THE PROBLEM OF TRANSMISSION IN TYPHUS FEVER.*

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I.

DEFINITION.

Typhus fever is an infectious disease which runs an acute course of from 12 to 15 days and culminates spontaneously in a more or less abrupt lysis. It is characterized by an incubation period of from 5 to 20 days, a high continued pyrexia, a petechial rash, is commonly considered to be extremely contagious and, although I hope to be able to show in later pages that this contagiousness is of a peculiar nature, not dependent upon the direct transmission of the contagium from the sick to the well, but rather by the transfer of body parasites (lice) carrying the contagium, nevertheless, if given the proper conditions of crowding and *vermin* the infection becomes readily communicable and spreads rapidly from individual to individual, flaring sporadically into widespread and dangerous epidemics.

II.

HISTORY AND GEOGRAPHIC DISTRIBUTION.

It would be out of place in the present paper to review in any but the most cursory manner the epidemic history of typhus fever, and the reader is referred for fuller study to the comprehensive works of Murchison and Hirsch.

The Greek term typhus (*τίφος*), meaning smoke, mist, or fog, was employed by Hippocrates to define a confused state of the intellect with a tendency to stupor (*stupor attonitus*) such as is found in typhus fever. The expression was used, however, with broad application until applied to typhus fever by Gaultier de Sauvage in 1760 and Cullom of Edinburgh in 1769 (Murchison). Previous to Sauvage the disease was known as pestilential or putrid fever, or by some name indicative of its certain peculiarities or characteristics, such as contagious fever, jail, army, or ship fever. A list of a hundred or more synonyms is given by Murchison. Those met with in the modern literature are: typhus, typhus fever, exanthematic typhus, contagious typhus, spotted fever, and petechial typhus of English and American authors, typhus exanthématique of the French, Fleckfieber and ansteckende typhus of

the Germans, and tabardillo or tifo of the Spanish and Mexican literature.

The disease was formerly confused with other continued fevers of similar clinical symptoms, particularly with typhoid fever, the doentheritis of Louis, and typhus abdominalis of the German authors, and it is to the credit of American medicine that a Philadelphia physician, W. W. Gerhard, was the first to insist positively and conclusively on the non-identity of these two diseases. Typhus has absolutely nothing in common with typhoid, either in etiology, in the manner of its transmission, or in its chief clinical symptoms, and Gerhard's conclusions have been repeatedly reiterated by others (Stille, Jenner, Curschmann) and generally accepted. It must be borne in mind, however, in studying the history of typhus fever that epidemics reported in the older literature as typhus may have been typhoid.

Similarly, recurrent or relapsing fever, caused by the spirillum of Obermeyer, has repeatedly been confused with typhus. Relapsing fever like typhus is prone to assume an epidemic form in times of distress and famine, and the names "famine fever" and "Irish ague" have been applied to both diseases, particularly in Ireland, where they existed side by side. The distinction between the two affections was first drawn in Ireland in 1826 and later upheld by the writings of Henderson in Edinburgh and Wm. Jenner in London. The discovery of the spirillum of relapsing fever in 1868 settled any doubt that might still have lingered.

Plague has also been confused with typhus in the history of infectious diseases. This is particularly true in ancient writings of epidemics in which the two diseases were long confounded and named alike "pestis" and "febris pestilens." Murchison believes that the plague of Athens, which broke out during the siege of that city when the population was suffering from famine and overcrowding, was typhus, and it is possible that many of the epidemics of antiquity referred to in the writings of Livy and Tacitus, and even in the books of the Old Testament as "pestilence" were typhus fever.

From this confusion of terms it is obvious that the historical study of any of the continued fevers becomes very difficult. The

difficulty is still further enhanced by the frequency with which one epidemic has accompanied another. Thus it is supposed (Creighton) that the "great plague" which depopulated London in the year 1665 was ushered in by an epidemic of typhus fever and it seems clear that nearly all of the great "famine fevers" of Ireland were mixed epidemics of typhus and relapsing fever. During the epidemic of 1846 in Ireland when nearly a sixth of the entire population contracted the contagion, three diseases, enteric fever or typhoid, relapsing fever, and typhus, occurred simultaneously.

During the siege of Granada in 1489 the Castilian army under Ferdinand was decimated by a fever, which from its character was named "el tabardiglo," "the cloak," by the Spanish authors. The fever is described by Vilaba as being accompanied by a profuse spotted eruption. The name tabardiglo or tabardillo was undoubtedly later applied to typhus fever, is indeed used today in the Spanish and Mexican literature, and it is highly probable that the disease in question was typhus fever.

The first unmistakable account of epidemic typhus is found in the writings of Fracastorius and concerns a fever which raged in Italy in 1505 and again in 1528. The disease is described both as to symptoms and contagiousness and is differentiated from the plague "febris vera pestilens" and measles. Epidemics, many of which were undoubtedly typhus, followed each other at short intervals in Europe during the following years. Ambrose Paré recorded a pestilential fever which occurred in France in 1568 accompanying true plague, from which it was differentiated. An epidemic which occurred in Verona in 1580 is described in detail by Petrus y Castro, who considered it identical with "La Pourpre" of the French, tabardiglo of Spain and the Fleckfieber of the Germans. This disease was highly contagious, prevailed in the winter months, and followed a famine. The symptoms noted are a small, weak pulse, a dry, black tongue, the face and eyes injected, delirium and stupor passing into coma, and an eruption which resembled flea bites, but could be distinguished from these, and which appeared in the fourth to seventh day of fever.

From 1619 to 1648 when Europe was in the throes of the Thirty Years' War whole towns and armies were decimated by a maculated fever, and as late as the twentieth century typhus has followed in the van of European armies. During the Napoleonic wars the disease was spread by the imperial troops over France, Italy, Germany, and Russia, while among the troops engaged in the Crimean War it wrought terrific havoc, and during the Russo-Turkish war of 1878 Michaili estimates that over 100,000 Russian troops were attacked with typhus fever. The mortality reached 50 per cent.

Since the Napoleonic era epidemics of typhus have been frequent in Ireland and England but fewer on the continent. The fever of 1817–19 in Ireland during which time 737,000 cases are recorded was probably chiefly relapsing fever (Welch, 1819),

as was also the epidemic of 1826–29. The mortality in both of these periods was very low and the exanthema of typhus seems to have been very rare (Graves). In 1836 an epidemic of undoubted typhus began in Ireland, involved the entire United Kingdom, and spread to the United States and Canada. The mortality during this epidemic amounted to over 20 per cent. Again in 1847 an epidemic of frightful extent commenced in Ireland, spread to Liverpool and London, and raged throughout England and Ireland until the summer of 1848. Like many other typhus epidemics this was preceded by extensive failure of the crops. The disease was carried in crowded ships of immigrants to America and Canada, where a series of epidemics of greater or less extent occurred during the following years (Wynne).

Epidemics in England in 1862 were attributed to disorganized industrial conditions, numerous strikes, and consequent distress among the poor. Admissions to the London Fever Hospital reached 14,000 during the following seven years. Since this date no great exacerbations have occurred in Great Britain, although small outbreaks have repeatedly been reported, particularly in Dublin, Glasgow, and Liverpool. An epidemic was reported by Dudfield, McWeeney, and others to have occurred in London in 1898; Hay reports 131 cases in Aberdeen in 1906, and Wilson in a publication of recent date mentions sporadic cases and small epidemics which arise from time to time in Belfast.

As regards Western Europe: after the Napoleonic wars typhus practically died out, and France has suffered comparatively little from the disease, even the Franco-Prussian War leaving her untouched (Chauffard). A curious epidemic referable to certain provinces of Brittany from whence it was spread to the capital and other cities by wandering vagrants is reported by Thoinot and Dubief and others in 1893. The disease was controlled in 1893 but recurred in 1894 and caused in all 149 cases in the department of the Seine, of whom 69 died.

Germany because of her proximity to Poland has been less fortunate. In 1847–48 there arose a severe epidemic in East Prussia, imported from Poland, and since this date, according to Curschmann, typhus has become endemic in Ober Schlesien and has even taken root in East and West Prussia so that Guttstadt (quoted by Curschmann) was able to collect statistics concerning 10,600 typhus patients received in the Prussian hospitals during the five years between 1877 and 1882. Of late, owing to the adoption of hygienic precautions, the number of cases in these centers has been reduced to a minimum (Leonhardt).

