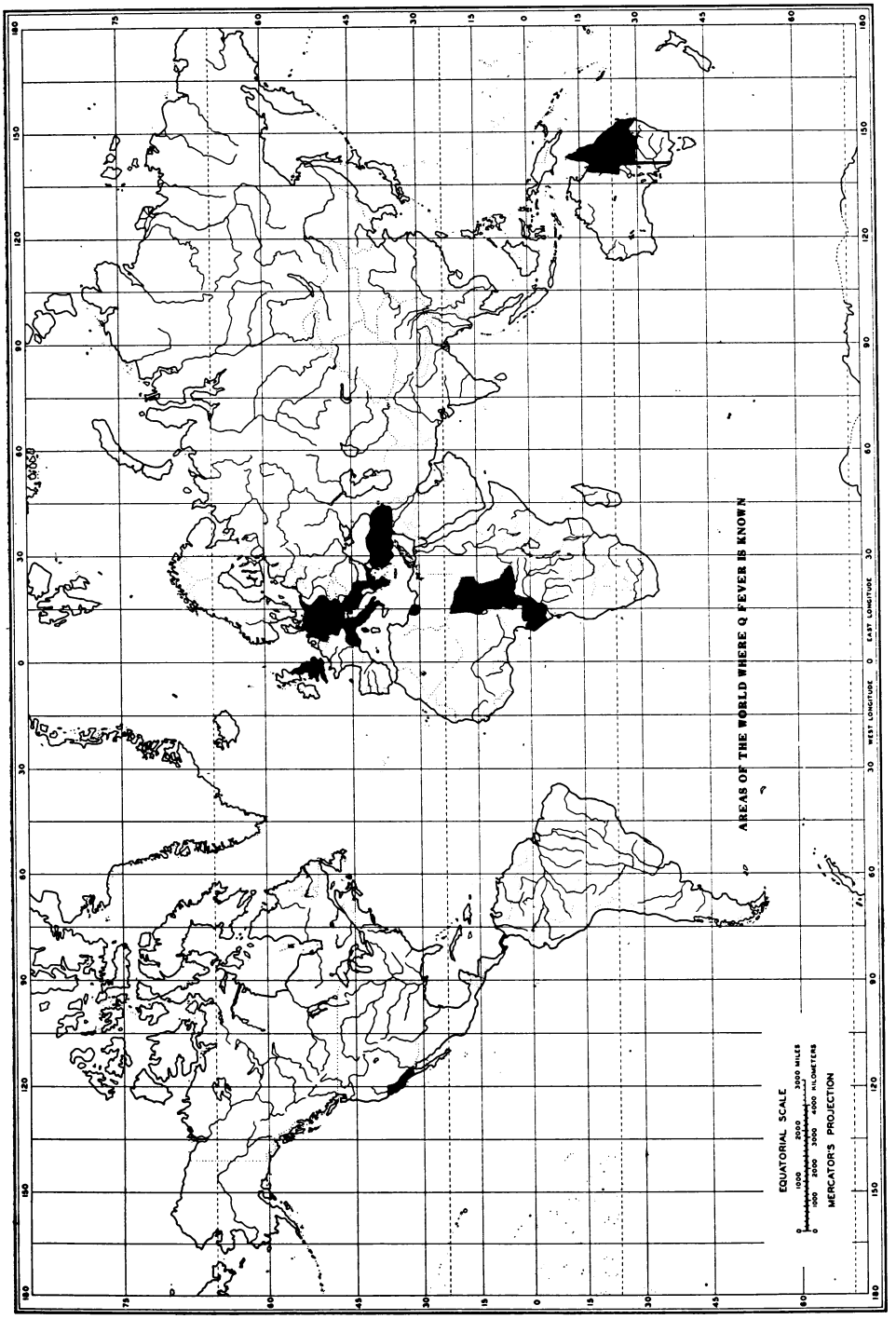

Figure 2. Areas of the world where Q fever is known.

complement-fixing antibodies can be demonstrated in the sera of cattle, sheep, goats, and dogs, as well as geese and pigeons (87), and *Coxiella burneti* has been isolated from cow's milk and sheep placentas (88). Babudieri *et al.* (89) report an outbreak of 46 cases at Maccarese (Rome) in 1951, in which sheep are involved. He studied experimental infection in sheep and isolated rickettsiae from blood, milk, and urine (90). Dogs are thought possibly to serve as a reservoir of infection, transmitting the disease to sheep and cattle through the tick vector, *Rhipicephalus sanguineus*. Domestic fowl may also be a source of infection for humans, since fowl associated with human cases had serum antibodies, whereas fowl not associated with cases of Q fever did not (91).

