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DEPARTMENT OF THE ARMY  
Fort Detrick  
Frederick, Maryland

## LABORATORY INFECTIONS WITH Q FEVER

Following is a translation of an article by Dr. E. G. Nauck and F. Weyer, of the Bernard-Nocht-Institut für Schiffs- und Tropenkrankheiten (Bernard Nocht Institute for Shipboard and Tropical Diseases), Hamburg, of which Dr. Nauck is Director, in the German-language periodical Deutsche medizinische Wochenschrift (German Medical Weekly), No 7, 18 February 1949, pages 198-202.

### Introduction

Since the first reports on Q fever, small epidemics of Q fever, limited in time and extent, have been described repeatedly, including also some laboratory epidemics. The detailed analysis of such epidemics represents an important contribution to knowledge on this in some respects still puzzling disease and it is especially suitable for helping to clarify the question of its transmission. Therefore, in what follows an account will be made of a laboratory epidemic that appeared in our Hamburg laboratory at the end of 1947 and in the spring of 1948 in a series of experiments on the study of virus biology and of transmissibility by arthropods. Some cases could be subjected diagnostically to a detailed examination in this connection.

### 1. Background

In December 1944, we received from Professor Herzberg a strain of "Balkan grippe" in the form of intranasally infected mice. We lost this strain in the autumn of 1945, and then we produced it once more in April 1947 in the form of an organ trituration adsorbed in  $\text{Al}(\text{OH})_3$  on guinea-pigs and subsequently in mouse lungs. From this time on, the strain was run uninterruptedly by us, up to the fifteenth transfer in the

mouse lungs. It wore out several times in the mouse and glycerin reserves had to be resorted to. We inoculated the agent for the first time on 4 September 1947 with a lung trituration on mice i.p. and we have been running it through spleen transfers since 29 September 1949. We have now arrived at the 54th transfer, in which the transfer spleens were inoculated specifically only after a 2-3 week retention in glycerin-Tyrode solution. We have already reported on our experience with the behavior of the strain and on some experiments with its transfer (Nauck and Weyer, 1948).

We learned from Professor Herzberg that no laboratory infections had occurred with him. Our own protective and precautionary measures regarding isolation, disinfection, etc. were guided by the experience gathered in connection with spotted fever, since the strain was handled together with our spotted fever strains. Special protective clothing and mouth masks and similar items were not worn. Incidents did not occur during a period of six months. In this period of time, the strain was kept in mouse and guinea-pigs lungs and for a short time on the chorio-allantois of chick-embryos. Early in 1945, we had already undertaken experiments on transfer to arthropods. These experiments were resumed in June 1947. On 25 August 1947, the strain was inoculated ingeniously on two ticks (*Ornithodoros moubata*, Murr.) in the form of a mouse lung trituration. The first tick was emulsified on 8 September and the second one on 15 September 1947, and put in the mouse lungs. In both cases, typical bronchopneumonic foci developed in which the agent was also detectable microscopically. This strain branch has subsequently been transferred by intraperitoneal inoculation into the mouse spleen and is now still carried in this form. Transfer experiments with lice were undertaken in June, with ticks in August, with mouse fleas in October. Since the end of October 1947, the strain has no longer been kept in mouse lungs.

## 2. Report on a Laboratory Epidemic

From August 1947 on, some outbreaks of feverish disease appeared in our spotted fever laboratory, in which rickettsiae of the *R. wolhynica* species, proliferated extracellularly by means of the louse test, could be detected. These cases, diagnosed clinically as trench fever, on which a report will be made in another place, caused the first laboratory outbreaks of illness from Q fever not to be immediately recognized by us, because we were thinking primarily of trench fever or spotted fever. Therefore, in the first cases not all the diagnostic possibilities for clarifying the diagnosis in the direction of Q fever were not exhausted.