Russia has suffered heavily for years from typhus fever, and in 1908, following a period of political unrest, an epidemic flared up which left scarcely a place untouched (Rabinowitsch).

Our own country has been fortunately almost entirely spared from any very severe ravages of the disease. The early epidemics described by Wynne in Baltimore, Gerhard in Philadelphia, Clark in Boston, and Russell in Connecticut were relatively insignificant in size and rapidly extinguished in every instance. They seem to have been imported by foreign immigrants. The Civil War left us practically untouched by typhus. In 1863 and 1864 there occurred an outbreak in New York (Corse), and an epidemic of 39 cases occurred in Philadelphia in 1864, but Da Costa, who reports the latter event, is of the belief that it was not brought from the camps to the city. The disease, he says, was scarcely a disease of the American army and certainly not of any portion of it from which soldiers would have been apt to be sent to Philadelphia and he believes that it was imported from other parts of the world. Since

this date there are but few records of typhus in the United States, and these, with but few exceptions, concern isolated cases (Shannon, and see *Report of the State Board of Health, Michigan*, Vol. 21). An epidemic of no small significance broke out in New York City in 1880 and 1881 (Janes). The epidemic began in September, 1880, and was at first confused with typhoid fever. The contagiousness of the disease, its typical eruption and fever promptly led to a true diagnosis of typhus. The epidemic was confined for the most part to crowded lodging and tenement houses and although by the enforcement of strict hygienic measures it was soon controlled, the number of cases as recorded at the Riverside Hospital, where all were quarantined, numbered 506. The mortality equalled 24.5 per cent.

Mexico has for years been ravaged by typhus or tabardillo. According to Indian hieroglyphics translated by Spanish authors and studied by Liebermann (quoted by Chauffard) the disease reigned on the tableland of Anáhuac at the time of the Aztec Empire under the name of "masahuathl" (Chauffard), and in the last century terrific epidemics have occurred in Mexico City, notably those of 1812–14, 1824, 1839, 1846–48, 1861, 1867, 1875–77, 1892–93, and 1896. In 1893 there were 3,000 deaths from typhus in the federal district and over four times this number of cases; this out of a population not exceeding 350,000. In 1896 there were over 3,000 cases during the early spring months, and every year a toll of several hundred lives is exacted by the disease.

The typhus of Mexico is curiously confined to the central plateau and does not affect at all the lower hot country which borders the coast, a subject which will be considered later.

Epidemics of typhus are today fewer and smaller than they have been in the past, and the disease is restricted to certain regions. Here it smolders endemically, flaring up from time to time. The chief of these regions have already been mentioned, namely Dublin and Belfast in Ireland, the central plateau of Mexico, the provinces of Morbehan and Finister of Brittany in France, and Russia, particularly Poland and the East Sea provinces. Other places where the disease occurs more or less regularly are Tunis, Algeria, and Egypt in northern Africa, Spain, Hungary, and the Balkan States in the valley of the Danube, and Turkey. In India typhus has been described by Lyell and Facquhar (quoted by Husband) and more recently by Husband and Hepper. The disease here as in Mexico seems to be confined to the cooler hill country and rages most extensively in the winter months of February, March, and April. According to Husband it is endemic in the trans-Indus districts from Baluchistan to Yusufzai and Hagara, and in the Himalayan Hill tracts. In 1897 Matignon reported typhus to be endemic in Pekin and the entire north of China, the affection taking on an epidemic character of greater or less severity every year in the spring. In 1898 Yersin and Vassal published a short account of a limited outbreak of typhus in the French possessions of Indo-China. The disease is apparently unknown in the tropical parts of Central and South America, in southern Africa, New Zealand, and Australia.

III.

THE EPIDEMIOLOGY OF TYPHUS FEVER.

A correct theory of the cause of a disease should be able to explain not only its specific origin, but all the varied aspects of its

epidemiology regardless of how puzzling these may be, and before proceeding with the question of the exciting cause of typhus it is my purpose to consider the several factors of its epidemiology. Many of these may be looked upon as predisposing factors.

FACTORS WHICH INFLUENCE SUSCEPTIBILITY TO INFECTION.

There is no question of the greater susceptibility to infections of individuals and populations exhausted by famine, starvation, and distress. This is true of all diseases, but the history of typhus in particular is filled with instances of the disease accompanying and following times of misery and want. The Irish and English epidemics of the past were almost invariably preceded by failure of the crops, or periods of distress from famine or strikes (Murchison, Graves). On the other hand widespread exacerbations of the disease have occurred in Ireland independently of such influences and at times of general prosperity; witness the fever which broke out in Dundee in 1865, which was induced by the inhabitants of the surrounding country flocking into the town in consequence of work being uncommonly abundant and wages high (Pie-Smith).

Typhus fever is in general considered to be a disease of that part of the population most afflicted by poverty. An investigation of the condition of life of 18,268 typhus patients admitted during twenty years to the London Fever Hospital revealed that 95.76 per cent were inmates of workhouses or dependent upon philanthropic relief. In London typhus is almost unknown among the better classes except where there has been direct intercourse with patients. The same is true of Dublin, Glasgow, and the European cities.

In Mexico City a relatively large percentage of cases occur among the better classes, but here conditions exist which are somewhat different from those found in Europe. The poor population of Mexico is proportionately very much greater than that of London, and the streets, particularly the crowded business streets of the center of the city, are filled with poor Indians, clothed in rags and infested with vermin, who beg alms and sell lottery tickets, periodicals, and small wares of one kind or another. Indeed, as one walks along the street he cannot avoid brushing against these

people and picking up from their clothes any infection which they may harbor. All classes are crowded together in the street cars, and the public cabs are used as lounging places by the cocheros (coachmen) and their uncleanly friends. Finally it must be remembered that in Mexico the servant class is drawn from among the very poorest of the population. Domestics taken into well-to-do families come from the most squalid and disgusting "dobi" houses, and as they return to their homes for frequent visits, often to sleep at night, it is readily understood that they may serve as carriers of the disease from the poor to the rich. It is no uncommon thing to find lice in the hair and clothes of these servants. The same is true of the "portero," who is usually quartered on the first floor of the large apartment houses of the better classes. He and his family are poor people and dirty, and he visits his unclean friends in their part of the city, while they visit him in his quarters. Thus in many ways opportunities are afforded for the infection of the well-to-do and cleanly portion of the population by a disease which in other countries is ordinarily confined to the poor.

Other factors which predispose to infection with typhus by decreasing the general resistance of the individual are overwork and bodily fatigue, mental distress, worry, and loss of sleep (Murchison, Graves, Terrés). Dread of the disease is supposed to be a powerful predisposing cause by Murchison. The example of a medical student in Edinburgh is cited, who possessed such a dread of typhus that he could scarcely be induced to enter a ward, and who was one of the first students to fall a victim to the epidemic of 1847.

Finally, other diseases undoubtedly predispose to typhus. This is particularly true of acute infections such as relapsing fever and cholera, as witness the fact that large epidemics of typhus are frequently preceded or accompanied by other epidemics. As regards the individual cases it is commonly supposed that chronic diseases and alcoholism predispose to typhus. In this connection, however, it has been noted in Mexico by Ulrick that typhus cadavers which come to autopsy are singularly free from cirrhosis and other liver affections as well as from tuberculosis. This observation may of course be explained by the fact that typhus usually attacks

rather young individuals, whereas the large majority of cases in the ordinary run of autopsies are old chronic diseases.

The resistance of the individual to typhus is further influenced by the following factors:

Age.—On the relation of age to the occurrence of typhus fever all authorities are agreed. The disease is most common in young adults, and although not uncommon in children is relatively rarely met with in individuals below 15 years of age. In older adults the number of cases is fewer, but the severity of the disease increases. Murchison ascertained that the mean age of 3,456 cases admitted to the London Fever Hospital during the ten years 1848 to 1857 was 29.33 and Rabinowitsch in the epidemic in Kiew found that 1,895 cases out of 3,099 occurred between the ages of 15 and 30. These figures do not differ materially from those of other infectious diseases, excluding children's diseases and typhoid fever, in which the mean case age is considerably lower. It is clear that that part of the population which is above 20 years of age, granting equal susceptibility to the disease, is more exposed to the danger of picking up a communicable infection than are children and older people, who are more protected.

