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TRENCH FEVER*

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DISEASE is the accomplice of war. To the uninitiated, at first glance, it seems that the chief wastage of man power in armies is produced by weapons of the enemy; to the initiated, on the other hand, it is well known that the wounds produced by bacteria are as fruitful a source of disability as those caused by bullets. One reason for this attitude on the part of the casual observer is that the injuries of battle are more spectacular than those of disease. They are more unusual, both in their mode of production and in the manner in which they respond to treatment. The care of the wounded often yields striking results. The humanitarian instincts, aroused by the fact that the injuries were received as a direct result of sacrifice, properly lead to the building up of an intricate organization for the care of the wounded. The problems must be largely solved in the actual presence of war. Sickness, on the other hand, is more easily tolerated, because it is the lot of most men to suffer illness. The problems of disease are always with us; most of those presented by war have been studied in times of peace. Almost in direct proportion to the rate at which a given disease causes fatalities, in contradistinction to casualties, are effective prophylactic measures studied and put into effect. The antivenereal disease campaign in our own army is a striking exception to this statement. The prophylaxis of typhoid fever and small-pox was more effective than that of dysentery or the pyodermias. It may be urged that the measures for preventing the first two diseases are more easily applied in war. This is true; but had the prevalence of the fatal disease, typhus fever, been as great as that of the non-fatal, but disabling affection, trench fever, no doubt more effective measures would have been early instituted for combating it.

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The complete ignorance of the existence of such a disease as trench fever, with the consequent lack of knowledge as to its mode of spread, made it impossible to apply prophylactic measures until this information was available. A very real impediment to the study of a disease during war is that the patients are rarely under the same observer or group of observers during the entire course of their illness. This was especially true during the first part of the recent war, before the lines had become stabilized and hospitals stationed close enough to the front to permit the retaining of the sick for longer periods.

For these reasons it was not generally recognized until the spring of 1915 that a hitherto unknown disease was fairly widespread throughout the combatant troops. At this time, medical officers in both the British and the German armies almost simultaneously noticed a five- or six-day relapsing fever in many patients, who complained of severe and persistent pains in the shins. Graham,[1] Herringham [2] and others saw many examples of this condition among British troops from the trenches but not among the troops in the rear; so the name of trench fever was applied. His [3] and Werner [4] saw their first cases on the east German front in Poland and Wolhynia. The former applied the name Wolhynian Fever to the disease because of the supposed source of the infection; the latter used the term five-day fever because of the interval between relapses. Because of the almost simultaneous appearance of cases on the two fronts, it is difficult to determine the original source of the infection; but Grätzer,[5] a battalion medical officer in the 84th Austrian Infantry Regiment, states that he had observed cases among soldiers under his care since the winter of 1914. He gave a very good description of the malady; and because of its increase in winter and when crowding of the soldiers was necessary, attributed the spread to some insect vector. He saw his first cases when his regiment was on the Nida, and learned from the inhabitants of that region that a similar condition was known to them before the war. Franke [6] also states that he recognized the disease as having occurred in Lamburg in previous years, when it was known as influenza with relapses. It seems, therefore, from the evidence at hand, that

the original source of the infection was somewhere in Russia and that the disease was spread to all of the battle fronts in Europe by German and Austrian troops as they moved from one area to another.

It was early noted by some observers that an enlarged, hard spleen often accompanied by perisplenic tenderness could be demonstrated in many of the patients. The outstanding features of typical cases were, however, the sudden onset with marked febrile reactions, headache and general body pains, closely resembling the onset of influenza, but followed in a few days by pain and tenderness of the shins and a spiky type of relapsing fever. There were many patients who complained of painful shins, especially at night, but in whom there was no history of an abrupt onset, or of a distinct febrile bout. Various explanations, such as long marches, flat feet, standing in mud and water, rheumatism or myalgia were suggested to account for these unusual pictures. In still other patients with similar symptoms, the pyrexia was continuous, resembling that of typhoid or paratyphoid fever, or intermittent, like that of sepsis.

Much confusion in diagnosis arose from the presence of so many patients having certain symptoms in common, yet presenting, on the other hand, so many individual variations. In fact, it was so difficult to establish a normal or typical picture of the disease that the terms P.U.O. (pyrexia of undetermined origin) or influenza were applied in many instances.

The ignorance of the existence of atypical forms of trench fever, the practical impossibility in many cases of making a positive diagnosis and the great difficulty of establishing adequate sanitary measures during war of movement, were all factors that resulted in the infection being widespread before the disease had become recognized as a separate entity. A serious study to determine its nature was soon undertaken by investigators on both sides of the line. The first extensive report was that of McNee, Brunt and Renshaw,[7] who used as experimental subjects British soldiers who had volunteered for inoculation. These workers showed that the virus of the disease was contained in the whole blood and that it could be transferred from man to man by intra-

venous or intramuscular injection. In their experiments the plasma or serum obtained from infectious blood did not contain active virus unless hæmoglobin tinged. The red blood cells, on the other hand, were infectious, even after five washings. Material known to contain virus was not infectious after passage through a Berkefeld filter; but in spite of this fact these workers were unable to demonstrate microscopically any microörganism. This work was unfortunately interrupted before it was shown conclusively that trench fever was not a modified form of typhoid or paratyphoid fever, and before it had been established that the infection was transmitted by some insect vector. In spite of the questions that were left undecided, the observations of McNee, Brunt and Renshaw stand as the first important contribution to the nature of this disease. They showed that the inoculation of blood from a patient with the short form of fever might result in infection showing a prolonged course, with spiky relapses every fifth day; the essential unity of a disease with multiform manifestations was therefore established.