Stokes (92) reported additional cases of Q fever among abbatoir workers in Australia, but Lee (93) failed to isolate *C. burneti* from the raw cows' milk of the Queensland area.

Q fever in England has been described by Marmion (94) and an outbreak occurred in Canterbury in 1951 (95). Dairy cattle also have been found to be infected in England and *C. burneti* isolated from milk (96).

Serological studies in Oubangui-Chari, French Equatorial North Africa, demonstrated antibodies of Q fever in the natives, and in cattle, sheep, goats, donkeys, and dogs (97). Two epidemics of Q fever occurred in Ruanda-Urundi during 1950 (98), where the disease was severe, due to concurrent malaria and malnutrition. Three months following one of these epidemics *C. burneti* was isolated from the body louse of the area (99). The milk of cattle was also found to be infected, and rickettsiae were isolated from the tick species, *Haemaphysalis leachi*, from cattle and from dogs (100). Giroud prepared a skin-test antigen from chick embryo cultures of *C. burneti* and demonstrated intradermal reactions in shepherds, cattle herders, livestock dealers, slaughterhouse workers, veterinary assistants, and butchers (101).

In February and March of 1951 an outbreak of Q fever occurred among United States military personnel stationed at Tripoli, Libya, North Africa (102). A strain was isolated from this epidemic and sent to the Army Medical Service Research School at Washington, D. C. for study. This strain appeared to be serologically slightly different from the Italian and American strains commonly used as antigens. Patients infected with the North African strain failed to develop rise in titer to the usual antigens until very late in the course of the disease, some not showing rise until the twelfth week after onset.

LABORATORY STUDIES

Comparison of Strains

Since the isolation of Q fever organisms from widely reported outbreaks, much work has been done to compare the various strains both in regard to their infectivity for laboratory animals and their antigenic properties.

Extensive studies of the "Balkan Grippe" agent were made in the Laboratory of the Respiratory Disease Commission (103). The agent was established in guinea pigs, and Caminopetros' observations were confirmed. The infection in guinea pigs was similar to that produced by the Australian strain, and not so severe as that produced by the American strain. No splenomegaly, fibrinous peritoneal exudate, nor organisms in splenic impression smears were observed. In contrast to guinea pigs, infected mice developed enlarged spleens, pleural and peritoneal effusions, and intracytoplasmic inclusions, most commonly in the liver and spleen. These inclusions were found in the endothelial cells lining the sinusoids, but not in the Malphighian corpusles of the spleen or in the liver cords. In general the appearance of the organisms was consistent with that of rickettsiae, *i.e.*, gram negative, minute, pleomorphic rods, staining red with Macchiavello, blue with Castaneda, and purple with Giemsa stains. Many of the organisms were plump rods, while some exhibited coccoid morphology. Occasionally filamentous forms appeared. Intracellular organisms, either singly or in large masses, were found. Some inclusions of tightly packed forms were of 20 to 30 microns in diameter.

The organisms were readily propagated in embryonated eggs when inoculated by yolk sac, allantoic, or intravenous routes. This strain showed a distinct tendency to agglomerate, and allantoic fluids were useless as agglutination test antigens because the organisms were invariably aggregated into masses clearly visible to the naked eye at the time of the fluid harvest. Clumps of organisms also appeared in smears from yolk sac cultures, but the tendency to

agglutinate was not so marked as in allantoic growth. Yolk sac preparations were used as antigens in agglutination tests to diagnose the Grottaglie epidemic, an outbreak which occurred in February, 1954, among British parachute troops stationed in Greece, and an outbreak among personnel of the Respiratory Diseases Commission Laboratory at Fort Bragg, North Carolina.

Q fever strains isolated from the Mediterranean outbreaks were studied in the Virus Section of the 15th Medical General Laboratory (30). Pigs infected with Italian strains developed fever about the ninth day and the infectious agent could be maintained in guinea pigs by blood, spleen, lung, or brain passage. Three of the strains were chosen arbitrarily to represent the Italian *Rickettsia* and named the Henzerling, the Paige, and the Seale. These three strains were then compared with the Australian and American strains of Q fever. Infection in guinea pigs resembled that produced by the Australian strain in that few deaths occurred and no rickettsiae were found in preparations from guinea pig tissue. In contrast, the American strain produced a highly fatal disease with marked splenic enlargement and demonstrable rickettsiae.