Sex.—According to all the European authors sex plays no rôle in influencing susceptibility to typhus. In general the number of cases among men and women is about equal. In an epidemic of 3,099 cases in Kiew in 1908 (Rabinowitsch), 2,383 were males. This preponderance of males is attributed to the greater number of men in the prisons from which most of the cases were taken and also to the greater personal cleanliness of the women. Thoinot in epidemics observed in Brittany in 1893 recorded a considerably greater number of cases among the women, which he attributed to the absence of many of the men in the fishing boats and to the exposure of the women to infection by their duty of nursing the sick.

In Mexico, on the other hand, there seems to be a constantly greater proportion of cases among the men. A glance at the accompanying Chart II on which are graphically recorded the number of male and female cases in the Federal District for the period 1893 to 1906 reveals a constant majority of men, a majority

which is relatively greater than the majority of male inhabitants. Sr. Dr. Terrés in his scholarly exposition of the etiology of tabardillo calls attention to this fact and comments upon it to the effect that this greater proportion of male cases is not what should be expected in an easily communicable disease such as typhus, in which the women who are employed in nursing the sick are more in contact with patients than the men. But Terrés disregards the fact that a very large number of the cases in Mexico City arise in the armies and the prisons, where relatively few women are exposed to infection, and that the total number of male patients is bound to be swollen by this account. In general it would seem that men and women are equally susceptible to the disease.

Idiosyncrasy.—It is a strangely curious fact that many individuals show an unusual immunity to typhus fever. Cases are on record of physicians and nurses who have been daily exposed to infection for years and yet have never been taken ill. On the other hand individuals may succumb on the first exposure. Certain individuals have taken the disease after several years of immunity to constant exposure. Murchison mentions the case of one of the engineers at the London Fever Hospital, whose duties took him daily into the typhus wards and included cleansing of the dirty bedding, who died of typhus contracted for the first time after fifteen years of service.

It is a rather commonly accepted idea that highly intellectual people are more susceptible to typhus fever, and it is certain that the disease assumes in them a more severe form, the nervous symptoms, convulsions, delirium, and coma being greatly exaggerated. The mortality among this class of patients runs very high.

Racial immunity.—Whether residence in an infected district or constant exposure to infection of a mild character increases the resistance of an individual to typhus as it seems to do in the case of typhoid fever is doubtful. Physicians and nurses acquire no immunity from daily contact with the disease, as is evidenced by the fact already noted that many eventually succumb after months or years of exposure. On the other hand it is certain that the European and American population of Mexico City is more sus-

ceptible to typhus than are the native inhabitants, and this seems to indicate that a racial immunity to the disease may be acquired.

The greater part of the foreign population of Mexico City lives in the eighth ward, the Quartel VIII. This quartel is a clean and prosperous quarter of the city, and is composed in large part of well-to-do individuals of naturally cleanly habits, well nourished, and dwelling in modern and sanitary houses. It is true that in the same quartel there may be found a large number of poorer people, but in general the more prosperous condition of this section of the city is apparent. On the other hand Ward II is made up of the poorest and dirtiest people of the city, where all conditions seem to conspire to produce a situation most favorable for the spread of typhus, and yet we are confronted with the astonishing fact that there occurs approximately as much, even, according to Terrés, relatively more typhus in Ward VIII than in Ward II.

A greater susceptibility of the inhabitants of Ward VIII over those of Ward II would alone explain this apparent anomaly, for, although the well-to-do classes residing in Ward VIII are far from protected from exposure to infection, as mentioned, nevertheless in Ward II the population is so much denser and the people live in such crowded and filthy conditions that the opportunities for the transfer of the disease from one to another must be much greater. Ward VIII is a new and rapidly growing section of the city, and a large part of its population has never been exposed to typhus, while Ward II is peopled almost exclusively by Mexicans of the lower class, who for years and generations have lived in the midst of typhus fever. A considerable proportion of these have had the disease and recovered and are consequently immune, and the possibility that many others have passed through mild and unrecognized infection cannot be excluded. But further than this, typhus fever during the countless epidemics that have ravaged Mexico in the past has killed off a very large number of people. In each of these epidemics the less resistant of the population succumbed, and thus gradually a racial resistance to the disease may have become established.

The statistics of the American Hospital of Mexico City indicate a much greater mortality among the American and foreign patients

of that institution than is observed among the natives of the Mexican hospitals, and this even in the face of the greatly superior nursing and care received by the patients of the American institution. Nearly all of these are private cases, and the rules of the hospital necessitate their employing special trained nurses. On the other hand, the statistics collected at the Hospital General and the Hospital Juarez concern charity ward cases who are given little individual attention and the poorest of nursing. And yet the mortality among the Mexicans rarely exceeds 20 per cent, while that observed in the American hospital has been 34 per cent.[1]

Immunity conferred by previous attack of typhus.—Recovery from a single bona-fide attack of typhus fever apparently grants immunity from subsequent infection. This has been generally believed for years and is confirmed by the results of experiments performed on monkeys, to be described later. Instances of two successive attacks of the disease are rarely authentic, although some appear in the literature which apparently cannot be discredited. Murchison never observed a single instance of a nurse or patient at the London Hospital having had an unequivocal second attack with eruption, which in his opinion is a much rarer occurrence than a second attack of variola or scarlatina. Jacquot (quoted by Murchison) employed hospital attendants in the Crimean War who had had typhus and in no instances were any attacked again.

Most of the physicians of Mexico City seem to be of the opinion that a second attack of the disease is quite possible. Dr. Escalona informs me that he himself has had two attacks, but in general it must be admitted that the immunity of an individual who has recovered from typhus fever is quite as complete as that following typhoid, measles, or smallpox. In any of these diseases the immunity conferred by one attack occasionally becomes exhausted, at least in particular individuals. A good example of this is seen in diphtheria. Although most people have but one attack of diphtheria, an occasional individual is encountered who suffers from repeated attacks.

Occupation.—There is probably no truth in the assertion that

[1] These statistics were given me by Miss Wilson, the superintendent of the American Hospital of Mexico City. The number of cases of typhus fever treated from 1888 to January, 1910, was 144, of whom 50 died.

butchers and tanners enjoy a peculiar immunity to typhus fever, and in general occupations play no rôle in the epidemiology of the disease, excepting in so far as they expose to infection. Thus those who attend the sick and are naturally in constant danger of infection, as physicians, nurses, and priests, are frequently attacked with typhus. In older days when hospitals were not maintained up to the standards of the modern institutions as regards cleanliness, when baths were unknown, and patients were crowded into ill-kept barracks, physicians and nurses were particularly prone to contract the disease, and the fatalities in these professions from typhus fever became appalling. In Ireland during the epidemic of 1847, no fewer than 500 physicians took the fever, of whom 147 died, and in an epidemic which was carried to Breslau by the retreating troops of Napoleon, 18 out of 40 of the total number of doctors of the town died. In the Crimean War 58 deaths from typhus occurred among the 400 military officers of the French army (Thoinot).

Of peculiar interest in the light of the possibility of insect transmission of typhus fever is the relative frequency with which those who handle the clothing of patients contract the disease. Repeated mention is made in the literature of the susceptibility of laundresses to typhus. In Mexican literature Terrés quotes O. Galvan to the effect that the only case of infection in the hospital of Lagos, which harbored 243 typhus patients, occurred in the laundry. Several cases broke out in a steam laundry of Mexico City while we were studying the disease in that metropolis.

FACTORS WHICH FAVOR THE DISSEMINATION OF THE DISEASE.

Overcrowding.—Typhus fever is a disease of cities, armies, ships, and prisons, and the overcrowding of human beings is of undoubted importance in the propagation of epidemics by facilitating the transmission of the disease.

Among the earliest accounts of jail or "gaol" fever which from description permit of recognition as typhus are those of the "black assizes," which occurred in England during the sixteenth and seventeenth centuries and have become historical. In the assize at Exeter, in 1586, 38 Portuguese sailors were tried. These men

had been captured some time before and cast into "a deep pit and stinking dungeon" in Exeter Castle. A contagious disease broke out among them and at the trial was communicated to several of the attendants of the court. The judge and many others died of the fever, and an epidemic started which spread widely. The disease, from the description of the symptoms, was undoubtedly typhus. Those exposed at the court did not develop fever until fourteen days later, indicating an incubation period which corresponds with that observed in typhus.