In the year following this work there were many unconfirmed reports from German workers that they had been able to transmit the infection to animals. Jungmann and Kuczynski [8] claimed to have produced a fatal infection in mice, and Strisower [9] reported that both cats and mice succumbed to a fatal infection following inoculation with blood from trench-fever patients. The animals did not present a clinical picture similar to the disease in man; nor were they successfully inoculated through several generations. Most workers agree, however, that it is impossible to transmit the typical disease to the ordinary laboratory animals, although extensive experiments have not been attempted with the higher apes. For this reason all experimenters have found it necessary to resort to the inoculation of human volunteers in order to obtain any definite, useful information in reference to the nature and mode of transmission of the infection. Werner and Benzler [10] successfully inoculated themselves by means of intramuscular injections of blood from trench-fever patients. Six months later Werner allowed himself to be bitten by lice that had previously fed upon trench-fever patients, and after an incubation period of

eight weeks developed a mild illness that was diagnosed as Wolhynian fever. Kuczynski [11] also contracted the disease after being bitten by supposedly infected lice. In all of the experiments carried on by the German workers there is no mention that the inoculated subjects had been isolated from other cases of trench fever, or that special efforts were made to eliminate other sources of infection. It is a well-known fact that doctors, nurses and attendants in military hospitals wherever the disease was prevalent were especially subject to accidental infection. Furthermore, there is little evidence to show that the stocks of lice were free from infection before use in the experiments. Davies and Weldon,[12] of the English army, allowed themselves to be bitten by lice immediately after an infecting feed on trench-fever patients; the lice were originally collected from soldiers. One of them developed trench fever twelve days later. The same criticism that has just been made of the German work can be equally well applied to their experiment. It is not intended to underestimate the efforts of any of these workers, but rather to point out that the results were not sufficiently conclusive to warrant the undertaking of extensive prophylactic measures along any particular line.

Late in 1917 Pappenheimer and Mueller,[13] of the Presbyterian Base Hospital of New York, succeeded in transmitting the disease to one of three volunteers by allowing lice to feed first upon several trench-fever patients and then upon the volunteers. In their experiments the volunteers were kept carefully isolated. Unfortunately, the patient to whom the disease was transmitted suffered from a complicating femoral phlebitis. I saw him on several occasions and have little doubt that he had true trench fever. Here again it could not be positively asserted that the lice were not infected before they fed on the trench-fever patients.

These isolated observations were all highly suggestive, but awaited confirmation by more extensive experiments before they could be translated into active effort. In fact, there were negative experiments, such as those recorded by Sundell and Nankivell,[14] and many reports of patients who denied having been bitten by lice that threw doubt upon the louse-transmission hypothesis.

Epidemiological studies were highly unsatisfactory because of the constantly changing population in most military units. The proof that rats were the active agents in the transmission of spirochætal jaundice naturally suggested that trench fever might be spread in a similar manner. It is evident that it was impossible to frame any effective program to combat the spread of the disease in the face of so much conflicting evidence and opinion.

In the meantime, accumulated evidence showed that trench fever was one of the largest sources of wastage of man power in the fighting armies. It is estimated that during the years 1917 and 1918, before the influenza epidemic, it was the cause of from one-fifth to one-third of all of the cases of illness in the British armies in France. The German reports indicate that this disease was responsible for at least one-fifth of the illness in the armies of the Central Powers. Although the illness was never fatal, it resulted in prolonged disability. A report from the Boulogne Base [15] of the British army shows that patients with trench fever were unfit for military duty for an average of from sixty to seventy days, and that in addition at least 10 per cent. of them became semipermanent invalids.

This is a brief sketch of the state of our knowledge at the time of the formation of two commissions to study the disease more carefully. It was perfectly evident that to obtain the most accurate information it was necessary that the experimenters should be free from the manifold duties of an army medical officer. The conditions under which members of these commissions worked satisfied these requirements. The British Commission in London had the advantage of permanent hospital and laboratories and the assistance of the workers of the Lister Institute. Volunteers for inoculation and fresh cases of the disease were not so available as in France. It was possible to conduct the experiments in a more leisurely manner and thus to study in more detail the problems as they arose.

The Commission * formed under the auspices of the American

* The Commission consisted of Majors Strong and Opie, Captains MacNeal, Baetjer and Pappenheimer, Lieutenant Rapport and myself, all of the Medical Corps of the United States Army, and Captain Peacock, an entomologist from the Royal Army Medical Corps.

Red Cross, on the other hand, started its work under field conditions. Later it was necessary to move the laboratory, patients and personnel to Paris, where better facilities were available. We were compelled to answer the problems as quickly as possible. We had the advantage of starting the work in a place where numerous examples of fresh infection of the disease were available and where the Trench Fever Commission of the British Expeditionary Force had been carrying on clinical studies for some time. The advice of experienced observers was, therefore, available both in the selection of suitable patients from which to obtain the virus and in the decisions as to the nature of the disease produced. Every facility at their disposal was offered by both the British and American military and medical authorities. The members of the commission were chosen because they could carry out their particular part of the work with the least possible delay. Captain Peacock was loaned by the R. A. M. C. to help in the entomological work because of his previous experience with the life and habits of insects.

These details are related in order to make clear the conditions under which the answers to the various problems were obtained. Throughout the entire period of our work there was the closest coöperation between all of the interested organizations. As fast as positive results were obtained by one commission they were made known to the other, and thus much time was saved to both. It is only natural that different lines of investigation should have been followed by different workers and somewhat divergent results obtained; but in the main facts the two commissions agree. This communication, therefore, will consist largely of a résumé of the work of these two bodies.

Before proceeding, however, it is well to credit the volunteers for the large part they played in the success of the experiments. Probably in the investigation of no other disease have so many men submitted themselves to artificial inoculation. Even though they could be reasonably sure that their illness would not be fatal, they knew that they would suffer much pain and incapacity for an indefinite period. In spite of this knowledge, both our own soldier volunteers and the British civilians who offered them-

selves underwent the trying experience with the greatest fortitude. As a direct result of their sacrifice, much information was obtained that led to the institution of measures for the prevention of the spread of trench fever in both military and civilian population.

