Q Fever

History and Present Status *

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MUCH progress has been made in our knowledge of Q fever since it was first described in 1937. The story had two beginnings at about the same time curiously enough; one in Australia, the other in the United States. In each instance an infectious agent was isolated and classified as a rickettsia. These infectious agents, isolated on opposite sides of the globe, were soon shown to be identical.

In 1940 this disease, scarcely considered as of more than minor importance up to that time, suddenly assumed greater stature when, through the study of a laboratory outbreak, it was found to produce a pneumonitis and clinically in many instances to resemble the atypical pneumonias. At the present time the known endemic areas, spotted with epidemics, are widely scattered over the globe—Australia, the United States, various countries of the Mediterranean area, Panama, and Switzerland. Finally, Q fever has added one more to the ever increasing list of animal diseases transmissible to man.

In 1937 Derrick [1] published a report on cases of a hitherto unrecognized disease entity which had been occurring in a large abattoir in Brisbane, Australia, since 1933. To this disease he gave the name Q fever. In his original report he described nine cases in detail while brief notes on additional cases resulting from laboratory infections were made by Burnet and Freeman,[2] and by Smith, Brown, and Derrick.[3]

It has been stated in the literature that the name Q fever was given the disease because it was first described in the state of Queensland, Australia. This apparently is in error. Derrick and Burnet [4] give interesting accounts of the choice of the name.

In the early investigations the disease was known as abattoir fever. This seemed undesirable on account of implications of possible danger to meat supplies, and also on account of probable objections on the part of the industry. It soon became clear to the Australian investigators that the disease was also present on farms. Derrick tried to find a suitable name of Latin or Greek derivation without success and finally chose "Q" fever, the "Q" standing for "Query." The name, "Queensland Rickettsiosis" was discussed, but rejected, as it was thought cases might be found outside of Queensland. It is evident from the foregoing that the use of the name Queensland fever is historically incorrect.

Although many additional cases have been reported by Australian investigators, no very definite epidemiological deductions have been drawn. As has been noted, the cases first reported by them occurred among workers in an abattoir. The individuals affected were not engaged in the same activities in their daily work, nor did they work in any particular section of the abattoir, and there was no evidence which would suggest person-to-person transmission.

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Using serologic methods, cases have been identified in Australia outside the original Australian focus. These cases have been among foresters and dairy workers.

In the abattoir we at once think of the possibility of acquiring infection through actual contact with the animals in process of slaughtering and preparation of animal products, or by infected air-borne particles containing matter from animal sources. In cases among farmers that source of infection is probably present, as it may be among foresters, but the rural group also suggests contact with infected arthropods.

Derrick [5] succeeded in transferring the infectious agent of Q fever from some of his cases to guinea pigs by blood inoculation, and later he and his colleagues found other common laboratory animals and several species of native rodents and three native marsupials to be susceptible. Burnet [6] found that the etiological agent passed through bacterial filters and discovered rickettsia-like bodies in the spleens of infected mice. He was able to grow these organisms on the chorio-allantoic membrane of the developing chick embryo. Derrick [7] subsequently suggested the name, *Rickettsia burneti,* for the organism observed by Burnet.

Probably influenced by the fact that the etiologic agent appeared to be rickettsial in nature rather than by any definite epidemiological evidence, Derrick and Smith [8, 9] made search for infected animals and infected arthropods in nature and succeeded in isolating three strains of *R. burneti* from bandicoots and six strains of the organism from ticks (*H. humerosa*). Smith [10] was able to show transmission of the infection to guinea pigs by infected ticks of the same species during the process of feeding.

In 1938, Davis and Cox,[11] and Parker and Davis [12] at the Rocky Mountain Laboratory at Hamilton, Mont., reported the isolation of a filter-passing agent, infectious for laboratory animals, from the tick *Dermacentor andersoni.* The ticks from which this infectious agent were recovered had been collected in the spring of 1935 near Missoula, Mont., at a place called Nine Mile Creek, and the disease produced in animals was called "Nine Mile Fever." This name was used in one of the early publications. The authors noted in their first publication that this was probably the same infectious agent encountered by Noguchi in 1926 under similar circumstances.

