Typhus Fever (1915)
(John F. Anderson)

COMMENTARY
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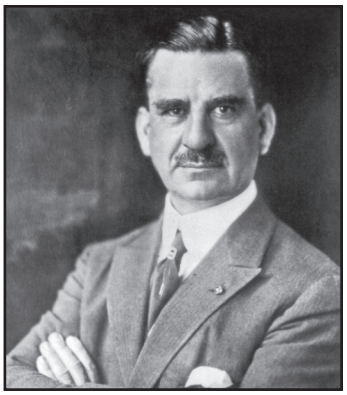

John F. Anderson

John F. Anderson, MD, was Director of the USPHS Hygienic Laboratory when he wrote this important paper on typhus in 1915. He studied bacteriology in Paris, Vienna, and London. Anderson was the first to describe Rocky Mountain spotted fever and to identify the tick as the vector. The Dermacentor species was later named *andersonii* in his honor.

Anderson's report begins with an historical review of the difficulties faced by early clinicians in differentiating typhus from another "typhus-like" fever later called typhoid. Anderson's observations on the immunology of typhus are revelatory. He noted an attack of Mexican typhus ("tabardillo") conferred immunity to epidemic (European) typhus. He determined the incubation period of typhus was 5–14 days. Typhus was accompanied by a rapid increase in fever during the first 36–48 hours, reaching as high as 106°F. He noted, as had others previously, that the typhus fever remains elevated until defervesence either by crisis or lysis. In his experiments, he noted an attack of Brill's typhus conferred immunity to Mexican typhus and conversely, Mexican typhus conferred immunity to Brill's disease in monkeys. He concluded that Brill's disease (recrudescent epidemic typhus) and typhus fever differed only in severity. On the basis of cross-immunity, he reasoned that Mexican typhus was the same as Brill's typhus of New York and that the European and Mexican forms of typhus were identical. The clinical manifestations of Mexican (murine) typhus were subsequently shown to be a mild form of the epidemic typhus caused by *Rickettsia typhi* and not *Rickettsia prowazekii* as with epidemic typhus. It was later shown that Brill's disease, a mild form of American typhus, was a reactivation of epidemic typhus in epidemic typhus survivors. Brill-described patients at Mount Sinai Hospital in New York were Jews of Eastern European origin who had epidemic typhus in Eastern Europe before coming to the United States. Subsequently it was determined that *R. prowazekii* can remain suppressed, but viable, in the lymph nodes of epidemic typhus survivors. When immunity to *R. prowazekii* wanes, there is a relapse/recrudescence of epidemic typhus, albeit in milder form. Therefore, Brill's disease (American typhus) was the same as the Mexican typhus known as murine typhus.

Anderson carefully described the key differential diagnostic points between typhus and typhoid fever, including acuteness of onset, mental status, rapidity and height of fever, relationship of the pulse to the fever, appearance of the face, and cutaneous manifestations. To this day, students of infectious diseases can learn much from his lucid descriptions.

In addition to his important observations on typhus, Anderson stressed the importance of controlling the insect vector (e.g., human body louse) in limiting the spread of typhus. He correctly reasoned that without the louse vector, person-to-person transmission of typhus would not occur. His emphasis on control of epidemic typhus through elimination of the louse vector is one of his many enduring legacies.

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TYPHUS FEVER

Its Etiology and the Methods of its Prevention[1]

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By John F. Anderson, Director, Hygienic Laboratory, United States Public Health Service

The subject that I have chosen for my address is at once an old one and a new one. It is old because the disease has been known for a great many years, even back to the time of the Great Plague in London, many deaths during that great epidemic having been undoubtedly due to typhus fever. It is new because of certain recent additions to our knowledge of the etiology, method of transmission, and distribution of the disease.