It will be recalled that although McNee, Brunt and Renshaw had fairly well proven, by human transmission experiments, that trench fever was a disease entity related in no way to the typhoid-fever group, there were many clinicians who still held that the malady was a form of enteric fever modified by the immunity that had been induced in soldiers by protective inoculations. There were many cases in the British enteric-fever hospitals diagnosed by means of agglutination reactions as typhoid or paratyphoid fever that presented clinical pictures resembling trench fever in almost every respect. One of our first problems was, therefore, to confirm McNee's observations and to establish definitely that the patients with whom we were working were not suffering from any other disease than trench fever. Over thirty volunteers [17] were inoculated with blood or some fraction of blood. In all of the original patients from whom the virus was obtained, as well as in those that developed the disease as a result of inoculation, it was proven by bacteriological examination that no known bacterium played any etiologic rôle in the condition under consideration. Like McNee and his co-workers, we found that the whole blood contained the virus, but in contradistinction to their findings, we determined that the plasma, obtained from citrated blood, was always infectious. In four out of five experiments the incubation period in the patient inoculated with citrated plasma was shorter than in control patients inoculated with the whole blood. It seemed, therefore, that the plasma contained the virus in greater concentration. Clear serum, obtained by centrifugalizing coagulated blood, no longer contained active virus. A similar result with serum was recorded by the British Commission.[18] It seems, therefore, that the virus is either enmeshed in the fibrin network of the blood clot or is destroyed by some substance set free during clotting. The incubation period in patients inoculated with citrated blood after standing outside of

the body for two or three hours was longer than in those patients that were inoculated immediately.

In connection with the problem of immunity in trench fever it is interesting to note that the injection of blood obtained from patients on the first to the fourth days of the disease resulted in positive infections with an incubation period of from five to seven days; while in those that were inoculated with blood obtained on the sixth or seventh day the incubation period was thirteen to twenty days. Furthermore, a susceptible subject injected with blood from a patient during an active relapse on the eighty-second day did not contract trench fever. Later experiments make it reasonably certain that this blood contained virus. This evidence points to the development of immune bodies in the serum of patients as the disease progresses; such immunity explains to a certain extent the mechanism of recovery.

Our attempts to pass the virus in the plasma through a Berkefeld filter met with failure, as did the filtration experiments of McNee and his co-workers. One patient inoculated with the filtrate of crushed and ground infectious erythrocytes, developed symptoms and signs of the disease from the eighth to the eleventh day, but no fever until the fiftieth day after inoculation. While the results in this single experiment were suggestive, more conclusive evidence of the filterability of the virus was not forthcoming until later, and hence will not be discussed until other evidence of the nature of the infectious agent is presented.

In none of our experiments was the virus demonstrable in the fæces of trench-fever patients; on the other hand, it was occasionally present in the mixed sputum and saliva. In contrast with these findings, the frequency with which the urine of trench-fever patients was infectious was noteworthy. All of five subjects inoculated with unfiltered urine sediment developed the disease, although one patient was inoculated three times before positive results were obtained. The material for inoculation was prepared by contrifugalizing urine, drying the sediment to a gummy mass and keeping it at room temperature. The combined sediment collected on different days from several patients was used in all of the experiments. Here again the inoculation was effected

by applying the material to lightly scarified skin. This series of experiments demonstrated somewhat the resistant nature of the virus in that the high salt concentration that resulted from evaporation of urine was sufficient to kill most bacteria and spirochæta. There is, however, some evidence that this manipulation did decrease the virulence of the infectious material, for in four out of five patients inoculated with urine sediment the incubation period was two weeks or more. Another explanation for this longer incubation period is that the virus may have been present in the urine in not so high concentration as in the blood. In framing measures for the prevention of trench fever, these experiments indicate the necessity of considering the urine and sputum as possible if not the chief sources of infection.

While the foregoing experiments were an important part of our work in that they proved beyond doubt the essential nature of trench fever and provided known sources of infection for the elucidation of other problems they were only contributory to the main object of our commission—namely, the determination of the rôle of insects in the transmission of the disease. From the beginning it was evident that military operations might interfere with the continuation of the work. The experiments were, therefore, planned to give a positive answer in the shortest time.

All of the lice used were reared from eggs and fed upon normal subjects. Altogether, eleven different people served to feed these normal lice, without developing the disease. Similar findings of the British Commission should serve to quiet the contention that the symptoms of trench fever may be produced by the action of normal lice.

In order to infect the lice they were allowed to feed upon trench-fever patients by means of the box method. Between feedings they were kept at about 30° C. in entomological boxes prepared from ordinary cardboard pill boxes and were fed two or three times a day by placing the open side of the box upon the arm of the subject for thirty minutes. After several infecting feeds, they were transferred to especially prepared cells and placed upon the normal subject. These cells were designed so that the lice might live under as normal conditions as it was pos-

sible to reproduce artificially. A piece of flannel shirting was placed inside of a larger piece of calico, which was then fastened to the arm of the subject by means of adhesive tape; the arm was finally covered with cotton and enclosed in a sleeve that was fastened to the skin at the top and bottom. In this form of container the insects could feed, breed, live and die in almost the same manner as when they infest the clothing of soldiers. The only limitation of their normal activities was that they could not migrate to other portions of the body or to other persons. It was difficult for the volunteer to scratch the skin through the several thicknesses of cloth and cotton, so that at times when the cell was removed for inspection he was allowed or encouraged to scratch. In some instances, however, there were no lesions of the skin other than those produced by the stabbers of the lice. Among twenty-three subjects who harbored infectious lice in this manner, eighteen, or 78 per cent., developed trench fever. Two others, in whom an especial effort was made to prevent any skin lesion except that resulting from the bite of the lice, also developed the disease after an incubation period of four and five weeks respectively. In these two experiments the lice never came into direct contact with the skin of the subject, but were allowed to feed by biting through the meshes of the chiffon cover of the box in which they were kept; in the intervals between feeds the boxes of lice were put in the incubator. In the large majority of our experiments, therefore, infectious lice living under natural or artificial conditions were able to transmit the disease to susceptible subjects. In some instances the lice were on the subject for as short a time as three days; in others for as long as thirty days. In some experiments, after the infecting feeds, the lice were transferred to successive subjects in order to eliminate possible mechanical transference of the virus. The incubation periods varied between fourteen and thirty-eight days, with an average of about twenty-one days. This long incubation period should be kept in mind in connection with the scarification experiments discussed later.