The Montana workers described a rickettsia-like organism which was associated with the new infection and named it *Rickettsia diaporica* on account of its ability to pass through ordinary bacterial filters, differing, in this characteristic, from other recognized rickettsiae. In the laboratory it was noted that this rickettsia was transmitted to susceptible animals by *D. andersoni* in the process of feeding, and that it survived in ticks through successive moults and through the egg stage.

Cox [13–15] failed in attempts to cultivate this organism on a wide variety of media, including all those found suitable for the growth of such organisms as tularense, leptospira, and bartonella, but found that it grew readily in living tissue cultures.

Since the early work in Australia and Montana, several species of ticks have been found infected in nature or have been shown to be able to transmit the infection experimentally, but aside from occasional incident, it does not seem that ticks play an important part in the transmission of the disease to man, although they may be important factors in maintaining the disease in nature. The ticks so far incriminated are *Dermacentor andersoni,*[11] *Dermacentor occidentalis,*[16] *Rhipicephalus sanguineus,*[17] *Ixodes holocyclus,*[18] *Haemaphy-*

salis bispinosa,[19] *Ornithodoros moubata*, *Ornithodoros hermsi*,[20] *Amblyomma americanum*,[21] *Hyalomma savignyi*,[22] and the spinous ear tick, *Otobius megnini*.[23]

In 1938 one of the workers[24] of the staff of the National Institute of Health, Washington, D. C., spent 4 days in the laboratory in Montana where the infectious agent isolated by Davis and Cox from Montana ticks was being carried in laboratory animals. This worker returned to Washington and there developed an illness of about 10 days' duration; the incubation period was from 11 to 15 days. From his blood an infectious agent was isolated in guinea pigs and identified as the same infectious agent as was under study in Montana, (*R. diaporica*). How the disease was contracted in the Montana laboratory was never determined. This strain, called the X or Dyer strain, was studied in animals and found to produce no immunity against strains of Rocky Mountain spotted fever and typhus. As it happened, the individual who had contracted the Montana infection, had been working in the laboratory in Washington with the Australian Q strain which had been sent to him by Burnet. This strain had been lost several weeks before the time of his illness, but five recovered guinea pigs remained on hand. These animals were found to be immune to the Montana strain. A second strain of the Q fever organism was secured from the Australian workers and serological and immunological comparison with the Dyer strain showed that these strains were at least closely related, if not identical.[25, 26] Subsequently, work by Burnet and Freeman[27] in Australia confirmed these findings.

The knowledge of this disease and of the causative agent up to the spring of 1940 may be summarized as follows:

An infectious agent had been isolated from human cases of illness, and from naturally infected bandicoots and ticks in Australia, and identified as a rickettsia. A rickettsia had been isolated from ticks in Montana and, by accidental laboratory infection, had been found to be infectious for human beings. These two rickettsiae had been shown to have at least a very close relationship, being serologically and immunologically identical. These rickettsiae, or this rickettsia, had been shown to be present in arthropods in nature, and naturally infected animals had been found in Australia, and the conclusion seemed warranted that this disease was arthropod-borne in nature.

Although the etiologic agent of Q fever was classified as a rickettsia, it was recognized early that certain differences exist between it and all the other rickettsiae. Morphologically and in its tinctorial and cultural characteristics it belongs with the other rickettsiae. On the other hand, it does not develop agglutinins for any known strain of Proteus, and it readily passes bacterial filters. These variations, coupled with the fact that the organism shows greater resistance to physical and chemical agents than other rickettsiae,[33] justify the setting up of the Q fever organism as the type organism of a new genus, Coxiella (Philip 1943), hence, *Coxiella burnetii* supersedes *R. burneti* and *R. diaporica*.[28]

A few cases, apparently contracted in nature, have been reported in this country,[29, 30] but convincing epidemiological evidence incriminating arthropods as transmitters to human beings is lacking. Until the spring of 1940 we had the picture of a rickettsial disease fairly widespread and probably arthropod-transmitted from one or more animal reservoirs with probably some human cases being contracted directly from infected animals. At that time, there was no suggestion of pneumonic involvement in human cases.