The first case, that was still not identified as Q fever during its course, but, in retrospect, must be put down to Q fever, occurred on 6 November 1947. The first case of illness in which the Q fever diagnosis was confirmed, dates from 21 November 1947; the last one, from 21 February 1948. In this time, we had six clinically confirmed cases of Q fever and five uncertain cases in which the doubtful diagnosis of Q fever was made merely as a result of the timely coincidence and to some extent only subsequently. The fact that this doubt was not unfounded is shown by the circumstance that in one of these patients *R. burneti* could still be detected subsequently. We come up, therefore, with seven sure cases of Q fever. (Cf. note at the end.)

a. Clinical Course

The symptoms described since 1937 in various epidemics as characteristic of Q fever were present in the majority of our patients -- usually abrupt onset with quite severe malaise, severe headaches, typical fever course with high fever, bradycardia, lack of an exanthem, usually slightly pronounced symptoms on the part of the respiratory organs with a lung finding detectable by x-ray, relatively low leukocyte count and lymphocytic reaction, refractory response to sulfonamide and penicillin therapy. Cold agglutination yielded no positive values in most of the cases examined. The ESR is subject to great variations and is not usable diagnostically. In the absence of a sufficient number of antigens to perform a complement fixation reaction, we took great pains to secure a diagnosis also etiologically.

The following are some case histories (cf. in this connection Figs. 1 and 2) presented in abbreviated form and in chronological order:

1. Dr. F. W., 44 years old, Head of the Entomology Department. Confirmed clinically and etiologically. Fell ill on 21 November 1947. After many brief temperature rises, fever rose to 39.5° C., severe headaches, prostration, light, restless sleep, photophobia and pain due to bulbous pressure, conjunctivitis and flow of tears. General restlessness. Speech urgency. Leukopenia with a left shift rising from 3000 to 5000-6000 and relative lymphocytosis. No exanthem. Spleen slightly enlarged. Except for initial psychic alteration, no signs on the part of the nervous system. Treatment with penicillin without effect. On the x-ray picture shadows the size of the palm of the hand in the lower part of the spleen. No physical finding, slightly irritating cough and pains in the side. 1 December, fever completely gone. Clearing up of the pneumonic foci. Undisturbed convalescence.

On 7 <sup>[sic]</sup>; obviously should read 27 November (sixth day of illness) inoculation of two mice with tracheal mucus in a salt solution. After intraperitoneal injection on the eighth day, unmistakable evidence of agent in a spleen smear. Lung smears after intranasal infection, doubtful. Transfer of the spleen trituration to another series of mice, without considerable increase in the amount of rickettsiae. A guinea-pig also infected on the sixth day of illness with 1 cc. of whole blood, began to become feverish on the eleventh day. Organ triturations inoculated in mice on the thirteenth day, and after seven more days rickettsiae detected unmistakably in two to four animals. On 13 January 1948 lice were again put on the same patient who some weeks before falling ill had had an attack of a trench-type fever with a positive louse test. A trituration of seven louse stomachs was injected in mice on 22 January and *R. burneti* was identified here after two transfers. The transfer of the 22 January louse passage to two *Onithodoros moubata* and reinoculation on the mouse were successful.

2. G. W., 22 years old, animal nurse. Not confirmed clinically. The patient had been employed for some time as a louse feeder; he only fed normal lice, but had daily business in the laboratory building. Fell ill on 7 December with a high temperature, moderate tachycardia, severe head and limb aches. Lungs negative clinically and on x-ray. No rash. Leukocytes, 7600. After three days, disappearance of fever and feeling well. Total agglutination reactions negative.

3. P. R., 25 years old, laboratory assistant in the Bacteriology Department. Confirmed clinically. Fell ill on 10 December 1947 with constantly high temperature accompanied by relative bradycardia. Fever disappeared after ten days. No exanthem; on the eighth day a pneumonic focus was determined by x-ray at the base of the upper left lobe. At onset, leukopenia 4800, increased to 6700; shift to the left and relative lymphocytosis. Louse test negative.

4. F. W., 23 years old, female, technical assistant in the Entomology Department. Confirmed etiologically. This patient had been suffering since July 1947 from fever attacks of short duration that subsided only in February 1948. In this case, rickettsiae located extra and intracellularly and that behaved like *R. wolhynica* or *R. mooseri* were isolated in the louse feeding experiment. An admixture with *R. burneti* occurred only in the course of the mouse transfers. Further passages provided evidence that the spleen of infected mice contained *R. burneti*, while its characteristic presence in spotted fever was absent from the peritoneal smear. Transfer

to guinea-pigs, that reacted with fever in five to seven days, and reinoculation in mice, also had similar results. The clinical course could not be followed in detail, since the patient was not confined to bed and was not hospitalized.