The British Commission [18] was less successful in transmitting the infection by the bites of infected lice. In a total of eight

experiments only two subjects developed the disease. In all of these trials, however, the lice were fed entirely by the box method, as in two of our experiments mentioned above. The difference in the method employed by the two commissions explains, no doubt, the difference in their results. The failure of the workers in London to transmit the disease by the bites alone of infected lice led them to study the effect of applying the excreta of such lice to scarified skin. This resulted in positive infections in the large majority of their experiments. This fortunate outcome opened up a fruitful field which was explored by them with brilliant results. In demonstrating this form of inoculation they developed a method that permitted the study of the evolution of the virus in both lice and patients.

It was shown that the excrement of practically all lice that have bitten trench-fever patients is infectious when applied in suitable quantities to the skin of normal individuals, either by scarification or subcutaneous injection. Volunteers could also be infected by introducing the material into the conjunctival sac but not by insufflation into the nose or by ingestion with the food. The incubation period in the majority of the patients infected by cutaneous scarification was from seven to nine days; that from conjunctival inoculation was about twice as long.

It was established that a certain interval must elapse between the infecting feed and the excretion of actual virus by the lice. In one series of experiments when the insects were fed upon a patient with trench fever on the second day of his disease, this interval was five days; in another, when the infecting feed was from a patient on the seventy-ninth day the interval was twelve days. An observation of even as great interest was the length of the incubation period in the volunteers infected with excreta passed by lice on different days after the infecting feed. For instance, the incubation period in the patients infected with excrement passed on the fifth and seventh days after the infecting meal was sixteen and thirteen days respectively; while in the patients infected with excrement passed from the ninth to the twelfth days, it was seven to nine days. This evidence points to one of two hypotheses: Either the virus of trench fever goes

through a developmental cycle in the body of the louse, or it is taken into the body of the insects in extremely minute quantities, and there must undergo an increase before it can be excreted in sufficient quantities to infect man. The fact that within certain limits the incubation period is shortened by increasing the amount of virus most easily explains why the first virus passed by the lice is less actively infectious than that passed after the ninth day. The minute quantity of the virus that may induce an attack of the disease is shown by the fact that 0.1 of a milligram of excrement injected subcutaneously was infectious, while 0.05 of a milligram was not. The proof that after a lot of lice have been infected they continue to pass the virus during the remainder of their life also supports the hypothesis that the virus simply increases in the body of the parasites. It was further demonstrated that a single louse may pass active virus as late as thirty-two days after it has fed on a trench-fever patient.

The British Commission also turned its attention to the length of time during which a trench-fever patient is capable of infecting lice—in other words, as to how long the virus is circulating in the blood. It is evident that in a disease such as trench fever, in which some patients show evidence of active infection for only two days and others exhibit symptoms for two years, it would be a tremendous, if not impossible, undertaking to determine when every patient is no longer infectious. Both commissions have shown that the virus is circulating in the blood of practically all patients during the first few weeks. Byam [19] and his coworkers demonstrated that lice may abstract the virus from the blood of patients showing evidence of chronic infection as late as the 300th and the 443d day after the onset of the disease. Lice were also infected by patients during periods of intermission from active symptoms in earlier stages. These subjects usually had relapses later. Two of our patients, on the other hand, failed to infect lice that were allowed to feed upon them about the hundredth day after the onset of fever. It seems that when a patient has recovered completely he is no longer a source of danger. It is difficult, however, to determine when this time has arrived, for many patients after long periods of freedom from symptoms have

late relapses. It seems probable that such carriers of the virus, among infested troops, often served to spread the disease throughout the armies.

Both commissions also showed that the virus is not transmitted to the offspring of infected lice through the eggs. The British demonstrated that pediculus capitus can transmit the infectious agent through the excreta in the same manner as does the pediculus corporis. Bedbugs, on the other hand, did not transmit the disease. Although no experiments are recorded on the transmission of the virus by other blood-sucking insects, it seems that the chief offender in the armies was the body louse.

We are now in a position to inquire into the nature of the infecting agent of trench fever. It is found in three different mediums: (1) Blood of patients; (2) urine of patients; (3) the excrement of lice that have fed upon trench-fever patients. Thus a variety of possibilities present themselves for consideration.

The early demonstration that the blood was infectious led many workers to search microscopically for the offending microörganism with widely divergent results. McNee and his collaborators were unable to find anything in blood films that could be definitely established as a microörganism. They were also unable to infect patients with the Berkefeld filtrate of infectious blood. Our own investigations as to the filterability of the virus in the plasma also yielded negative results. On the other hand, one experiment with the filtrate of crushed, washed erythrocytes, known to be infectious, suggested that the negative results with filtrates of plasma containing virus might have been due to the blocking of the pores of the filter with the large colloid particles of globulin and albumin.