Another equally grewsome assize occurred in "Old Bailey" in 1750. A hundred prisoners, many of whom were ill at the time of the proceedings, were on trial. These were seated at the bar or confined in two small rooms which adjoined the courtroom. The court was crowded to excess, so that the air became exceedingly vile. Within a week or ten days following the trial a large number of those who had been present, including the judge and other dignitaries of the court, were seized with a fever characterized by a weak pulse, delirium, and petechiae, which lasted for two weeks. Over 40 persons died.[1]

A dozen noticeable instances of jail fever are recounted by Murchison, and more recent epidemics still emphasize the proclivity of typhus for prisons. A large number of the patients received in the hospitals of Kiew during the epidemic of 1908 came from the prisons which were "shamefully crowded" (Rabinowitsch). In Alexandria the disease is frequently epidemic in the jails, where it always shows great contagiousness (Sandwith).

The common city prison of Mexico City, the "Carcel de Belem" (Bethlehem), seems to be a perfect brood-oven for typhus. Its characteristics are overcrowding, poverty, and filth. Its inmates are chiefly composed of the lowest and most miserable of the population, people with absolute disregard for personal cleanliness, abhorrent of baths, clothed in soiled and vermin-infested rags. These people come from crowded and insanitary homes. On their arrival the dirtiest are bathed, but the number so treated is but a fraction of the whole, and even those receiving a bath are dressed again in the same filthy clothes to mingle with the other prisoners.

[1] See Charles Creighton, *A History of Epidemics in Britain*, 1891.

Later they are required to wash their clothes more or less regularly, but a condition of cleanliness is never even approximated.

The population of Belem varies between 4,000 and 4,500. The edifice is very old, and was founded as a refuge for indigent religious women in 1683. Additions have been made since that time, but in general the buildings are those of a century or two ago, the walls massive, the ceilings low, and the rooms poorly ventilated. No statistics are available concerning the floor space allotted to an individual, but it cannot exceed 4 square meters. The courts, corridors, and wards are literally packed with human beings, and during our visits I was shown cells not exceeding 12 by 8 feet occupied by five or six prisoners. The more dangerous criminals are confined in these small cells.

The infirmary accommodations in the prison are admittedly insufficient. The women's ward is an ill-ventilated, dark, low-vaulted room of dimensions not exceeding 50 by 30 feet. The walls and floor are of stone. On the occasion of my visit the dozen beds in the room were all filled, and patients were lying on the floor. This was not at the time of an epidemic. Contagious cases, including typhus, are taken to the Hospital Juarez as soon as recognized, but as no quarantine is held over them while in the prison infirmary, and as typhus cases are not diagnosed earlier than the fourth or fifth day of their sickness, abundant opportunity is open for the communication of their disease to others.[1]

Under such circumstances there is small wonder that typhus occurs constantly in Belem. During many epidemics 80 and 100 patients have been removed from its walls daily, and while we were pursuing our investigations in the city in the winter and spring of 1910, a non-epidemic year, there occurred in the prison, in January, 32 cases, in February, 130, in March, 43, and in May, 16 cases. These statistics are obtained from the records of the Hospital Juarez. Records of previous years reveal that at no time does the disease ever die out in the prison, and that occasionally epidemics flare

[1] In justice to the director of the prison and others concerned in its administration it should here be mentioned that the shortcomings of the institution are thoroughly appreciated by them and by the city and government authorities; that efforts are being made to improve the conditions in Belem, and that work has been already begun on the building of a new general prison which is to accommodate 6,000 inmates. This institution is to cost 12,000,000 pesos and will be as thoroughly modern as is the present Mexican penitentiary, a model institution.

up in Belem quite independently of those in the city. Thus in October of 1908, at a time when there was relatively little typhus in the city, there were removed from Belem to the Hospital Juarez, on the third, 17 cases, on the fifth, 12, on the seventh, 74, and on the eighth, 28 cases.

The importance of Belem as a center for the perpetuation and distribution of typhus will be considered again later. Its inmates return to all parts of the city on leaving the prison, and if there is such a thing as carrying typhus in one's clothes, either in the form of the virus or of carrying insects, Belem must be regarded as an important distributing center.

Further evidence of the influence of crowding and congestion upon typhus fever is the well-known prevalence of the disease in ships and armies, which has earned it the names "ship-fever" and "military fever." The overcrowding which is so likely to occur in the ships and barracks is probably the chief factor in ship and military fever, but it must also be remembered that other conditions favorable to the growth of epidemics are commonly present in armies and navies. Among these may be mentioned neglect of personal cleanliness, bodily fatigue, exhaustion, and poor food.

Furthermore, it is widely recognized in Europe that typhus commonly affects to the greatest extent the most congested sections of the city. In Edinburgh it has practically remained restricted to the wretched and crowded parts of the "Old Town," even at times of the greatest epidemics. The same can be said of London and Dublin, and Gerhard, speaking of the epidemics which broke out in Philadelphia in 1836, says that the disease first occurred in the filthiest and most crowded parts of the city. A similar restriction of the disease to the poorer and more congested parts of Philadelphia was true of the epidemic of 1866 described by DaCosta. Cases were met with among those living in comfortable circumstances, but the greatest ravages took place in the southeastern section among the poor.

The same segregation of the disease to the poorer localities of the city does not apply quite so strictly to Mexico City, where typhus continuously occurs in every quartel, and where, as stated, relatively as many cases arise in the prosperous Ward VIII as in the most

crowded and miserable Ward II. The explanation of this apparent anomaly is to be found, I believe, first, in the greater susceptibility to typhus fever of the foreigners who comprise a large part of the population of Ward VIII and, second, in the abundant opportunity for exposure of the better classes to contact with the poor, both of which conditions have been discussed.

Neglect of cleanliness.—Monjaras believes that pauperism constitutes one of the principal etiologic sources of typhus, and personal squalor and filthy apparel—attributes of poverty and congestion of human beings—are universally conceded to be predisposing factors of typhus fever. More will be said about this later, but an interesting example of their importance may properly be cited at this point. In the history of the epidemic which occurred in France in 1893 and 1894, the importance of "vagabondage" in keeping up and spreading the disease is repeatedly emphasized by those writing on the subject. Typhus had been endemic in Brittany for some time, but in 1891 and 1892 it assumed an epidemic exacerbation in the commune of Carnoit. Its spread from here was later traced step by step along routes followed by wandering tramps and vagabonds to Paris, which was reached by the disease in 1893. In all of the cities along the routes the resorts of vagrants—prisons, police prefectures, "refuge communal," and "asile de nuit"—were first attacked, and in Paris typhus was first noticed in the prefecture of police. For the most part the epidemic in Paris was confined to vagrants and habitués of the commonest lodging places, whose regard for personal cleanliness was at a minimum. Aside from these the only persons who took the disease were some of those whose duties brought them in contact with the sick—physicians, nurses, and attendants (Thoinot and Dubief, Proust, Deschamps, Spillman).

In this connection the report of Richter on an epidemic of 58 cases in Marienburg, West Prussia, in November, 1893, is of interest. The author comments on the fact that the first two cases appeared simultaneously and were both vagabonds. Shortly thereafter other cases arose in West Prussia which at first could nearly always be traced to a popular tavern in Marienburg.

Cases of typhus have arisen persistently in Berlin for years, but

are confined to certain of the poorest inns, the resorts of tramps and indigents.

In the case of the Paris epidemic the prefecture of police which had been such a pesthole of contagion ceased to be dangerous and did not produce a single case after the day that a thorough disinfection was made and a rule enforced requiring all new arrivals, no matter what their class or state of health, to subject themselves to a bath and to the disinfection of their clothes.

CLIMATOLOGICAL FACTORS.

Typhus is in general a disease of the temperate and cold climates, as indicated by its geographic distribution (see p. 15). In India, as has been mentioned, the disease is confined to the hill country (Husband), and in Mexico, where temperate climate prevails on the central plateau and hot near the coast, it is restricted to the former. The altitude of the plateau of Mexico varies from 4,000 to 11,000 feet, and in Mexico City, elevation 7,500 feet, the temperature never becomes oppressively hot even at midday, and the nights, summer and winter, are chilly or cold. In contrast to this temperate climate the conditions in the cities bordering the coast and in the deep valleys at the edge of the central tableland are quite tropical. The heat during the greater part of the year is intense, and cold weather, although occasionally felt in Veracruz during a "norther," is rare and of short duration.