5. R. G., 33 years old, orderly. Confirmed clinically. This patient, who had undergone spotted fever in 1944, fed lice infected with rickettsiae and was ill from 3 September to 20 September 1947 with symptoms that were interpreted as trench fever. A new spotted fever infection was unlikely, due to his previous illness with spotted fever, although a slightly hemorrhagic exanthem, with small spots, appeared on belly and breast and faded very rapidly. Rickettsiae corresponding to *R. wolhynica* were detected in the louse test. On 3 February 1948, the patient fell ill with pains in the limbs, exhaustion, severe aches in the forehead. There was a slight, irritating cough, without sputum; mild conjunctivitis; temperature around 39° C. Spleen just palpable, otherwise no organic finding. Roentgenogram showed an infiltrate the size of a fist coming from the left hilus. Rapid regression in control x-raying. In this patient also a rash, consisting of small spots, all over the body, fading away on the following day. In the hemogram: leukopenia 3800, shift to the left. After subsidence of the fever, 6600, normal differential blood picture. At the onset, ESR 6/14, increasing to 26/52; at the end, 10/19. Cold agglutination 1:318; later, 1:32. Agglutination type 1:100, para A and B negative, OX<sub>19</sub> 1:50. Inoculation of sputum in mice had a negative result<sup>9</sup> (bacterial infection); same with injection of whole blood in guinea-pigs on 13 February, therefore shortly after subsidence of the fever. Louse test with subsequent transfer to mice, also negative.

6. A. R., 51 years old, laboratory assistant in the Bacteriology Department. Confirmed clinically and etiologically. Fell ill suddenly on 10 February 1948 with aches and pangs under the left ribs. Coughing and sputum did not occur. Fever rose to 40° C., then continued between 39° and 40° C. Headaches, extreme prostration, abdominal pains, loss of appetite, nausea. No vomiting or diarrhea. Bronchial respiration and sporadic, moist rales in the area of the lower left lobe in a circumscribed location. Moist area a hand's-breadth in size. No exanthem. On 19 February, cloudy shadow on x-ray picture of lower left area, located dorsally with lateral x-raying. Striped shadow similar to latticework. Leukocytes 4000. Lytic temperature fall within seven days, rapid improvement of the general condition. Cold agglutination negative. After subsidence of fever, rapid recovery and disappearance of the pneumonic infiltrate. -- Two ticks were applied for sucking only on 2 March, therefore a long time

already after subsidence of the fever. The first tick was worked up on 12 March; the second one, on 5 April. The mice inoculated with the second tick, negative, while with the first tick in two mice the agent was successfully detected in the first transfer.

7. H. W., 54 years, laboratory assistant in the Bacteriology Department. Confirmed clinically and etiologically. After short-lasting prodromal signs (exhaustion, weakness), onset of fever on 18 February 1948. Temperature 39.6° C., lack of air, dyspnea. In the x-ray picture, infiltrate in lower right lobe. With percussion, no fluid, normal breathing sound. As late as 22 February, weakened respiration and moist rales in the area of the infiltrate. No exanthem. Temperature constant between 39°-40° C., poor general condition. Cardiac insufficiency (cyanosis), tormenting cough with slightly viscous expectoration, slightly bloody, later rusty-brown. Slight mental exaltation, loss of appetite, thirst, desire for unusual food. Cold agglutination negative. Lytic temperature drop from 2 March, slow improvement and regression of the infiltrate. Increased loosening of sputum. During convalescence, weakness, limb pains, particularly in knee-joints and leg muscles, slow recovery protracted for weeks. -- On 18 February, two guinea-pigs were inoculated with 1 cc. of whole blood and two mice with 0.5 cc. each. Mice positive in the first transfer on 27 February. The guinea-pigs showed fever after 10 or 12 days. Immediately after the third day of fever, ticks were applied to one guinea-pig. After 13-34 days, they were triturated and injected into mice. Agent identified in the second passage. Two ticks were fed on the same patient on 2 March and were inoculated in mice on 12 March or 7 April. The mice injected by the first tick were positive in the first transfer.