In this experiment the patient presented an atypical picture of trench fever, in that he had such symptoms as pain and tenderness in the usual locations, and an enlarged spleen from the second to the eighth week after inoculation, but no definite fever until the fiftieth day. Then, after a short bout of fever, accompanied by an increase of symptoms, the spleen diminished in size, and all of the symptoms of the preceding six weeks disappeared entirely. No other explanation for the peculiar clinical picture

could be advanced except that a very small amount of the virus had passed through the filter, which had not been clogged with the plasma, because this substance had been removed in the washing of the erythrocytes.

After the demonstration of the infectivity of the urine of patients, and of the excrement of infected lice, it seemed advisable to repeat the filtration experiments with these substances, for in them there was probably the maximum quantity of virus with the minimum of admixed colloids. Two sets of experiments were therefore performed: The dried urine sediment collected from several patients was pooled and divided into two portions. One, without further treatment, was applied to the scarified skin of two volunteers in order to prove that the material under consideration was infectious; the other was suspended in normal saline and passed through an unglazed porcelain filter (Chamberland L), which held back bacillus typhosus. Two volunteers were injected intravenously with this filtrate. The controls, inoculated with the unfiltered sediment, developed mild types of trench fever, after incubation periods of fifteen and sixteen days respectively. One of them suffered relapses; the other did not. The mildness of the symptoms induced in these controls indicates that the virus in this particular set of experiments was either attenuated or present only in minute quantities. One of the volunteers, injected with the urine filtrate, did not develop sufficiently distinct symptoms to warrant a diagnosis of trench fever; the other volunteer, inoculated with the same filtrate, developed trench fever after an incubation period of twenty-one days. In order to confirm the diagnosis, however, lice were allowed to feed upon him from the fourth to the seventeenth days, and with their excrement another volunteer was inoculated by cutaneous scarification. He developed absolutely characteristic trench fever after an incubation period of nine days.

The last series of filtration experiments was carried out with the virus contained in the excrement of lice that had fed upon trench-fever patients. One and one-half grammes of this material was collected and divided into two portions. With one of them four volunteers were inoculated, all of whom developed trench

fever after periods ranging from seven to ten days. The other portion was suspended in normal saline, so that the final strength of the suspension was 2 per cent. It was then passed through a Chamberland filter that held back bacillus typhosus. It is calculated that under the pressure conditions (760 mm. Hg.) this filter would hold back any organism larger than that of pleuropneumonia. Three volunteers were inoculated intravenously with this filtrate. One remained free from symptoms. The second, after a period of five days, developed a low-grade septic type of fever lasting seven or eight weeks, during the latter half of which time the pulse rate was much elevated; the spleen was intermittently palpable from the tenth to the thirty-fourth day; pain and tenderness, except headache, however, were never distinct features. In connection with this case, it may be recalled that Byam has demonstrated by inoculation experiments that a patient may have trench fever with an afebrile course throughout the entire period of observation. No other condition could be found in our patient to explain the peculiar clinical picture. The third of the volunteers, inoculated with filtrate of saline suspension of excrement, after an incubation period of twenty-one days, had an attack of trench fever with two relapses. During the first bout of fever there was an accompanying bronchitis; but nothing except the occurrence of trench fever could explain the relapses with typical enlarged spleen, successive crops of macules, and characteristic pain and tenderness.

It seems definitely established, therefore, that the infectious agent, during at least one stage of its development, can be passed through a porcelain filter if the pores of the filter are not blocked with admixed protein. These experiments have been described in detail, because the negative filtration experiments of other workers have cast a certain amount of doubt upon the validity of our results. The failure of McNee, Brunt and Renshaw is easily explained. The only other details of experiments in reference to the filterability of the virus are a set of five reported by Arkwright.[20] Infected lice excrement was suspended in normal saline and subjected to filtration through either Berkefeld or Chamberland filters at different pressures. In two experiments

in which the pressure was between 300 and 400 mm. of Hg., the injection of the filtrate was followed by entirely negative results; in a third, in which the pressure was between 200 and 300 mm. of Hg., the injection of the filtrate into a susceptible subject was followed in eight days by fever and abdominal pain, the causation of which was in doubt. In these three experiments the filter held back bacillus prodigiosus. In two other trials in which the pressure was between 600 and 740 mm. of Hg. and in which the filter allowed bacillus prodigiosus to pass, the injection of the filtrate was followed in one subject by typical relapsing trench fever, and in a second by no unusual symptoms at all. It is of interest to note that in the last two experiments the filtrate was collected from the same material during two successive periods. The advantage of having several subjects with which to test a given filtrate is well illustrated. A similar demonstration was afforded by our filtration experiments.

In connection with the filterability of the virus of trench fever, it may be recalled that a similar divergence in results has existed in the demonstration of the filterability of several of the filter passing viruses. Many experiments were made before it was established definitely that the virus of small-pox and vaccinia was filterable. Ricketts [21] was unable to filter the microorganism shown by him to be contained in the blood of patients suffering from typhus fever. Both Nicolle [22] and Prowazek,[23] on the other hand, have demonstrated that the typhus fever virus, under proper conditions, will pass through a Berkefeld filter. In order to demonstrate the filterability of many unknown viruses suitable conditions must be fulfilled, and these conditions may differ with different microörganisms. On the other hand, filterability does not mean that the microörganism is necessarily "ultramicroscopic" during all the phases of its development. For some years the virus of yellow fever was thought to be ultramicroscopic because of the ease with which it would pass through an earthenware filter; but Noguchi [24] has lately established the spirochætal nature of the microörganism.