Dr. Iglesias, Dr. Macias, and other physicians of Veracruz, members of the Board of Health of that city, were consulted concerning the absence of typhus fever. All of these gentlemen assured me that the disease is never known to develop in the city. A careful watch has been kept for the last few years over the whole population in order to guard against yellow fever, and an endemic case of typhus has never come to the attention of the board, although an occasional case is imported into Veracruz from the plateau. Dr. Iglesias has seen several soldiers who have come down with typhus shortly after the arrival of their regiment from Mexico City. These men were cared for at the military hospital without any attempt at isolation, and in no instance did contagion occur or the disease spread to others.

In Jalapa (altitude 4,000 feet), which lies just below the edge of the plateau, Dr. Canovas y Pasquel, attending physician of the general hospital of that city, informed me that he had not seen or heard of a single case of typhus except such as were imported from the higher country. Most of these come from the near-by town of Perote.

Terrés comments at length upon this freedom from typhus of the *terre caliente*, and according to this author a line may be drawn paralleling the coast and circumscribing the elevated tableland. The altitude of this line approximates 1,800 meters (6,000 feet), and all the typhus of Mexico is restricted to the region above it.

This geographical limitation of endemic typhus in Mexico is probably of climatological significance, although other factors may enter into the problem. The traveler voyaging from the capital is impressed shortly after his arrival at Orizaba and the hot country by the greater personal neatness and cleanliness of the poorer population over that of Mexico City, and he learns on inquiry that the people bathe frequently and pay great attention to the cleanliness of their apparel. Many are dressed in white cotton garments. The body lice, which are universally distributed among the poor Indians of Mexico City, and tolerated without repugnance, are here looked upon with disgust and horror, and although occasional vermin-infested individuals may be found, they are quite rare.[1]

But besides paying more heed to personal cleanliness the natives of the *terre caliente* live as a rule in better sanitary conditions than those of the plateau. The dwellings of the poor are built of straw and poles, are well ventilated, and as a rule fairly neatly kept. Also food in abundance is found, and famines such as prevail on the tableland are unknown. These factors deserve consideration, but none of them can be considered as of primary importance in limiting typhus to the plateau.

In temperate climates where winter is distinguished from summer, typhus is a disease of the winter and spring, a decrease

[1] Dr. Iglesias, in Veracruz, was unable to obtain any *Pediculi vestimenti*, the white body louse, for experimental purposes, and Dr. Garcia experienced the same difficulty. Dr. Canovas informed us that he seldom if ever found body lice on the entrants of the general hospital of Jalapa. The head and pubic lice are more abundant, although even these are relatively far less prevalent than among the natives of the plateau. The importance of this scarcity of lice I desire to consider later. Bedbugs and fleas are numerous in the hot country.

in the amount of the disease invariably occurring in the summer months. This is true of England, of France and Russia, of Tunis (Conseil), of Egypt, and of India (Husband), and as a rule has been attributed to the greater crowding of people indoors during the winter months, and the consequent greater opportunity for the communication of the disease from one person to another.

The same predilection of epidemics of typhus for the winter and spring months of the year is observed in Mexico (see Charts I and II), and annual exacerbations which almost always assume epidemic proportions commence usually in November and persist until the late spring. Here, as in Europe, the greater crowding encouraged by the colder weather undoubtedly facilitates the spread of the disease. However, the seasonal changes are relatively slight, and the cold ceases long before the decline of the epidemic. Another factor must be considered in Mexico, where the typhus season besides including the colder winter months is the *dry season*. A strange relationship seems to exist between the duration of the typhus epidemic and the beginning of the rains, as well as between the amount of typhus in any given year and the relative degree of drought. The rainfall which is abundant during the remainder of the year decreases to a minimum during the months December to May, the period of the greatest prevalence of typhus. The fields are arid, the ditches which are running with water during the rainy season are empty, and in March, April, and May clouds of dust are blown into the air by the high winds. The onset of the rains corresponds roughly to the decline in the epidemic, as may be seen by a glance at the accompanying charts.[1] Furthermore the amount of typhus which will develop in any given year seems to be indirectly proportional to the amount of rainfall of the preceding rainy season. Pruneda calls attention to the fact that in 1905, preceding the severe epidemic of 1906, the rainfall was decidedly less than the average (compare Chart II), as 423.07 mm. is to 581.9 mm.; that furthermore in this year the rains began late, and heavy precipitation was delayed until September. Terrés is firmly convinced that an abundance of rain in any given year indicates less typhus for the following year, and that the reverse

[1] It is worthy of notice that the number of cases of typhoid in Mexico City increases with the advent of the rainy season.

occurs after long continued drought, but does not hazard an opinion as to the reason for this relationship. Monjaras in San Luis Potosi was able to see but little connection between the amount of rainfall and the annual exacerbation of the disease.

IV.

THE PROBLEM OF THE TRANSMISSION OF TYPHUS.

We are now in a position to consider the actual means of transmission of typhus fever from one person to another.

CLASSIFICATION OF INFECTIOUS DISEASES.

Infectious diseases are commonly classified into contagious and non-contagious infections. In the former class belong smallpox and diphtheria, which are ordinarily considered as "catching" and are communicable either by immediate contact of individual with individual or indirectly through the intervention of "fomites," such as bedding, drinking cups, and clothing. *Contact* is the essential factor in the transmission of contagious infections.

In the case of the non-contagious infections, examples of which are typhoid and cholera, this contact is not essential. Typhoid may be transmitted by milk contaminated with the typhoid bacillus to individuals all living widely separated from one another and far distant from the patient who originally supplied the infecting germs. In cholera a contaminated water supply may spread the disease throughout that part of a city which is supplied by the infected water, leaving the other sections of the town unharmed, as happened in the case of the epidemic in Hamburg in 1892. In anthrax and tetanus the micro-organism may live for years outside the human body and finally, invading a susceptible host, produce sickness. These diseases may, it is true, be communicable by contact, and nurses attending typhoid patients not uncommonly contract typhoid, but they are relatively far less likely to be thus communicated than are the so-called contagious diseases. Therefore a disease is usually classed as non-contagious if it is possible to eliminate contagion by precautions designed to prevent the invasion of the body by the specific germ. Thus in typhoid,

if a nurse exercises scrupulous care in handling the excreta of her patient and excludes all possibilities of contaminating her own food, either by soiled hands or by the use of dishes from which the patient has eaten, she need have no fear of herself contracting typhoid; the disease is not "catching."

There exists a third class of infectious diseases, namely those which are transmitted by the sting of insects. Attention was first called to this method of infection in 1893 by the work of Theobald Smith and Kelbourne on Texas fever, an infection of cattle, which was shown to be caused by a pear-shaped protozoon (*Pyroplasma bovis*) and to be transmitted from animal to animal by a certain tick (*Boophilus bovis*). Subsequently insects have been found to transmit malaria (*Anopheles*), yellow fever (*Stegomyia fasciata*), and the sleeping sickness of Africa (the tsetse-fly, *Glossina palpalis*). The spirochaetae of relapsing fever have been demonstrated in bedbugs which are collected from the beds of patients, and monkeys have been infected with relapsing fever by exposing them to the bites of infected bugs. The spotted fever of the Rocky Mountains is transmitted by the wood tick (*Dermacentor*), and the reports of recent plague investigations in India emphasize the prominent part played by the flea in carrying plague from rat to rat and from rat to man.

Such insect-borne diseases may or may not be communicable by direct contact and without the intermediation of insects. Plague is an example of this kind. The pneumonic form of plague is readily spread from one person to another by contagion. However, most insect diseases are not "contagious" and are commonly transmitted by the bite of one specific insect, and in no other manner; witness the success attending the prophylactic treatment of yellow fever directed against the mosquito in Havana, the Panama Canal Zone, and Veracruz.

Nothing in the epidemiology of typhus supports the theory that it is transmitted by water, like typhoid or cholera. Some authors, particularly Mexican, have advanced the supposition that decaying vegetable and animal matter or the accumulation of the excreta of human beings propagates the disease (Mendez), but there seems to be no reliable evidence in favor of such a view.

THE CONTAGIOUSNESS OF TYPHUS.