Typhus fever has been confused, especially, with two other diseases, namely, relapsing fever and typhoid fever. The distinction was first clearly drawn clinically between relapsing fever and typhoid in Ireland about 1826, and their nonidentity was conclusively settled by the discovery of the spirillum of relapsing fever in 1868. Gerhard, in 1837, was the first to set forth clearly the clinical and pathological differences between typhoid and typhus fevers, and the discovery of the typhoid bacillus by Eberth in 1880 definitely established this distinction.

The disease has been the subject of a large amount of painstaking and careful work without any very great advance having been made in our knowledge of it until the latter part of 1909, when Nicolle infected a chimpanzee with blood drawn from a human case of typhus fever. Sometime later, working with Comte and Conseil, he reported the successful transmission of typhus fever from one monkey to another by the bite of the body louse.

Just about that time the studies by Goldberger and myself were begun in Mexico City and we were not aware of the work of Nicolle and his coworkers until after the publication of our first two notes. We found, contrary to the first reported experiments of Nicolle, that the lower monkeys, such as the rhesus and capuchin, could be infected by inoculation of blood drawn directly from human cases of the disease, and without the passage of the virus through one of the higher apes, such as the chimpanzee, as was claimed to be necessary by Nicolle. We found that one attack of Mexican typhus in the monkey conveyed a definite immunity to subsequent attacks and, in our opinion, the epidemiological evidence pointed unmistakably to the correctness of Nicolle's observations as to the part played by the body louse in the transmission of the disease.

Just at this point our work in Mexico was interrupted by the illness of Dr. Goldberger with typhus and after his recovery his condition was such as to necessitate our return to the United States. For this reason our work on typhus fever was discontinued, as it was not believed that cases of the disease, except at rare intervals, occurred in this country.

About this time, however, Dr. Nathan E. Brill published a paper giving the results of a study of 221 cases of an acute infectious disease of unknown origin observed by him in the wards of Mount Sinai Hospital during several previous years. He had previously reported 17 cases of the same disease. The important features of the disease, as observed by Dr. Brill, are so well summarized in his definition that I shall quote it:

> *An acute infectious disease of unknown origin and unknown pathology, characterized by a short incubation period (four to five days), a period of continuous fever, accompanied by intense headache, apathy, and prostration, a profuse and extensive erythematous maculo-papular eruption, all of about two weeks' duration, whereupon the fever abruptly ceases either by crisis within a few hours or by rapid lysis within three days, when all symptoms disappear.*

In a third paper Brill reported on a study of 34 additional cases observed since the 221 reported in his second paper. This paper was of especial interest to us, as it gave the results of the inoculation of monkeys with material obtained during life and at autopsy from cases of the disease and it gave the postmortem findings in the fatal case. When Brill's second paper appeared in April, 1910, we had recently returned from the City of Mexico where we had seen many cases of typhus and we were struck by the very remarkable resemblance between the disease described by Brill and typhus fever as observed by us in Mexico and as observed by one of us in certain places abroad. For this reason we endeavored to obtain access to cases of Brill's disease for purposes of study in order that we might determine if possible their relationship to typhus. A case was finally seen in the wards of Mount Sinai Hospital and blood was drawn from the arm vein of this patient and used for the inoculation of monkeys. One of these animals, after an incubation period of 10 days, developed a fever which reached its maximum six days later and fell by rapid crisis 14 days after the rise began.

Blood was drawn from this animal and used for the inoculation of other annuals which, after an incubation period of nine days, developed a fever which, in its rise, duration, and termination, was similar in all respects to that in the monkey first inoculated. Since then this strain of typhus fever has been passed through 76 monkey generations and over 150 generations in the guinea pig.

After intraperitoneal or intravenous inoculation of infective blood into a monkey there follows an incubation period of 5 to 14 days. At the end of this time there is usually a rapid rise of the animal's temperature, which not infrequently reaches a maximum in 36 to 48 hours of 41 to 41.5° C. The temperature remains high until toward the end of the febrile period, when it may show a gradual decline; but it usually declines by crisis or rapid lysis, frequently to subnormal.