Other biologic characters, moreover, place the etiologic agent of trench fever in close relationship with the group of filter pass-

ing viruses. Mention has already been made of the manner in which the virus in infectious urine resists the concentration of salts resulting from desiccation. Byam and his co-workers have demonstrated that the virus in the excrement of lice retains its activity for at least 120 days, even though it is exposed to the ordinary laboratory temperature and humidity and to sunlight. They [25] have also shown that it is not killed by several weeks' exposure to 50 per cent. glycerin. In their hands it resisted dry heat of 80.5° C. for twenty minutes, but was killed by exposure to 100° dry heat for a similar period. When moist heat was applied, it was killed by twenty minutes' exposure at 60° C. In our experiments the virus in infected louse excrement resisted 60° C. moist heat for one-half hour, but was killed after exposure to 70° C. moist heat for a similar period. The discrepancy can probably be explained by the fact that only one series of tests was carried out by each commission; no doubt heat resistance experiments would more nearly correspond, were several series performed. The important lesson from both experiments is that higher degrees of heat are necessary to disinfect the excreta than are required to free clothing from lice and viable eggs.

The low thermal death point of the virus demonstrates that the other resisting qualities of the microörganism are not due to ordinary bacterial spores. The peculiar behavior of the trench fever virus in the presence of various physical and chemical agents practically rules out the possibility that it belongs to the spirochæta group.

Aside from some unsubstantiated claims that a spirochæta is the etiologic agent in trench fever, the most suggestive finding, from the morphological point of view, is that of the so-called Rickettsia bodies. These bodies were first described by Ricketts [26] in the blood of patients suffering from Rocky Mountain spotted fever and in the bodies of the ticks that transmit this disease. A short time later similar bodies were observed by Ricketts and Wilder [27] in the study of typhus fever. These findings in spotted fever have been amply confirmed by Wolbach.[28] In typhus, in addition, Prowazek,[29] da Rocha-Lima [30] and many other observers have shown that lice which had fed upon patients with this

disease pass large numbers of the bodies in their excreta, and also harbor many of them in epithelial cells of the intestinal mucosa.

Morphologically they are small bodies that vary in size from 0.3 to 0.5 by 1.5 microns. In shape they present various outlines: Cocci, diplococci and short bacilli. In the diplococcoid form the two bodies are often joined by a faintly staining substance, so that dumb-bell or figure 8 forms are seen. Observed under the dark field microscope, these forms have a tumbling motion, but possess no distinct motility of their own. They stain readily in films with either Giemsa or concentrated Gentian violet; they are Gram negative, and not acid-fast. With Giemsa stain they take a red violet color of much the same shade as that of the nucleus of a polymorphonuclear leucocyte. Arkwright [31] states that he can distinguish the Rickettsia in lice that have fed upon trench-fever patients from those that have fed upon typhus-fever patients by the following characteristics: In trench fever the bodies are more purplish and smaller; in typhus they are larger and redder. In blood they are best demonstrated in thick drop preparations from which, after drying, the hæmoglobin has been removed by distilled water or acid alcohol. Because of their small size and small numbers in the circulating blood, it is often necessary to make prolonged examination of blood films in order to demonstrate them. They are much more easily found in the bodies of the insect vectors of these diseases. Attempts to cultivate the pathogenic forms on artificial media have resulted in failures; but both Nöller [32] and Jungmann [33] report that they have succeeded in cultivating on dextrose serum agar the Rickettsia bodies found in sheep ticks. The latter observer has shown that this species, the Rickettsia melophagi, is simply a parasite of the tick and does not produce any disease in the sheep harboring the insects. Films made from the culture of Rickettsia melophagi show all of the forms that are seen in excrement and bodies of lice and in the blood of patients.

Early in their studies various German observers described small microörganisms that resembled the Rickettsia bodies of typhus fever in the blood of patients suffering from trench fever.

This finding, combined with the supposed similarity in the mode of spread of the two diseases led Töpfer,[34] Jungmann and Kuczynski [35] and da Rocha-Lima [36] to search for these bodies in the excrement and bodies of lice that had fed upon patients with Wolhynian fever. Their demonstration of Rickettsia bodies in the intestinal mucosa and excrement of these lice was the chief support for their hypothesis that lice were the insect vectors of this disease. They reported that these bodies could not be found in lice until the lapse of at least five days after the insects had fed upon a patient. This time corresponded so closely with the period between relapses in patients with spiky periodic fever that the German observers felt this fact furnished a further support to the hypothesis of the etiologic relationship of these bodies. Jungmann states that he was able to find them in the blood of patients with the spiky type of relapses only at the time of the relapses; on the other hand, he found them in the blood of patients with continuous or typhoid type of pyrexia at any time during their fever. In spite of the attractiveness of this evidence as to the etiologic rôle of Rickettsia, it does not correspond with the findings of the British Commission as to the infectivity of patients for lice. In the experiments of the last-named observers, lice could be equally well infected by feeding upon patients during the febrile and afebrile periods. Jungmann's observations, therefore, merely indicate a correspondence between the demonstrable presence of Rickettsia bodies in the blood and the occurrence of fever.

Jungmann and Kuczynski [37] claim that they were able to find these bipolar bodies in the blood of mice that had been inoculated with the blood of patients or with the excrement of lice that had fed upon patients. Da Rocha-Lima,[38] on the contrary, was unable to infect mice, but reported that he produced the typical disease in seven out of forty-four guinea pigs inoculated with blood, urine or lice from trench-fever patients. He was, however, unable to pass the infection on to a second generation of the animals. In a series of experiments in which he allowed normal lice to bite seventy trench-fever patients, 73 per cent. of the insects showed Rickettsia bodies; on the other hand, 20 per cent. of the

lice that had fed upon patients who were supposed not to have had trench fever also showed the bodies. He explained these findings on the assumption that normal lice might be infected with a non-pathogenic type of microörganism that he called Rickettsia pediculi. Probably a better explanation is that the patients were suffering from atypical trench fever or that some of them had trench fever complicating the disease for which they were admitted to the hospital. Jungmann,[39] in contradistinction to da Rocha-Lima, states that he has never found Rickettsia bodies in lice that have not fed upon either trench-fever or typhus-fever patients. Both of these observers claim that the interval between an infecting feed and the time that the Rickettsia bodies appear in the insects is about five days for trench fever and nine to twelve days for typhus fever.