Serological comparison showed that the strains behaved similarly as agglutinating antigens but markedly different in complement-fixation tests. Antigens prepared from Australian and Italian (Henzerling) strains exhibited much broader activity than the American (Dyer) strain, which failed to detect antibody in most convalescent sera unless used in extremely concentrated form. The authors felt that the experimental evidence obtained from the complement-fixation studies indicated the interplay of two antigen-antibody systems. There appeared to be at least two antigenic fractions in the Q fever rickettsiae, with quantitative differences between strains. Apparently, antigens prepared from the Henzerling strain contain an antigenic fraction in large amounts which is present in only slight amount in the Dyer strain, since the Dyer strain will react with all sera reacting with the Henzerling strain when used in great enough concentration. When convalescent guinea pig sera is tested with these two strains, it is found that up to the fortieth day after infection Henzerling antibodies are found, but those against the American strain are absent, or present in only very low titer. Between 40 and 70 days antibodies to the American strain appear and approach the same level as those to the Henzerling strain.

Following the isolation of the Panamanian strain, the National Institutes of Health Laboratory made an immunological comparison of its six Q fever strains (104), an Australian, an American (Dyer), the Balkan Grippe agent, a strain isolated during the Fort Bragg laboratory outbreak, the Panama, and the Italian (Henzerling) strain. The Australian strain had been only infrequently passed in eggs for four years, and would no longer initiate infection in guinea pigs, but when the remaining five strains were tested, they showed complete cross immunity. The Panama and American strains produced an average of one more day of fever than did the Italian, Balkan Grippe, and Fort Bragg strains.

Complement-fixation tests showed a definite division of the strains into two immunological groups. The American and Panama strains gave high antigen titers against homologous standard antisera, but produced low serum titers when used as the standard two units of antigen in the test. On the other hand, the Italian and Balkan Grippe strains gave low antigen titers with homologous standard antisera, and extremely high titers when used as standard antigens in the complement-fixation test. Agglutination-adsorption tests also revealed marked differences in sensitivity between strains used as test antigens; the Italian and Balkan Grippe strains being more sensitive than the Panama and American antigens. In reciprocal agglutination-adsorption tests it was more difficult to remove antibodies reacting with the Italian and Balkan Grippe strains than those reacting with American and Panama antigens. However, these tests failed to reveal any definite evidence of specificity of antibody response, and it is doubtful that any convalescent serum would give evidence identifying the infecting strain. But it would seem that an unknown strain could easily be identified as a highly reactive strain, such as the Italian, or as a member of the low reactive group (American).

Berge and Lennette (105) made a study of the serological relationships between eight new strains isolated in California and the Henzerling, Dyer, and Nine Mile strains, the strains commonly in use as antigens in this country. The

eight California strains comprised: the Chino, isolated from sheep in southern California; the Konitzer 5609–5, from sheep in northern California; the Armstrong 8460–1, also from sheep in northern California; the Tickner 553P10, from goats' milk in central California; the Ralph 5941–1, from a cow in the Los Angeles area; the Boren 6191–10, also from a Los Angeles cow; the Otobius megnini, from ticks of that name in southern California, and the Amblyomma americanum strain, from ticks in Texas. When these strains were compared by means of the complement-fixation technique and complement-fixation antibody adsorption tests, they were found to differ widely in sensitivity as antigens in tests with early convalescent sera. However, all reacted almost equally with late convalescent sera. It seemed there was a high content of some common antigenic component.

Agglutination Versus Complement Fixation

Comparison of agglutination and complement-fixation tests on human sera from California cases (106) suggested that the agglutination test may be advantageous for early diagnosis. When sera from patients in the first week of illness were tested, 50 per cent were positive at a dilution of 1:8 or above in agglutination tests and only 9 per cent in complement-fixation tests. By the end of the second week after onset, 92 per cent of the sera gave positive agglutination results and 65 per cent complement fixation. After the third week the results were about the same, 95 per cent positive for agglutination and 97 per cent positive with complement fixation. The median titers were about equal. Maximum median titers for complement-fixing antibodies of 1:128 to 1:256 were obtained by the end of the first or second month, remained essentially unchanged for approximately six months, and then declined slightly. An additional slight decrease in titer was noted after 12 months. Median titers of 1:32 to 1:64 were seen 12 to 28 months after illness. Median agglutination titers were similar to complement-fixation titers at the various time intervals studied, although maximum titers were reached at three to four weeks, with a 2- to 4-fold decrease after three months.