8. A. St., 45 years old, female, technical assistant in the Serology Laboratory. Clinically probable. Patient had a severe case of typhoid fever in 1945-46 with two relapses and was received on 18 February 1948 with high fever and in a painful condition. ESR 65/90. No leukocytosis. Pronounced shift to the left. No exanthem. Nausea. Because of discomfort and the finding of leukocytes in the urine pyelitis was thought of at first and she was treated with Albuclid [proprietary = para-amino-benzene-sulfonacetylamide]. Slow subsidence of fever and improvement of the general condition. Q fever was suspected, because of the laboratory infections that were showing up at the same time. In spite of a lack of physical finding, x-raying revealed an infiltrate in the lower right quadrant. Cold agglutination 1:64. After abatement of the temperature, regression of the ESR and healing of the accumulation in the lower right lobe.



C. Dr. H. J., 30 years old, laboratory assistant in the Bacteriology Department. Confirmed clinically. Fell ill on 21 February 1940 with high fever; after three days, remission to about 38° C. and further rise in temperature, then rapid lysis within three days (Fig. 1). At the onset, restless, mentally unstable with bursts of euphoria, then apathetic and dejected again. After abatement, anamnestic rags, drowsiness, heavy sweating. From the third day of illness on, coughing, blood-tinted, otherwise mucous, sputum. Roentgenogram showed rather shaggy defined shadow, the size of an apple, at the base of the upper left lobe (Fig. 2) that quickly decreased in the control x-ray. ESR rose to 75, then regressed rapidly; cold agglutination 1:32, moderate leukopenia. In this case, two ticks each were applied to suck at the onset on 23 February and after subsidence of the fever on 5 March. The ticks were transferred to mice in the first test after 7 and after 24 days; in the second test, after 14 and 26 days, without successful detection of the agent until the second passage.

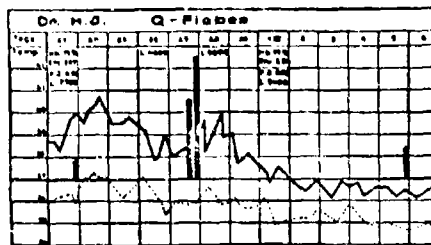


Figure 1. Fever Curve in Case 9.

Legend: Fieber = fever; Tage = days; temperature Centigrade.

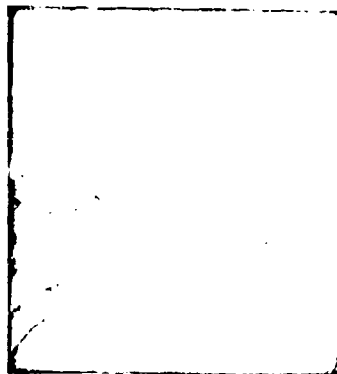


Figure 2. Roentgenograph of lungs in Case 9 on Fifth Day of illness.

b. On the Etiological Diagnosis

Methods intended for etiological diagnosis could not be used in every case, nor always to their full extent. They were used in five clinically unmistakable cases (1, 5, 6, 7, 9), three times to a great extent, once incompletely, including three times successfully; in the doubtful cases, three times in an incomplete form, including once successfully. Consequently, the agent could be identified microscopically in four patients.

Detection was successful with the following methods:  
 1. intraperitoneal transfer of tracheal mucus to mice;  
 2. transfer of whole blood to mice; 3. transfer of whole blood to guinea-pigs with subsequent passages to mice and ticks; 4. feeding of ticks and transfer to mice; 5. feeding of lice with passage to mice. This last certain microscopic identification of the agent occurred thus specifically in mouse spleen.

An outline of the identification of the agent in the four positive cases is given in Table 1. The following is a legend for Table 1:

m = transfer to mice  
 l = transfer to lice  
 c = transfer to guinea-pigs  
 o = transfer to Ornithodoros moubata

Capital letters indicate microscopic determination of the agent in mice or fever in guinea-pigs; small letters indicate failure to detect the agent.