The British Commission has confirmed with certain exceptions the observation of the German authors. Arkwright, Bacot and Duncan,[40] who carried out this portion of the work, had the advantage of working with a pedigreed stock of lice, as well as with experimentally produced cases of the disease from which to infect the insects. Finally they were able to compare the appearance of the Rickettsia bodies with the infectivity of the lice for normal subjects. They [41] have lately reported that they were able to find Rickettsia bodies in all of 108 boxes of lice that had fed several times upon sixty-four trench-fever patients. In only one out of many lots of the insects that had fed only on normal persons were forms found that suggest trench-fever Rickettsia bodies. In their experiments a volunteer inoculated with a single louse that contained the Rickettsia contracted trench fever, while another subject inoculated with a single louse from the same box, but free from Rickettsia, remained well. There was also a remarkable correspondence between the appearance of Rickettsia bodies in the excrement of lice after the infecting feed and the virus content of the same excrement when inoculated into susceptible volunteers. The interval between the infecting feed and the appearance of the bodies varied between five and twelve days, with an average of from seven to ten days. This time is longer than that reported by the Germans, but corresponds

closely with the average incubation period in patients inoculated with the excreta of infected lice. Lice that were fed upon patients with experimentally produced trench fever during the first day only did not subsequently show Rickettsia bodies; although lice fed later on the same patients did show them. In this connection it is of interest to note that the only lice that were usually not infectious in our original experiments were those that were fed upon patients during the last two days of the incubation period and during the first two or three days of the fever. Blood from these same patients, however, contained virus, as demonstrated by intravenous inoculation. In all types of experiments, with one exception, therefore, there is a striking parallelism between the infectivity of the insect vectors and the appearance of Rickettsia bodies. This exception was reported by Arkwright and Byam [42] and is as follows: Two lots of lice were allowed to feed upon a trench-fever patient; one lot was kept at a temperature of from 27° to 30° C. and developed Rickettsia bodies; the other lot was kept at 17° C. and did not develop them. The excrement from both lots of lice proved to be infectious by inoculation into normal volunteers.

While it is difficult not to believe that there is a causal relationship between the virus of trench fever and the Rickettsia bodies, it will be difficult to establish definitely such a relationship until it is possible to obtain pure culture of the bodies and with them to reproduce the disease. In this connection it must be recalled that the relation of Rickettsia bodies to other microörganisms has not been established. They may be specific microörganisms; they may be a granular stage through which some other microörganism is passing; or, finally, they may be cell inclusions, the result of the action of some invisible virus on the cell protoplasm and thus resemble the Guarnieri bodies in vaccinia, the Negri bodies of rabies, the molluscum bodies in molluscum contagiosum and the cell inclusions in trachoma.

In our efforts to determine the pathogenesis and histological changes in this disease, we are handicapped by inadequate knowledge as to the nature of the virus and by a total lack of autopsy examinations. The non-fatal character of the disease has made

it impossible to examine thoroughly all of the tissues of the body for the site of attack of the virus. In addition, the failure to reproduce the typical disease in lower animals has forced us to resort entirely to the study of the various clinical manifestations in man in order to arrive at some understanding of the nature of the infection.

In the two other well-known diseases that are associated with the appearance of Rickettsia bodies in the insect vectors of the virus it has been established that the chief structures showing definite histologic changes are the small blood-vessels. Wolbach [43] has shown that the reaction in Rocky Mountain spotted fever is "an endangitis, characterized by endothelial-cell proliferation, local necrosis of endothelium and smooth muscle and thrombosis. Perivascular accumulations of large mononuclear cells are of common occurrence." The lesions are limited practically to the skin and genitalia. Fraenkel [44] has demonstrated that the essential lesion in typhus fever is the same; but in the latter disease the vessels of the viscera are also involved. Schminke [45] has compared the histologic changes in the exanthems of trench fever and of typhus and shown that in the hyperemic and œdematous corium of trench-fever macule there is a perivascular lymphocytic infiltration mixed with some polymorphonuclear leucocytes. The endothelium and vessel-wall necrosis and hyaline thrombosis found in typhus-fever lesions was entirely absent. This probably explains why the trench-fever exanthem is not petechial. In typhus fever the intensely toxic nature of the virus leads to an actual death of the cells and often of the patient; while in trench fever the less toxic virus does not lead to a destruction of either cell or host. A similar action on the body of the insect vector of the two diseases has been found. Both the English and German observers have noted that lice that have bitten trench-fever patients live their normal number of weeks; on the other hand, Jungmann and da Rocha-Lima call attention to the fact that the life of lice is shortened by feeding on typhus-fever subjects.

Clinically the main tissues that seem to be involved in trench fever, aside from the skin, are the hæmatopoietic organs and the nervous system. The polymorphonucleosis during the febrile

paroxysms, followed by an increase in the mononuclear elements of the blood, and the peculiar enlargement of the spleen all indicate that the virus has a marked effect upon the blood-forming and blood-destroying organs. There has been much discussion as to the cause of the peculiar pain and tenderness in patients with this disease. The symptoms are not accompanied by other signs of local inflammation of the periosteum, muscles or tendons, such as swelling, redness or œdema. The description of the pains given by many patients resembles the pains that occur in the early stages of tabes dorsalis. Byam,[46] Carmalt Jones[47] and others have called attention to the peculiar distribution of cutaneous hyperæsthesia in the areas supplied by the eighth cervical, first and seventh dorsal, and all the lumbar segments of the cord, during the active stages of the disease. Sundell[48] has observed that later there is a distinct blunting of the cutaneous sensibility over similar areas. These sensory disturbances, coupled with the increase in tendon, cutaneous and pilomotor reflexes, all point to some abnormal condition of the sensory tracts, probably in the regions of the dorsal roots. The condition of "disordered action of the heart," a late complication in certain patients, can best be explained upon the basis of a disturbance of the autonomic nervous control of the cardiac action. In patients suffering from this peculiar group of symptoms or from neurasthenia following an attack of acute trench fever, there is usually evidence that the disease is still active in a chronic form.