Typhus has always been considered to be one of the most contagious of all diseases. Hare, in his *Practice of Medicine*, expresses the opinion that exposure for a considerable time to the atmosphere of a room which is poorly ventilated and which contains typhus patients is the most effective way of contracting it. Curschmann regards the disease as highly contagious in the beginning and probably during all stages of the fever. Pie-Smith considers that the most conspicuous factor in the etiology of typhus is its contagiousness. Murchison is very emphatic on the matter of contagiousness, and Graves, Tweedie, Gerhard, and others all believe in the extreme transmissibility of typhus by contact.

The Mexican writers on tabardillo are less positive as to its contagiousness. Thus Bernaldez writes: "On many occasions in the course of my duties as sanitary inspector in the City of Mexico I have had to see typhus patients, and I have found that for six or eight days or sometimes for even a longer time several relatives had lived in the same room as the patient without any of them being attacked, and out of 1,089 cases reported by the medical inspectors of the wards of the city only 110 appear arising from contagion, and these all in persons of the lowest class who are extremely careless of the rules of hygiene." Chico reports that during a period of 20 years in Guanajuato only two physicians contracted typhus, and Warfield comments upon the lesser contagiousness of Mexican typhus to the European disease described by Murchison and others.

Now there are several respects in which the Mexican form of typhus fever differs from the European disease, and it may be that the former is less readily communicable than the latter, but in the light of my own experience with Mexican typhus I cannot agree with the authors quoted that it is not readily communicated among people living in crowded circumstances and infested with vermin. In the Mexican General Hospital during the six months in which we were pursuing our investigations in that institution not less than eight persons were infected. These included three nurses, one medical student, an ambulance porter, and three of the six men who were at the time pursuing investigations of the

disease in the hospital. Of course it may be objected in regard to these investigators that they were exposed to sources of infection other than the contagion of the hospital, but the incidence of the other five cases cannot be denied. Furthermore, from many of the patients who were examined by Dr. Ricketts and myself histories of exposure to previous cases could be obtained.

The belief in the contagiousness of typhus by European authors is firmly held and based on strong authority. The chief reason for this belief is the susceptibility to infection of those exposed to contact with the sick. This we have seen illustrated by the especial susceptibility to typhus of physicians and nurses. A second strong argument in its favor is the frequency with which epidemics can be traced from case to case and from point to point. "An outbreak which occurred at Carlisle, in 1871, was found by Dr. Heysham to have started from a particular house in Richard Gate. One of the persons afflicted there was a weaver, who on his recovery communicated the disease to his fellow-weavers in a large workshop and by them it was spread all over the town" (Pie-Smith). Thoinot and Calmette were able to trace nearly every case in epidemics studied by them in the Ile Tudy of Brittany to previous patients. Hlava, in a tabular record of 2,639 cases of typhus, draws the conclusion that the spread of the infection occurs only by direct contact. In a typhus outbreak of 30 cases which occurred in London in 1899 the epidemic was traced to a single family (Waldo).

Apparently the disease is highly communicable, but that this communicability differs from the contagiousness of diseases like diphtheria is indicated from the occurrence in the literature of such observations as the following:

Overcrowding is considered by the early authors on typhus as almost *essential* to its production. Thus, to quote from Murchison, "although scarlet fever and small-pox are propagated by overcrowding and defective ventilation, epidemics of them commence and spread irrespective of these influences. It is not so with typhus, which never becomes epidemic except under circumstances of overcrowding and bad ventilation."

Great importance is set upon personal uncleanliness and filthy clothes as predisposing factors to typhus by Murchison, Graves, and others. Filthy apparel is commonly vermin-infested, and it is interesting in this connection to note the repeated comments (Bancroft, 1811, Murchison, Terrés, and others) upon the exemption from typhus fever of the naked negroes in slave ships. These poor creatures were crowded

for weeks below decks in foul, stinking holds and yet, though they suffered terrifically from dysentery and other ills, they were spared from the very disease which from analogy might be expected to cause the greatest trouble, namely "ship fever" or typhus. Their escape was not due to racial insusceptibility, for negroes are quite as susceptible to typhus as whites. This was shown by the epidemic of 1836 in Philadelphia, in which a majority of cases occurred among the blacks (Gerhard).

Another illustration of the importance of clothing in typhus infection is found in the following observation of Perry of Glasgow (quoted by Graves). The fever wards of the Glasgow Royal Infirmary were two, one for acute and one for convalescent patients. Typhus, smallpox, scarlet fever, and measles were admitted. In the acute ward the patients were confined in bed and "were not allowed the use of their clothes." Now it was found that while they remained in the acute ward none of the smallpox or other patients contracted typhus fever, but that when they were sent into the convalescent ward, where they necessarily mixed with the typhus convalescents who here were allowed to dress in their own clothes, "almost all seized the typhus in an intervening period, never less than eight days." Later these smallpox and measles cases were kept in the acute ward until well and discharged, and not one caught the disease.

"Sir R. Christison, speaking of the medical students who had contracted typhus at the Edinburgh Infirmary, and who had been *attended at their own homes* by himself and two of his colleagues during thirty-two years, remarks: 'I am sure I am within the limit when I say that we have attended 280 cases of this kind, that 1,200 persons must have been more or less exposed in attending on them, and only one instance of communication is known to have occurred.'" Murchison himself comments: "How different is scarlet fever in this respect!" It is to be presumed that the homes of these students were far cleaner than the charity wards of the hospitals of that day.

More recent authors are even more emphatic as to the non-contagiousness of typhus in *clean surroundings*.

Robinson and Potts (1905) in a report on 600 cases of typhus fever in the Liverpool City Hospital comment as follows: "The patients were kept in large wards with abundant fresh air; they were bathed on admission and their clothes disinfected, with the result that no cases of hospital infection occurred." Dr. Russell of the Liverpool Fever Hospital claims that the wardmaids and nurses of that hospital only very rarely contract typhus. Out of 800 cases of typhus during the past three or four years no doctor or medical student took the disease, a condition which contrasts most favorably with the records of former times and is to be explained by the scrupulous cleanliness of the modern hospital ward (Hay).

Gotschlich in a report from the Government Hospital of Alexandria, Egypt, states that typhus frequently occurs epidemically in the prisons of that city. These prisons are filthy and vermin infested, and the disease in them always manifests great contagiousness, nurses, physicians, and attendants being attacked. In marked contrast to this condition is the absence of any cases of contagion or spread from patients treated in better hygienic surroundings, in the hospital or home, this in spite of the fact that where the patient was nursed in his own family the opportunities for contact transmission were greatly enhanced, the relatives being in most intimate daily association with the patients and even kissing and hugging them before and after death. Gotschlich has never seen a single case of contagion in families in comfortable circumstances.

Conditions in Mexico resemble those in Alexandria. As has been mentioned, Belem, the city prison, is a hotbed of infection, and in the charity hospitals, the General and the Juarez, where the cleanliness of the patients and the disinfection of entrants is only laxly enforced, cases of typhus are constantly arising among the nurses and others whose duties take them in contact with the patients.[1] Yet we have been informed by numerous physicians of Mexico City that instances of contagion are met with with extreme rarity in the families of the well-to-do, where the patient is treated at home and under cleanly conditions. Also in the private hospitals which are maintained under modern ideas of hospital sanitation instances of infection practically never occur. During the last twelve years there has not been a single house infection from typhus in the American Hospital, although in this period 144 cases of the disease have been treated. In the same period three nurses have been infected with typhoid fever while attending typhoid patients.

Finally there have come to my attention the following instances in which very intimate exposure to infection failed to transmit typhus fever.

W. N., a boy, Irish, but born in Mexico City, ran a fairly mild course of typhus fever with petechial eruption. The mother, who was not immune, slept in the same bed with the child during the nights following the third and fourth days of his fever, and for the rest of the time that he was ill, although restrained from sleeping with him, remained in very intimate contact. She did not contract the disease. The boy was a patient of Dr. Schmidtlein of Mexico City.

M. R., an American visitor at Mexico City, slept in the same room, although not in the same bed, with a typhus patient during the first three days of a typical typhus fever from which the patient later died. He remained in perfect health during the following three weeks in which he was under observation. The room inhabited by these men was clean and free from vermin.