The originally held ideas of this disease changed rather abruptly in the

period from March 27 to May 17, 1940. During that time 15 clinically similar cases of infection occurred in one of the buildings of the National Institute of Health in Washington, D. C. From 3 of these cases, strains of the infectious agent of Q fever were isolated by Dyer, Topping, and Bengtson.[31] At that time two strains of Q fever were being carried in animals in the building. One of these strains was the original strain from Australia, while the second was the Dyer strain isolated from the first Washington case of 1938.

A careful investigation of the 15 cases at the National Institute of Health revealed little of epidemiological significance. The cases occurred in persons who worked in various sections of the building, with the exception that no cases developed in those employed in the group of rooms in which actual work on Q fever was being carried on. The most reasonable explanation of the absence of cases among those actually exposed in these rooms to animals infected with Q fever lies in the possibility of immunity produced by unrecognized infections. That this might be the correct explanation was suggested by the presence of Q fever rickettsia agglutinins in low titers found in the sera of 6 of the 10 persons working in the Q fever unit as compared to 4 of 20 persons working elsewhere in the building exclusive of those having a recognized infection with Q fever.

There was no evidence that the disease spread in the building by personal contact, nor were there any recognized cases in the families of the patients, nor was there any evidence that an arthropod vector was responsible for the transmission of the infectious agent. However, since the cases were limited to the building in which the disease was being studied, it seemed probable that the disease spread from infected laboratory animals or embryo cultures in some fashion, possibly being carried throughout the building by dust. Later in the year (September to November) 2 additional cases occurred in the same building. From each of these cases the infectious agent was isolated. Transfer of the Washington Q fever laboratory was made to new quarters in 1941. In the winter and spring of 1945 and 1946 (December to May), 47 cases of the disease occurred among the persons working in the building. The epidemiological findings corresponded closely to the indefinite findings of the previous outbreak.[32, 33]

At the time of the first outbreak at the National Institute of Health, the possibility of the presence of similar unrecognized cases in the general population was considered. This seemed possible since the causative agent was probably widespread in nature and since the clinical features of the disease bore a remarkable similarity[34] to the so-called cases of atypical pneumonia which had been reported in the medical literature with increasing frequency since Bowen's[35] report of 1935. Consequently, shortly after the initial outbreak at the National Institute of Health, thorough study was made of two institutional outbreaks of atypical pneumonia in an effort to determine their relationship to Q fever. The results were entirely negative.[36–38]

The cases described in Australia, and the later cases in Washington did not differ materially in the clinical pictures, and this is true of cases subsequently reported from other parts of the world. Additional clinical findings of lung involvement not noted in the Australia cases were brought out in the Washington cases. It is not the purpose of this paper to discuss the clinical picture, but it is important to stress the clinical similarity of Q fever cases with cases of atypical pneumonia. The case fatality rate is very low. Four deaths have been reported in this country to date, and two in Australia. A case fatality rate

less than one per cent is reported for Balkan grippe.