The many forms of fever that have resulted from the artificial inoculation of different individuals with the same strain of virus have demonstrated that the various clinical types of the disease are not due to different varieties of the microörganism, as is the case in malaria. The spiky type of paroxysm, requiring but a single day for its completion, can be best explained on the assumption that the virus requires a certain time for its complete development in the tissues of the patient; when that period is complete the microörganisms, or a toxin that they develop as a result of their activity, flood the patient and give rise to the explosive picture. If, on the other hand, the microörganisms are of different age, either as a result of multiple inoculation, or

because of a mixture of virus of different ages, they will attain their maximum growth in the patient's body at different times, and produce a septicæmic or typhoid type of fever.

Recovery from the disease is evidently due to the development of an immunity on the part of the patient. The time required for the development of this immunity varies within wide limits. No doubt, some individuals possess a complete immunity to the infection. In others there is a partial immunity, so that the introduction of the virus into their bodies results in abortive or larval types of the disease. In the majority of patients complete immunity develops only after repeated flooding of the body with the virus, and on the average requires from three to six weeks for its production. Even then it may be only partial—sufficient to hold in abeyance all symptoms until the patient is subjected to some general depressing influence, when a relapse occurs. Among our volunteers we had a number of examples of such relapses after prolonged periods of absence of fever and symptoms; and lately I have seen in a physician a relapse that occurred twenty-six months after the original attack in Flanders. Such prolonged periods of freedom from symptoms with subsequent relapses remind one of similar conditions in malaria and syphilis.

In still a final group of patients months or years are required for complete immunity to develop. This group comprises from 5 to 10 per cent. of all of the patients afflicted with the disease. In them the manifestations assume a subacute or chronic form; the patients are never entirely free from symptoms; occasional low grade fever is found. The condition is variously described by the terms myalgia, neuralgia, neurasthenia, disordered action of the heart, or trench-fever cachexia. Byam and his associates have shown that at least some of these sufferers are carrying the virus in their blood as late as from three to four hundred days after the onset of fever.

The immunity that develops with recovery is of relatively short duration. The British Commission showed that reinfection was possible on the 132nd and 198th days after the onset; Werner [49] reinfected himself six months after his first attack.

On the other hand, the British found it impossible to reinfect some patients at periods varying from 62 to 182 days after the onset. Irregularity in the duration of immunity seems to be as much a feature of the disease as irregularity in the time of development of immunity and as irregularity in most of the symptoms.

The practical application of all the knowledge that has been gained by much effort is that eradication of the louse is followed by a cessation of the disease. The discussion that has arisen as to whether the chief mode of human infection is through the bite of the insects or results from introduction of louse excrement into excoriated skin is more academic than practical. The method of inoculation by applying louse excrement to scarified skin has resulted in much useful knowledge concerning both human and insect carriers of the disease. It has been the experience of many observers that the wholesale application of measures against louse infestation has been followed by a diminution in the incidence of the disease. This was strikingly brought out in the experience in the Third Army of the American Expeditionary Forces.[50] The experience in the Presbyterian Base Hospital Unit [51] of this city showed that infected and infested clothing and equipment may be handled with impunity, provided the people handling such material are protected against lice. The chance for contracting infection from patients was as great, or greater, after May, 1918, as before, but the simple institution of effective measures against the possibility of becoming infested with lice from the patients resulted in practical freedom from new infections among nurses and orderlies.

In summary: During the recent war a disease, hitherto unrecognized as a clinical entity, was widespread throughout the armies on both the eastern and western fronts. Although the manifold forms of the affection make accurate statistics impossible, it is estimated that between 800,000 and 1,000,000 cases must have occurred. Before the influenza epidemic it was the most frequent single disease in several of the armies. While not fatal, it usually resulted in disability for ten to twelve weeks, and in 10 per cent. of the cases was the cause of invalidism for many

months. In such instances the infection is active in a chronic form. The many clinical forms of the disease are apparently not due to the action of different types of microörganism, but to single or multiple infections with a single type of organism. The intensity and duration of an attack seem to depend upon the relation between the infectivity of the virus and the immunity in the patient.

It has been demonstrated that the disease is not a modified form of enteric or typhus fever, but is due to a specific infectious agent. This etiologic agent behaves in the presence of various physical and chemical environments in a manner similar to that of many of the filter passing microörganisms. Under suitable conditions the virus of trench fever will pass through the pores of a filter that are small enough to hold back ordinary bacteria. The virus is found occasionally in the sputum of patients, often in the urine, and always in the blood at some stage. It is also found in the excrement and bodies of practically all lice that have fed several times upon trench-fever patients, after an interval of from five to ten days following the infecting feed. After a louse has started to excrete active virus, it continues to do so for the remainder of its life. The virus is not transmitted to the larvæ of lice through the eggs. The interval elapsing between the time of the infecting feed and the first excretion of virus by lice closely corresponds with the length of the incubation period in men inoculated with a maximum dose of virus. There is a remarkable correspondence in the infectivity of louse excrement and the time of appearance of Rickettsia bodies; these bodies are also demonstrable, with difficulty, in the blood of patients during the periods of pyrexia. The etiologic rôle of Rickettsia bodies, however, as well as the relation of these bodies to microörganisms in general, remains to be established.

While men may be infected by the simple bites of infected lice, they are more surely infected by applying the excrement of such lice to scarified skin; infected lice, living under normal conditions transmit the disease to the majority of, if not to all, men harboring them. As a direct corollary, the eradication of lice is followed by an eradication of the disease.

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