The complement-fixation test appeared to be more economical for most laboratories and a better tool for epidemiological surveys, since these antibodies were observed to persist longer than did agglutinins. Babudieri and Secchi (107), describe a slide-test agglutination technique for 0.02 ml serum, which they believe is more economical and easier than the complement-fixation test for survey use. Their results for the agglutination test correlated well with those from complement fixations. In their work with complement-fixation tests, they (108) found that pyogenic abscesses appeared to provoke nonspecific reaction to Q fever antigen in these tests. However, no nonspecific reactions were observed in sera from patients with antibodies to eggs, syphilis, leptospirosis, typhoid, tuberculosis, hepatitis, typhus, Mediterranean exanthematic fever, ornithosis, or trachoma. They also comment that the use of sheep red blood cells from a ram serologically positive for Q fever does not alter the results of complement-fixation tests.

While at the present complement fixation is the more widely used in the United States for the sero-diagnosis of Q fever, agglutination tests are commonly employed in studies in other parts of the world. Giroud *et al.* (97) used a microagglutination technique in studies on sera from both humans and animals of Oubangui-Chari. They state that *Coxiella burneti* differs markedly from the other *Rickettsia* in agglutination tests, and no cross reactions occur (109).

Stoker and Marmion (110) in England employed an agglutination test to detect antibodies in whey. They found the direct agglutination test more sensitive than either the hemolytic complement-fixation or the conglutinating complement-adsorption test for this purpose. The anti-globulin sensitization test, however, gave the highest titers, as well as specific results, and was the authors' choice for testing. Just recently, the California workers report that continuing studies indicate that the capillary agglutination test on milk is fully as effective as tests on blood serum (111). Comparison of findings from capillary agglutination tests on milk, and blood serum, and from complement-fixation tests show close correlation.

VACCINATION STUDIES

Since outbreaks of Q fever have occurred so frequently among workers in laboratories dealing with this infective agent, Meiklejohn and Lennette (112) attempted the immunization of personnel in their California Laboratory. Bengtson (113) demonstrated active immunity in vacci-

nated guinea pigs, and Smadel *et al.* (114), after immunizing 108 guinea pigs with formalized yolk sac antigens prepared from both Henzerling and Dyer strains, injected 39 humans with similar vaccines. Human beings, like guinea pigs, first produced substances that reacted with Henzerling antigen, but unlike the pigs, few persons subsequently developed Dyer antibodies. In this respect vaccinated persons showed the same serologic response as convalescent patients (29). No serious local or systemic reactions were noted in the Smadel vaccinated group, where three subcutaneous injections of 1.0-ml amounts of vaccine were given. In the Viral and Rickettsial Diseases Laboratory of the California State Department of Health at Berkeley, 50 persons received injections of formalized yolk sac prepared from the Henzerling strain. None had complement-fixing antibodies to this strain prior to vaccination. The amount of vaccine required to stimulate demonstrable antibody response varied considerably. One-third to one-half of the injected personnel required two courses of three injections of 1.0 ml each before developing a titer of 1:8 or higher. Considerable decreases in antibody level occurred within five to six months. No frank cases of Q fever occurred among the vaccinated personnel in the year and a half following vaccination, but it appeared from serologic evidence that six subclinical infections occurred. Smadel *et al.* (114) had demonstrated that immunity in guinea pigs was incomplete, since short, nonfatal, febrile illnesses still resulted from challenge following vaccination. The one employee of the California laboratory who was not vaccinated developed typical Q fever three weeks after starting work in the serologic section. Evaluation of the protection afforded by the vaccine is difficult, since precautions to prevent contamination of the air and environment were observed. Luoto, Winn, and Huebner (115) attempted prophylactic vaccination of dairy cattle in the Los Angeles area. A control study was set up on uninfected immigrant cattle arriving as replacements for three commercial dairy herds known to contain many infected cows. The constant introduction of new animals, most of which are susceptible, obviously served to maintain the chain of infection in cattle in this area, since up to 50 per cent of the cows constituting the control group showed evidence of having acquired infection. Vaccination did not serve to eliminate completely shedding of organisms in the milk of infected cows, but it did seem to impart some resistance to the disease. Three times as many nonvaccinated as vaccinated cows gave serologic evidence of infection and five times as many nonvaccinated as vaccinated cows shed *Coxiella burneti* in their milk during the period of observation. These studies suggest that vaccination may be useful in the control of Q fever among dairy cattle and occupationally exposed humans.