Convalescence is usually rapid. We have never noticed the presence of an eruption, although careful search has been made for the same. In other words, the fever is the only definite index of a reaction. Although apparently a mild disease in the monkey, we have had four deaths in a total of 105 cases of typhus in that animal.

After we had established the susceptibility of the rhesus monkey to infection by inoculation with blood from a case of Brill's disease it became important to determine the relationship of Brill's symptom-complex to typhus fever, and for this purpose we tested the susceptibility of animals that had recovered from Brill's disease to Mexican typhus, as well as the converse of this. It was found that an attack of Brill's disease in the monkey conferred a definite immunity to infection with Mexican typhus, and that an attack of Mexican typhus in the monkey conferred a definite immunity to an attack of Brill's disease. In other words, Brill's disease, so called, and typhus fever are identical.

The results of these cross-immunity tests having plainly justified the conclusion that the disease described by Brill was identical with the typhus fever of Mexico, and inasmuch as the New York strain of typhus was undoubtedly of European origin, the further conclusion was made that the typhus fever of Europe and the typhus fever of Mexico are identical.

During the progress of the work necessary for the demonstration of the identity of the two diseases, a number of related problems were given attention. Among the first of these was work upon the method of transmission. It was found that the so-called Brill's disease, as well as the typhus fever of Mexico, could be transmitted to the monkey by the bite of body lice which had previously been allowed to feed either on human cases of the disease or on monkeys sick with typhus fever.

Attempts have been made by various workers, including ourselves, to transmit the disease from monkey to monkey or from human beings to monkeys by the bite of insects other than the body louse. The experiments with fleas and bedbugs have been frankly negative, and the experiments with the head louse by Goldberger and Anderson, while highly suggestive, were not conclusive.

Since the body louse has been shown to be the means by which typhus fever is transmitted, it has been possible to put into effect practical methods of preventing typhus which, when intelligently applied, have worked remarkable results. Thus the disease, which has always been endemic in Tunis and which each year has carried off a large number of victims among the native population, has now almost disappeared. According to Nicolle, in 1909 there occurred in Tunis 838 cases of typhus fever, but in 1912, after the efforts to control the disease in the light of recent researches had been put into effect, there occurred only 22 cases. The only prophylactic measure resorted to has been the systematic destruction of lice found on persons (and their clothing) in the vicinity of patients suffering from typhus.

Typhus fever has always been one of the great plagues of military camps, particularly in the temperate zone, and it is more than probable that, unless the newer methods are adopted for the control of the disease in the large armies now engaged in warfare in Europe, the disease may become a scourge among the troops. This is particularly true, as typhus fever is known to be endemic in certain German, Russian, and Austrian Provinces and in Eastern Europe.

The experimental work of various investigators of typhus fever has shown conclusively that the virus of typhus is present in the blood, at least throughout the febrile period, and we have found that the blood of the monkey may still be virulent from 24 to 32 hours after the return of the temperature to normal, but that the blood of the animals in the instances tested by us was not virulent in the pre-febrile stage. The infective agent is present in the different elements of the blood; that is to say, the blood serum collected by defibrination and centrifugation or by clotting, the washed blood corpuscles, and the leucocyte layer all contain the infective agent in about equal proportions.

The virus in the blood is not very highly resistant. It has been found that drying for 24 hours and heating at 55° C. for five minutes deprive it of infectivity. It may resist freezing as long as eight days.

We made a number of experiments to determine the filterability of the infective agent as it exists in the blood serum and we believe that the virus of typhus fever is not filterable and that therefore the infective agent is of a size sufficiently large to be seen with the ordinary powers of the microscope.

I have referred to the fact that the guinea pig is susceptible to infection with typhus fever. This is of importance because I have suggested that the inoculation of this animal with blood drawn from cases of fever giving a negative Widal and a negative blood culture for the typhoid bacillus will be of value in the diagnosis of suspected cases of typhus fever.

Now, just a few words in regard to the clinical differences between typhus and typhoid. This may be of special significance to the clinician. Both the older and the more recent history of the disease testify to its great clinical likeness to typhoid.