An outbreak resembling influenza occurred in Athens, Greece, in 1943. From a patient in this outbreak, Caminopetros [39] recovered an organism which was later shown to be *C. burnetii*. This disease was shown to be endemic in that area during the war and was called "Balkan Grippe" by the Germans.[40–42]

The presence of the organism in cows' milk has been reported in this country,[43] and in Greece, sheep and goats and their milk have been shown to harbor Q fever.[39] The disease probably exists in other countries in that region—Bulgaria and Roumania.[44, 45]

In 1944 and 1945, Robbins, et al., recognized epidemics of Q fever in the U. S. troops in Italy.[46–48] The findings in the study of these outbreaks confirmed the observations made during the laboratory outbreak at the National Institute of Health in 1940, that person-to-person contact was not important in the transmission of this infection, if, in reality, it ever occurred. This, in spite of the fact that *C. burnetii* has been recovered from the blood, urine, and sputum of patients suffering from the disease.

At about the same time (1945),[49] a strain of the organism of Q gever was recovered from a patient in Panama, the disease apparently being endemic in that area.

Outbreaks of Q fever also occurred among our troops returning from Italy.[50, 51] Comparison of various strains of *C. burnetii* (Australia, America, Balkan grippe, Fort Bragg, Panama, Italy) by Topping, Shepard, and Huebner [52] showed complete cross-immunity in guinea pigs while complement-fixation and agglutinin absorption tests showed similarity in immunological specificity.

In the outbreaks among our troops in Italy, association with domestic livestock, hay, and bedding was noted. Pigeons were numerous around the billets in some instances, but in one instance were absent. Arthropod transmission did not appear likely. It is interesting to note that complement-fixing antibodies were found in the blood sera of a large proportion of the native population in the Italian areas around army troops.

Laboratory cases were also reported at Fort Bragg, North Carolina.[53] In 1947, Caughey and Dudgeon,[54] reviewing 511 cases which had occurred among British and New Zealand troops in the Naples-Caserta area in 1945, with the aid of the complement-fixation test carried out at the National Institute of Health, found that 19 of 20 sera tested were positive for Q fever.

In 1948, Gsell [55] reported cases of illness which had occurred in Switzerland in April, 1947. The identity of these cases with Q fever was confirmed by Cox, using the complement-fixation test. Association with cattle was noted in these cases.

In the United States, although it was realized that the disease was probably present, no evidence of endemicity was obtained until 1946 when outbreaks occurred among abattoir and stockyard workers (reminiscent of the first Australian cases) in Amarillo, Tex.,[56–59] and Chicago, Ill.[60] Again, in these outbreaks, just as in the institutional outbreaks at the National Institute of Health and the Italian epidemics, the most likely mode of infection seemed to be the inhalation of, or contact with, infected material, most probably from infected animals. In this country the disease has also been recognized in Arizona [61] and Montana.[30]

In 1947, cases were recognized in Los Angeles County, California.[62] The first cases were not among abattoir or dairy workers,[63] but practically all gave history of exposure to cows, some of which were found to possess serum antibodies for Q fever. Further studies in Califor-

nia, which are being continued by the California State Department of Public Health, Los Angeles County and Los Angeles City Health Departments, and the U. S. Public Health Service, have shown that *C. burnetii* is present in raw milk[43] produced in the area, but the importance of infected milk as a factor in the transmission of the disease to man is not yet determined. Early experiments indicated that pasteurization eliminated most if not all of the demonstrable infection in milk. Contact with livestock by reason of occupation or residence, at present, seems to be an important factor. This was also suggested by the findings in the Balkan area.

Work has been done in the preparation of vaccines by Cox,[15] Bengtson,[64] and by Smadel.[65] Laboratory experiments indicate their value, but no field data are available as to protecting man against the infection. It should be noted that no cases of Q fever have occurred among laboratory workers who have been vaccinated. Huebner, Hottle, and Robinson[66] have produced some evidence that streptomycin may be of value in treatment.

SUMMARY

In Q fever we have a disease with known potential sources of infection in infected cows, sheep, goats, the milk of these animals, wild animals, and a wide variety of ticks. Epidemiologic studies of the occurrence of Q fever in abattoir workers, laboratory workers, dairy workers, and residents of dairy areas indicate that an important method of transfer of the infection to man is through the medium of contaminated air, whether this be by droplet infection or by dust.

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