Table 1. Xenodiagnosis in Q Fever

Case 1	C M	Blood
	M M	Sputum
	1 m m M	Feeding
	1 1 O M	Feeding
Case 4	1 m m M	
	1 m m C m m	Feeding
	1 m m C 1 M M	
Case 6	O m M	Feeding
Case 7	m M	Blood
	C O m m M	Blood
	O m M	Feeding

c. Epidemiology

Two of the persons who fell ill with the disease were immediately concerned with handling and working up strains of the agent and, therefore, were exposed to direct infection. One patient fed the infected lice, including also lice that had been infected artificially with *R. burneti*. Two other laboratory workers, who worked under the same conditions, did not incur the disease. The rest of the cases involved members of the Bacteriology Department which was located together with the Rickettsia Laboratory in a wooden building, but in a separate room from it. There were two corridors and a large room between the Rickettsia and the Bacteriology Laboratories, used jointly by some of the employees of both departments. The Rickettsia Laboratory, properly speaking, was not entered by personnel of the Bacteriology Department, only occasionally a room next to the Rickettsia Laboratory in which there were infected lice and ticks in a closed incubator. Three persons who came in this room from time to time to use a centrifuge were stricken. Two other patients probably did not enter this room at all, or only once for a very short time. -- No doubtful cases appeared in other departments of the Institute, just as there were no further contact infections in the vicinity of the patients.

Special experiments were not set up nor were changes undertaken in the strain either in the first wave of the disease in November-December 1947, or in the second one in February 1948. Yolk sac cultures were not run at this time. At the end of January, antigens were begun to be obtained from the spleen of infected mice. Due to a shortage of animals, these studies were conducted on a relatively small scale. The strain was kept in mouse spleen, and transfer experiments were undertaken with lice, mouse fleas and ticks. The infected mice were put in a separate room in glass jars 30 cm. high. The infected ticks and lice were kept in an incubator, each series separately in closed glasses or Petri dishes.

Free insects do not come into question as transmitters in our laboratory infections. Only cockroaches (*Phyllodromia germanica*) were present in great numbers in the building. We did determine experimentally that *R. burneti* can be transferred to mice with the intestines of roaches that had fed on infected mouse spleen three days previously. Nevertheless, roaches had no access to infectious material. Three experiments in which the intestines of roaches that were fed with infectious material, were worked up after 5, 6, and 9 days turned out negative. The possibility of germ spreading by roaches, to be sure, is not to be completely rejected. The intake of infectious dust by respiration remains the most likely

source of infection for causing our laboratory outbreaks of illness. We know that *R. burneti* remains virulent for a long time in a dry state. For example, we dried mouse spleen, containing agents, in an incubator and were still able to infect mice with pulverized spleen without difficulty after 45 days. The agents can get into the dust when infected organs are triturated, from the urine of sick mice and guinea-pigs and from the excrement of infected ticks, fleas and lice. The last possibility in the light of our epidemic seems to us to be particularly obvious, because the excrement dust of the lice gets into the environment easily and frequently unnoticed when the animals are fed and rearranged.

### 3. Comparison with Other Laboratory Epidemics

Our observations agree very much with experiments that have been made in other laboratories, particularly with the findings on laboratory epidemics in the National Institute of Health in Washington or Bethesda.

The first laboratory infection with *R. burneti* was described in detail by Dyer (1938). Properly speaking it gave rise to similar studies of the strain (nine-mile strain) isolated in Montana in Dermacentor ticks by Davis and Cox with the agent of Australian Q fever. A member of the National Institute of Health spent four days in the laboratory in Montana, in which infected ticks and guinea-pigs were worked on. After his return to Washington and an 11-15 day incubation period feverish symptoms appeared. The agent could be isolated by means of transfer from the patient's blood to guinea-pigs and the result from further studies was that the newly obtained strain was identical with the Montana strain. A cross immunity against Rocky Mountain spotted fever and spotted fever did not exist; on the other hand, there was a close relationship of the agent to an Australian Q fever strain. The identity was confirmed in a communication from Burnet and Freeman (1939) from Australia. It was not explained how the infection had come about. In the Spring of 1940, a group illness occurred in the National Institute of Health in Washington (Hornibroek and Nelson). Fifteen clinically similar cases appeared among laboratory employees in a certain building. During this time, they were working precisely in this building with Q fever strains, and the agent was successfully identified in three cases. The patients had worked in various departments in the building in which rickettsia strains had been experimented on already since 1938. Cases of illness did not appear among the personnel directly concerned with the rickettsia studies. These persons had perhaps unknowingly contracted residual infection. The causal relationships could not be clarified; there were neither clues

for contact infections nor for a transfer by means of arthropods. It seemed justifiable to assume that the infections that appeared scattered throughout the entire building were due to a transfer of infectious material by dust.