As a rule, the onset of typhus is more abrupt than that of typhoid fever. It is common in typhus to find a history of well-being on going to bed and of rising in the morning with a severe headache and malaise which, within a few hours, compel a return to bed. Chilliness or a distinct chill are common at the onset of typhus, very much more so than in typhoid. Headache with or without chilliness and with or

without malaise almost invariably marks the invasion of typhus. Indeed, the patient may complain of little else, either at the beginning or throughout the course of the disease.

In marked contrast to typhoid, the face is flushed and the conjunctive are congested in the first few days as the result of a capillary congestion not unlike that seen at the onset of dengue or of yellow fever.

The temperature rises rapidly, very abruptly indeed, and with it the pulse rate. In typhoid the evolution of the fever takes longer as a general thing, and the rise in the pulse rate is sluggish and not in proportion to the fever. The fever does not as a general thing range at high levels. In this, as well as in some features of its onset, typhus strikingly resembles yellow fever. The duration of the fever is about twice that of yellow fever and about half that of typhoid, namely, about 14 to 16 days. The defervescence also suggests yellow fever, except that it is not infrequently critical in typhus. Some of the older descriptions of typhus give the impression that a critical defervescence is invariable; this has not been our experience as we have seen typhus in Mexico.

An important distinction relates to the eruption. The eruption of typhus appears within three to five days after the onset, therefore earlier than is the rule in typhoid; it is general, sparing only palms and soles; its evolution is rapid, being fully out within 24 to 36 hours, and is permanent, in marked contrast to the typhoid eruption which appears in successive crops. It is important also to recall that the macules constituting the typhus eruption are polymorphic. They have not the regularity of outline or the uniformity of size and appearance of the typhoid rose-spots. Moreover, while most or all of the lesions may fade markedly on pressure in the early stages, some fade little if at all, and the proportion of these may and usually does rapidly increase, the eruption becoming petechial as it becomes older.

Recently, Plotz, working at Mount Sinai Hospital, has reported the cultivation of an organism from cases of typhus, using special anaerobic methods. Should his work be confirmed it is possible that methods may be developed, using the organism, for the serum treatment of cases and perhaps a vaccine may be devised that will be of value for prophylactic purposes.

Brill, in his three papers, has reported the observation of 254 cases of so-called Brill's disease, which we now know to be typhus fever, in the wards of Mount Sinai Hospital between the years 1896 and 1910. Eighteen cases were reported by Louria at the Jewish Hospital, Brooklyn, during the summer and fall of 1910. Cases have been reported from other hospitals in New York City, Chicago, Milwaukee, Washington, Atlanta, Providence, Boston, and points in Virginia and Indiana.

Roger Lee, in a study of the case records of the Massachusetts General Hospital for the 10 years from 1902 to 1912, concluded that typhus fever in mild form had been present in Boston and vicinity during that time. He found, in his study of the records of 1,404 cases of continued fever of a greater duration than seven days, 28 cases which corresponded extremely closely with Brill's description of typhus fever. This gave a ratio of 1 case of typhus to 47 cases of typhoid.

There is reason to believe that this same ratio would hold, not only for cases of typhoid fever in Boston, but for typhoid fever in other large cities of the United States. If we assume that the ratio of 1 case of typhus to 47 cases of typhoid, as found by Roger Lee in the Massachusetts General Hospital, holds for certain other large cities, we may estimate for 1912, based upon the reported cases of typhoid fever, that there were present in New York City for that year 72 cases of typhus, in Baltimore 22, Boston 10, Chicago 22, and Philadelphia 34.

That this is not altogether an unwarranted assumption is evident from the fact that, according to the reports from two hospitals in New York City, 36 cases of typhus were treated at Mount Sinai Hospital and 19 cases at the Jewish Hospital in the year 1912. The ratio of cases of typhus to typhoid in the Jewish Hospital for that year was about 1 to 2.3 instead of the ratio of 1 to 47, as found by Lee in Boston.