Anderson and Goldberger cite the following: "F. J., adult, American, non-immune. Lived at a hotel in Mexico City, but came in daily intimate contact with

[1] Typhus patients who arrive at the General Hospital are sent directly to the "tifo pavilion" instead of being previously bathed and cared for at the reception ward as are all the other entrants. This custom is recognized to be highly reprehensible by the physicians of the typhus department, but insurmountable difficulties have been in the way of correcting the condition. Arriving at the typhus pavilion, the patients are bathed and their clothes taken from them, but the bathing and undressing take place within the pavilion, and any insects which may be in the clothes have ample opportunity to be brushed off on to the floor or walls. Thus the pavilion is being constantly reinfested with vermin. But still worse is the reception of the patients that arrive at night. These are put to bed in the ward, still wearing their soiled clothes, and frequently when their beds are examined in the morning the sheets and blankets are found to be swarming with lice.

cases of tabardillo between November 22 and December 16, 1909. On the nights of January 5 and 6 he slept in a bed that had been occupied on January 2, 3, and 4 by a patient in the first three days of a well marked attack of tabardillo. None of the bedding or bed clothes had been in any way disturbed in the interval prior to their use by this individual. At the end of three days the bed clothes were changed, but with this exception the bed and room remained as they had been when occupied by the patient. F. J. inhabited this room for three weeks longer. On careful search no insects other than fleas were found in the room. During a period of observation of 17 days this man continued in his usual health.

Instances of indirect transmission of typhus, that is transmission by means of intermediaries, well persons, who carry the disease to others without themselves succumbing to infection, are very numerous (Curschmann) and it is easy to understand how this would be possible either under the insect theory or under the "contagious" theory, but in this connection it is interesting to read the following: "There are no instances on record where a medical man has been the medium of transmission of typhus to his patients or to his family, as may happen in the case of scarlet fever or smallpox" (Murchison).

TRANSMISSION OF TYPHUS BY INSECTS.

The belief that insects carry typhus from man to man is of relatively recent birth, although it is held by many physicians who are in daily contact with the disease and has been voiced by several writers on the subject (Eichorst and Sambdon). Fleas and bedbugs were long ago looked upon with suspicion by certain older Mexican physicians, foremost among whom was Dr. D. Francisco Marten.

Granting that typhus is a disease that is commonly, or at least frequently, carried about in the clothing and that it is an insect disease, three possible kinds of vermin immediately present themselves as open to suspicion. These are the flea, the bedbug, and the louse.

The flea.—This insect has been incriminated in plague as a carrier of that disease, and as typhus fever resembles plague in various clinical respects it is not unreasonable to expect that the flea may transmit the former as well as the latter. Typhus and plague are both septicemias, that is the blood in both has been

shown to be infectious on inoculation, and hence it might be expected that any blood-sucking insect could transmit either disease. Also Hay's observations in Aberdeen, which were detailed above, point toward the culpability of the flea in typhus, and yet it must be said that the flea theory does not harmonize with the etiological factors of typhus fever as we now know them.

Typhus is universally a disease of temperate climates and reaches its greatest epidemic exacerbations in the cold seasons of winter and spring, but the flea is found in greatest abundance in the tropics, and in temperate countries the flea season is not the winter, but the summer. In Mexico City during the yearly exacerbation of typhus from November to May fleas are relatively scarce; indeed, during the last year in January and February, the months in which the typhus curve reached its greatest height, great difficulty was experienced in obtaining a sufficient number of them for experimental purposes. On the other hand, in the summer when the number of cases of typhus is at a minimum fleas abound. In Tunis lice abound in the spring and early summer, the typhus season, while fleas and bedbugs are rare or absent (Nicolle). In India also it is reported that fleas almost disappear in the winter when typhus is most prevalent (Husband), and this is undoubtedly the condition in other countries.

In the second place the striking distance of typhus is short (Murchison), a condition which scarcely harmonizes with the astonishing agility of the flea. Finally, typhus is almost exclusively a disease of the poor, but in countries in which fleas are at all abundant, as for example Mexico, they are rather generally distributed among all classes of the population.

Unfortunately experimental investigation of the rôle of the flea has not progressed far. Toussaint in 1906 attempted to infect himself with fleas which he had previously fed on typhus patients. The experiment was negative; no symptoms were produced other than a temporary local infection of the skin at the point of attachment of the insects. The fleas used were collected from a cat. The experiment of Dr. Ricketts and myself with the macacus monkey and human fleas (*Pulex irritans*) will be detailed below. It consisted in the inoculation of a monkey with an emulsion of

the entire bodies of 10 fleas, each of which had been fed repeatedly on typhus patients. The monkey was not infected.

The bedbug.—Husband in India and both Gotschlich and Sandwith in Egypt incline toward the opinion that the bedbug (*Cimex lectularius*) plays the chief rôle in the distribution of typhus. Husband's arguments are as follows: Fleas are excluded because of their scarcity during the typhus season. The drabis (mule-drivers) commonly harbor lice, but these insects cannot live long apart from their hosts, while the contagium of typhus undoubtedly does. Furthermore cases continually occur among army prisoners, and the enforced cleanliness of these renders them free from lice. Bugs are active all the year, attach themselves to bedding and furniture, and feed repeatedly from fresh hosts. Furthermore it has been shown that the species of bedbug common in Europe (*Cimex lectularius*) is found in the northern frontier provinces, but not in the rest of India, a distribution which curiously coincides with that of typhus fever, which is rarely met with in the "down country" (Husband).

Husband's observations seem very conclusive, but theoretical considerations also argue against the theory that the bedbug is of importance in transmitting typhus. Typhus fever is a disease of a certain season of the year, but bedbugs are active throughout the year. Now it has been rather conclusively proven that bedbugs transmit relapsing fever (Tictin, quoted by Ricketts), but relapsing fever fails to show any such seasonal variations as does typhus. Leonhardt in a historical account of typhus and relapsing fever in Breslau, Schleswig, presents two very instructive tables, the one recording the case totals of typhus fever from 1856 to 1894 and the second the monthly case totals of relapsing fever for the period 1868 to 1894. These tables, which include a very large number of cases of each disease, reveal that the case totals of typhus constantly increase during the winter months and decrease in the summer. This is true both in epidemic and non-epidemic years. In relapsing fever the cases are about equally distributed through all four seasons, and in 1868 and 1869 by far the majority of cases are confined to the months from May to August, the season when typhus is at its lowest ebb. Rabinowitsch likewise

notes the absence of seasonal variation in recurrent fever and argues from this that the summer must have some rather concrete restricting influence on typhus.

In the second place, the bedbug is only a temporary parasite of man and is rarely carried about in the clothing, but the clothing of typhus patients is usually infectious, and numerous instances have been cited in the foregoing pages to illustrate how frequently the contagion of typhus is carried on the bodies of intermediaries from one person to another.

Were the bedbug the chief factor in the spread of typhus we should expect the disease to have more the characteristics of a "house disease," but such is not the case. The large majority of the patients which were studied in Mexico could not be traced to any typhus house, and it has been noted by numerous European authors that if a patient is removed from his home fairly early in the disease subsequent house infections rarely arise (Murchison, Hay).

Again, bedbugs, like fleas, are rather generally distributed among all social classes. Typhus is confined to the poor, but bedbugs may be found in the homes of well-to-do persons, where the disease is an extreme rarity and where its spread from one individual to another is practically unknown.

A further argument against both bedbugs and fleas is to be found in the geographical distribution of typhus in Mexico. Both of these insects are quite common in the hot countries bordering the coasts, but typhus is limited to the plateau.

An experiment which was performed for the purpose of determining whether the bedbug could carry typhus will be detailed later. I was unable to transmit the disease to the monkey with these insects.

The louse.—Without further study we cannot of course exclude the possibility that either the flea or the bedbug or both may under certain circumstances act as carriers of typhus, but in the light of the etiological conditions of the disease it seems improbable that either of them can play a very important rôle. Certainly their part is far less significant than that of the louse, which I now wish to consider.

The louse has been looked upon with suspicion by various authors, among others by Netter and Thoinot, who in their "Rapport Général sur le typhus en France" discuss the possibility of transmission by this means (Nicolle). Sambdon, in an article on "Rocky Mountain Spotted Fever" in Albutt's *System of Medicine*, suggested the possibility that the louse may carry typhus, but there were apparently no direct affirmations of the importance of the louse previous to the experimental researches of Nicolle in Tunis and Ricketts and myself in Mexico City.