An additional laboratory epidemic that included 47 cases occurred in the National Institute of Health, located near Bethesda, in the period of time between 7 February 1945 and 30 March 1946. Pneumonia was determined in only 13 of the 47 cases detected. This time also people who were employed in one building or who had entered it fell ill. A total of 370 persons were examined and, in fact, 142 were employed in the building and 55 were visitors; in addition, there were 43 contact people and 177 other employees who had never entered this building. In all cases, case history data were taken and seriological tests were performed by using the complement fixation reaction. While 44 of the 142 employees who had become exposed and 3 of the 55 visitors were diseased clinically and serologically, the test yielded negative results with all the others. It is assumed that the number of cases was reduced due to the preceding laboratory infections (1940). The previously administered protective vaccinations with a vaccine obtained from ticks against Rocky Mountain spotted fever appeared to have had a certain effect, although experimentally no cross immunity was detected. (Five out of twenty employees vaccinated against Rocky Mountain spotted fever were stricken, and thirty-one out of sixty-two who had not been so vaccinated.) On the other hand, spotted fever vaccinations had no effect on the number of infections. Also, in this outbreak, it happened that the highest number of patients was not among persons who were directly engaged in working on the material and who must have been most greatly exposed. By way of interest, just as in the epidemic that appeared in 1940, there was a time relationship with the work performed on yolk sac cultures to obtain antigens, including centrifuging a 0.5% formalin suspension. The fact that *R. burnetii* is quite resistant against chemicals like formaldehyde was ascribed an important role in addition to the one played by the manipulations necessary for obtaining the antigens. Guinea-pigs excreta were also considered as a possible source of infection, since the agent is preserved a remarkably long time in these experimental animals and can be excreted even months after the fever subsides. Sera from guinea-pigs that kept in the same building reacted positively in a considerable percentage, while guinea-pigs that were kept in other buildings were consistently negative. The simultaneous contagion of the guinea-pig stock with the human infections is particularly interesting and -- as is emphasized -- is not to be ascribed to contact infections, because a transfer from infected animals to normal guinea-pigs in the same cage does not occur.

It is likely that the guinea-pigs received their infection from the same source as the infected humans (dust inhalation). Nothing is said about the possibility of a transfer by passage to arthropods or by pulverized excreta. Possible changes in the virulence of the strains used were even less so taken into account. Twenty cases of the disease were also observed (Robbins and Rustigan) in the Medical General Laboratory of the U.S. Army in Italy, in the months of June to August 1945, among 107 persons who had worked with *R. burneti* or were connected with separation of the virus. Here also the outbreak appears to have been associated with work on yolk sac cultures, while no infections had occurred by keeping the strain on guinea-pigs. Mention must be made of still another epidemic caused by a "Balkan grippe" strain in the Fort Bragg Laboratory, North Carolina, and that appeared between 30 July and 27 December 1945. In spite of special precautionary measures, fifteen out of 49 employees fell ill. In this epidemic, also, yolk sac material is considered as the probable source of infection (Commission on Acute Respiratory Diseases). Six employees who had worked with infected eggs were stricken; two people who wore masks did not fall ill. Transfer with blood to guinea-pigs was successful in four out of six cases.

#### 4. Final Observation

The above-mentioned laboratory infections in the USA, Australia, Italy, show, just like the ones in Hamburg, that the danger of an infection by working with *R. burneti* is extraordinarily great, even under conceivably favorable working conditions and by observing the usual safety precautions. The danger in this case applies not only to the group of persons concerned with working up the material, but rather to all people employed in the same building. This circumstance admits the conclusion that the agent, which has a relatively high resistance, is preserved in a dry state and probably is scattered about with the dust. The clinical course of the laboratory infections agrees essentially with natural infections. As also emerges from the American observations, in laboratory infections the illness is more severe, perhaps as a result of relatively higher doses of infection or due to an increase in virulence in the course of the transfers. In individual cases, laboratory infections were even mortal (Lillie, Perries and Armstrong, 1941).