From this it is evident that typhus fever, instead of having disappeared from the United States, is present and has been present for years, at least in the large cities. This hardly need occasion any surprise when we recall how frequently the presence of certain diseases may be overlooked, as is shown by the history of pellagra and hookworm disease in this country.

There is no experimental evidence to support the view that typhus is acquired in any manner other than by the bite of lice, which have previously fed on a person sick with the disease. This being so, in our prophylaxis it is necessary only that we keep this important fact clearly in mind, and by so doing we may readily deduce the fundamental procedures on which prevention may be based.

In my opinion it may safely be assumed that association with a case of typhus, in the absence of the transmitting insect (the louse), is no more dangerous than association with a case of yellow fever or malaria in the absence of the proper species of mosquito.

All our efforts at prevention, therefore, are centered upon the louse, and these efforts may be broadly grouped under the following headings:

1. Measures for the reduction of lice infestation among the population in general.
2. The destruction of all lice and their eggs found on the bodies, clothing, bedding, and surroundings of all cases of typhus, typhus suspects, and contacts.
3. The adoption of measures, by persons in the vicinity of cases of typhus, to reduce or prevent the possibility of their being bitten by lice.
4. Inoculation with the mild type of the disease (Brill's disease) by persons contemplating entering localities where the disease is prevalent. Should Plotz's work be confirmed the use of a vaccine prepared from the typhus-fever germ may be substituted for this.

The measures to be adopted under the first heading are, to a considerable extent, educational, except in institutions and places over which the sanitary authorities have supervision, such as bathhouses, lodging houses, and other places where numbers of persons may gather.

In surroundings where lice may be found, systematic efforts should be made for the destruction of lice and their eggs. These efforts consist in the use of insecticides, both chemical and physical, bearing in mind the important point that the louse requires frequent feeds of blood and therefore is most apt to be found on recently used clothing or bedding. It is not difficult to kill when exposed to insecticides, while its eggs are much more resistant to chemical agents, but are destroyed by heat or steam.

Under the second heading comes, first of all, the institution of measures requiring the prompt report to the sanitary authorities of all cases or suspected cases of typhus fever. Such cases should be promptly seen and the inspector should be satisfied that the patient's surroundings are free from lice, in which case the patient may, without danger to the community, be treated at home. If, however, such is not the case, or there is doubt, the patient should at once be removed to a hospital and the place from which he is removed be treated to destroy all lice and even their eggs. For the treatment of materials, such as clothing and bedding, the use of steam is the method of choice. All suspects and contacts should be bathed, the lice and their eggs in the hair being destroyed, and then be given a change of clothing, and their old clothes disinfected. They should be kept under observation for at least 12 days.

The measures to be adopted under the third heading are such as should prevent or minimize the possibility of persons near cases of typhus being bitten by lice. It should be borne in mind that the louse has not the radius of action of the mosquito or even of the flea; and therefore the striking distance of typhus is shorter than that of yellow fever, malaria, or plague. For the transference of lice from one individual to another, rather intimate association with the lice-infested person or his surroundings is necessary; and by reason of the fact that the louse requires frequent feedings to maintain life, this means, for practical purposes, surroundings recently occupied by persons, and possibly by animals.

There is but little to say in regard to the procedures suggested under the fourth heading. The case mortality of the mild form of typhus (Brill's disease), so widespread in the United States, is very low, probably not over 1 per 100 attacked, while the case mortality in Serbia, for example, is possibly 20 or perhaps more per 100 attacked. For this reason alone (and there are other reasons) the advisability of inoculation with the mild form of typhus would certainly seem worthy of serious consideration for those going to places where typhus is prevailing in a virulent form.

The following papers on the subject may be consulted by those interested:

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[1] Abstract of a lecture delivered before the Minnesota Pathological Society Mar, 30,1015, and before The Army Medical School, Apr. 23, 1915.