THERAPY

The demonstration of effective antibiotic therapy has now improved the outlook for those who contract Q fever. The one case occurring in the California State Laboratory (112) responded promptly to "aureomycin" therapy. Earlier work had shown that neither penicillin, sulfonamides (29), nor immune blood (38) exerted any effect on the course of the disease. Experiments (116) with cultures of *Coxiella burneti* in the yolk sac of developing chick embryos demonstrated that crystalline streptomycin in doses of 0.5 to 1.0 mg. exerted a rickettsiostatic effect on the growth of the agent, but there was no indication of any rickettsiocidal action. The same effect was noted with chloramphenicol in similar dosage (117).

Ormsbee (118) showed there was a characteristic growth curve of *Coxiella burneti* in yolk sac cultures, with no spread to the other tissues of the egg. In terms of titer by the complement-fixation test, there was a lag phase followed by a period of exponential growth. The time necessary for 50 per cent of the chick embryos infected with *Coxiella burneti* to die varied inversely and in a regular manner with the log of the complement-fixation value of the inoculum. The number of infective doses of *Coxiella burneti* in a suspension, as titrated in chick embryos, and confirmed in guinea pigs, varied directly with the complement-fixation value of the inoculum (119). Therefore a predictable relationship exists, with *Coxiella burneti*, between the complement-fixing power, the number of infective doses, and the 50 per cent death point in chick embryos. Ormsbee and Pickens (120) compared the effectiveness of 5 antibiotic agents on embryonated egg cultures and ranked the antibiotics in descending order of effectiveness as follows: "terramycin," aureomycin, chloramphenicol, streptomycin, and

penicillin G. The effective antibotics delay the time in which yolk sac titers appear, but do not seem to affect the subsequent rate of increase or height of titer. Zarafonetis and Bates (121) reported apparently favorable results from "chloromycetin" therapy in a case from the National Institutes of Health. There was clinical improvement in 18 hours and the patient became afebrile in 48 hours. The drug was administered in an initial dose of 2 g, followed by 1 g orally every 8 hours for 6 days and then 0.5 g every 8 hours for 3 days. Clark, Lennette, and Meiklejohn (122) investigated the effect of aureomycin therapy on 45 patients with confirmed Q fever. Three general types of response, based on results at the end of five days, were noted: (a) 71 per cent of the patients responded promptly and were afebrile in five days, (b) 20 per cent of the patients showed subjective improvement with a drop in temperature, and (c) 9 per cent showed minimal or no improvement. Aureomycin was administered in varying dosage and by three different routes. When given orally, 1–5 g per day were given; 200–300 mg per day were given intravenously, or 40–400 mg per day intramuscularly. All three routes of administration gave similar results. In contrast to these observations, of 25 patients who received 300 to 800,000 units of penicillin per day, 72 per cent showed no clinical improvement at the end of five days. Aureomycin exerted no effect on the rickettsemia of patients, for *Coxiella burneti* was recovered from the blood of patients during therapy, even when blood levels were as high as 9.9 μg of aureomycin per ml, or even after the patient had shown objective clinical improvement. Likewise, aureomycin therapy in dairy cattle failed entirely to stop the shedding of organisms in the milk (123). The drug was administered both by intramammary infusion and intravenous injection without any effect on the shedding of rickettsiae or the production of serum antibody.

SUMMARY

Q fever is an acute, specific, rickettsial disease of man, of variable severity and duration. Its clinical course is characterized by sudden onset severe headache, fever, malaise, and patchy infiltration of the lungs. Diagnosis rests upon isolation of the etiological agent from the blood during the acute stage of the disease or upon the demonstration of complement-fixing or agglutinating antibodies in convalescent sera. Aureomycin and chloramphenicol have been shown to be effective in therapy.

The etiological agent of Q fever is known as *Coxiella burneti* (Derrick), and is a gram negative, pleomorphic, filterable organism, appearing both extra- and intracellularly in the tissues of infected animals.

Q fever was discovered in Australia in 1937 by Derrick, and since that time has been described in many parts of the world. It appears to be endemic in California in the United States, in England, Italy, Turkey, North Africa, Germany, Panama, and in the Balkans. Infection occurs in such domestic animals as cattle, sheep, goats, dogs, and donkeys, as well as in domestic fowl and pigeons.

Although the exact mode of transmission of the disease has not been established, epidemiological evidence points to the spread of infection by the inhalation of dust contaminated with infected secreta or excreta of diseased animals or ticks. The role of the tick in the spread of Q fever is uncertain, but six strains of ticks common in various parts of the world have been shown to harbor the etiological agent.

Vaccination appears to have some value in the control of the disease among occupationally exposed humans and among infected livestock. However, no definite measures for control of the disease in general have yet been established.

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