It is worth noting that in the previously described cases this illness does not appear at the start of work with Q fever strains, but rather only after a bit of time or after definite tasks begin (obtention of antigens from yolk sac cultures tick transfers). The disease has a sudden onset, covers a definite group of persons, and not always the ones

primarily exposed, and abates again by itself after a short time. Susceptibility to it appear in general to be equally great. The fact that not all persons directly concerned with working on the strain or who are working in the near vicinity fall ill, may be based on an unnoticed immunization due to their continuously taking in smaller amounts of the agent. Prior protective vaccinations against spotted fever and even an attack of spotted fever, according to our experience, also do not protect against an infection with *R. burneti*. However, the sudden onset and the sudden abatement of these epidemics is unexplained. It is also strange that the disease did not spread further in spite of the great infection image -- the agent circulates for rather a long time, even after subsidence of the fever, in the blood, can be eliminated with sputum, urine and milk, is very resistant, grows in various arthropods and is eliminated with their excreta --, and it is also peculiar that the epidemics do not acquire a greater extension outside the laboratory. In many laboratories in which work has been done for a long time on strains and under the same kind of conditions that produced infections in other laboratories no clinically detectable transmissions occurred. These phenomena let one think that the agent either passes through a special growth cycle in which it is assigned to certain intermediate hosts for the attainment of a particular virulence and ability to multiply, or that there are erratic variations in its virulence.

Our own epidemic set in only after the agent had passed through the ticks. On February 2 1948, we sent our strain, from the 18th spleen passage in the form of a glycerin spleen, to Elberfeld where a laboratory epidemic involving about 20 persons occurred. On 13 February 1948, we sent the same strain from the 21st passage to Marburg. Laboratory infection has not appeared there up to now. The weak virulence and multiplication of rickettsia after a natural infection by ticks on mice and on humans lie in the same direction. Microscopic proof of the agent could not be produced with certainty either in the tick organ smear or originally in the mice inoculated with crushed ticks, but only in mice with the first or second spleen transfer. The behavior of the agent with flea transfer was also strange in two experiments. Although the rickettsiae were able to multiply greatly in the stomach of mouse fleas after natural infection by sucking on sick mice and could be unmistakably established microscopically, we were unable to infect any mice with the trituration of flea stomach containing agents, that is to say, the agent was not to be found subsequently in the mice. We were also unsuccessful in transferring the disease in the natural way to mice by planting infected fleas on them. However, if the flea intestine trituration is first introduced into ticks artificially and inoculated

on mice with a tick trituration, then they also multiplied again in the usual form in mice. An explanation of this biologically very strange behavior may perhaps afford a new insight in the epidemiology of Q fever.

#### Summary

1. A laboratory epidemic of Q fever appeared in the Hamburg Tropical Institute at the end of 1947 and beginning of 1948. The diagnosis was confirmed clinically or etiologically in seven persons. In four other cases there was merely a suspicion that it was also a question of Q fever. The cases ran their course clinically in the same manner as is known to have occurred in other laboratory epidemics.

2. In four cases the diagnosis could be based on the microscopic detection of the agent. A successful verification of the agent was made after transferring whole blood to mice and guinea-pigs, after transferring sputum to mice, after feeding lice and ticks on the patient with subsequent inoculation of organ trituration in mice. The agent also still circulates in the blood for rather a long time, but was not detected in all cases studied in this way. Confirmation of the diagnosis by means of the complement fixation reaction was not possible, because not enough antigens were available to us.

3. The disease appeared only when the strain kept in mouse lungs and mouse spleen had undergone a tick passage. The real source of the infection is not known. An infection probably occurs due to dust containing the agent.

4. The peculiarities of the epidemiology of Q fever may find an explanation in variations in the agent's virulence.

#### Note made at time of proof-reading:

After the manuscript had been completed, two more clinically and etiologically confirmed cases of Q fever appeared in employees of the Institute who only momentarily entered, in the meanwhile, the Rickettsia Laboratory located in an isolated stone building. Here also the infection can only have occurred due to inhalation of dust. The cases occurred at the end of November 1948. The first case followed a course of average severity with ten days of continuous fever. Blood previously transferred on the third day of illness to mice, guinea-pigs and ticks with subsequent inoculation in mice yielded in all three cases a microscopic verification of the agent, in the most favorable case eleven days after drawing the blood. The second case ran a mild course with an abnormal



five-day fever. After guinea-pigs had been inoculated on the second day of illness and characteristically ran a fever, the agent could be found abundantly in the mouse spleen after thirteen days, while nothing happened to the directly inoculated mice.

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