In 1909 Charles Nicolle succeeded in infecting a chimpanzee with typhus fever and was then able by inoculation with the blood of the chimpanzee to infect other monkeys of an inferior species (*Macacus sinicus*). Later, in conjunction with Compte and Conseil, he successfully transmitted the disease from one macacus to two others by means of human lice (*Pediculus vestimenti*) applied in the following manner:

Twenty-nine lice were placed on the skin of macacus No. 1 in the third day of his fever. Twenty-four hours later and again on each of the following days they were fed upon the two monkeys A and B. A was bitten for 6 successive days by 15, then 12, 31, 8, 6, and 3 lice, and B for 12 days by 14, then 15, 13, 9, 5, 6, 5, 4, 2, and 1. These monkeys, after rather long incubation periods of 25 and 40 days respectively, both succumbed to high fevers which in the case of the first, after an irregular course of twenty days, culminated in death. This monkey was quite perceptibly ill after the thirtieth day following his exposure to the lice, but failed to show an eruption. The autopsy findings were negative, the spleen being small. The general symptoms noted in the case of Monkey B were few; there was some weakness and loss of appetite with the elevation of temperature, but on the sixth day after beginning of his sickness a macular eruption was observed. Six monkeys were inoculated with the blood of A and B. Of these, five ran rather mild courses of fever which were difficult to interpret, but the sixth, inoculated from Monkey B, developed a typical typhus.

In experiments performed in Mexico City during December, 1909, and January, 1910, Anderson and Goldberger undertook to transmit typhus from human patients to the macacus with lice.

One of these animals showed a slight rise in temperature 8 days after its last exposure to the bites of the infected insects. This febrile elevation persisted for only two days and as it was but a trifle above the normal range for the rhesus monkey it was not interpreted as fever. Unfortunately no immunity test could be given to the animal at the time. It is very probable that the elevation of temperature observed was due to typhus.

The experiments of Ricketts and myself, the protocols of which are included in a later section, prove, I believe, to a reasonable degree of certainty, that the infected louse may by its bite transmit Mexican typhus fever or tabardillo. Thirteen monkeys of the species *Macacus rhesus* were the subjects of experiments on louse transmission. Of these, eight were exposed to the bite of infected lice, that is, lice which had been fed on human patients for two or three days before the beginning of the experiment. Five of these monkeys were infected with typhus fever by the lice. In two other experiments transmission by lice from monkey to monkey was obtained, and two "scarification experiments," which consisted in the subcutaneous introduction into monkeys of the intestinal contents of infected lice, resulted in positive transmission. Thus, in all, nine monkeys were infected by lice.

Infected lice have been shown by experiment to retain their ability to produce the disease for a period of at least seven days and the result of one experiment seems even to indicate that the infectivity of the mother louse may be inherited by her young. It is evident therefore that the louse may actually be infected by the typhus germ and that this insect may by its bite transmit the disease to a well individual. Under these circumstances it is highly probable that the usual manner of transmission of typhus fever is by the louse, especially since all of the epidemiological factors of the disease, as we now know them, point to and may be explained by such a theory.

The habits of the louse agree with the etiology of typhus and clear up the peculiar nature of the supposed "contagiousness" of the infection. Emphasis has already been laid on the short striking distance of the typhus contagion, its predilection for the clothes and bedding of the patients, and its apparent absence after

patients have been undressed and bathed. Human body lice are blood-sucking parasites and are only rarely and accidentally found away from the bodies or clothing of human beings. Their movements and habits are sluggish; they secrete themselves during most of the time in the folds and seams of the clothing, and make only rare and short excursions to the skin for food. It is only under conditions of rather intimate contact that they are passed from host to host. On the other hand, they are rather active in seeking a new host after they have been removed from their source of food, as for instance with the discarded clothing of a patient, and this activity explains the particular danger of contracting typhus of those whose duties require them to receive and undress typhus patients or to handle such discarded clothing preliminary to its disinfection.

Attention has been called in preceding pages to the restriction of typhus to the lowest and filthiest classes of the population. The body louse is limited to people of this class. As a rule lice are regarded with disgust in homes and families where fleas and bedbugs are tolerated, and even approximately cleanly habits will render people free from lice, inasmuch as bathing and the regular washing of clothing is incompatible with the life of these insects. It is true that cases of typhus occasionally occur among the better classes, but all such cases can be traced to contact with louse-infested persons. This was the observation made by Hay, who is quoted below (p. 47). In Mexico City it is not uncommon for well-dressed persons of perfectly cleanly habits to find an occasional louse on the clothing, after a walk through streets crowded with poor people, and hence, as might be expected, there occurs relatively more typhus among the better classes of that city than is described by the European authors.

Of still greater interest is the almost exact concurrence between the geographic distribution of lice in Mexico and the distribution of typhus, of which mention has already been made. *Pediculus vestimenti* is almost never found in the "terre caliente," or hot country, which is free from typhus, while on the typhus-infested plateau it is very abundant.

The absence of body lice in the hot country is due to several

factors. In the first place the habits of the people of this part of the country are more cleanly; the warmth of the climate and the abundance of water encourage bathing, and the clothing worn is made of light material, frequently white cotton, which can be washed.

Of equal or greater significance is the heat of the lower country, which appears to be unsuitable for the life of the louse. I am disinclined to insist too strongly upon this point because of the scantiness of evidence at hand, and yet such evidence as there is all indicates that the louse does not thrive at high temperatures, and I feel convinced that further observation will bear out this statement.

During the course of the experiments conducted by Ricketts and myself in Mexico City lice were used almost constantly, and at times it was found very difficult to keep the insects alive. This difficulty increased to a great extent during the warmer months of March and April, and it became necessary to keep the lice at a low temperature, 16 to 20 degrees Centigrade. Several experiments were performed in order to determine the effect of heat on their vitality. Groups of lice were placed in a thermostat, at a temperature of 35° C., death from desiccation being guarded against by supplying abundant moisture. In every instance this temperature resulted in the rapid death of the entire group, indeed a few hours at 35° usually sufficed to kill. The protocols of one such experiment are as follows:

EFFECT OF TEMPERATURE ON THE LONGEVITY OF THE LOUSE.

Lice of group 16 (*Pediculus vestimenti*) were collected from the clothes of children of a neighboring school and were presumably normal. Two hundred healthy adults were given a feed on normal monkey No. 8. They were then divided into four groups of 50 each (A, B, C, and D), each group being folded separately within a piece of muslin and placed in a cotton-plugged test-tube. The tube containing group A was put in a large air-tight jar containing a water-soaked sponge for moisture and incubated in a thermostat at 35° C.

Tube B was placed in a similar moist jar, but kept at the room temperature, which reached a maximum of 20° C.

Tube C was kept at room temperature without moisture.

Tube D was kept without moisture at a temperature of 10° to 12° C.

Sixteen hours later all the tubes were examined:

Tube A, all lice dead.

Tube B, 1 louse dead.

Tube C, 3 lice dead.

Tube D, 1 louse dead.

The difference between the room temperature of 20° and the temperature of tube D, namely 10° to 12°, had no appreciable effect, but the mortality of 100 per cent in tube A is quite striking. Some of the lice in B, C, and D were alive at the end of the fifth day, although not fed in the interval, while 16 hours at the incubator temperature proved fatal for the first group.

Nicolle, Compte, and Conseil also comment on the effect of high temperature on the viability of the louse (*Ann. de l'Inst. Pasteur*, April, 1910), and these authors found it necessary to keep the insects at a temperature below 24° C.

Anderson and Goldberger had a similar experience (*Pub. Health Report*, February 18). Lice were carried in bottles on the body, at a temperature approximating that of the body, with the result that at the end of 36 hours, although fed in the interval, all had died. The authors also comment on the significance of the influence of temperature on louse longevity in view of the limitation of typhus to the Mexican plateau.

It is a fact frequently noticed by the natives of Mexico that louse-infested individuals who go from the plateau to the warm coast countries rapidly lose their body lice independently of bathing or washing. I have been frequently told of this occurrence, although I have not had an opportunity to confirm the correctness of the information. In any case the temperature of the coast cities frequently reaches 35° C. even during the winter months, a temperature sufficient to kill the lice in the incubator; indeed it is not uncommonly still higher in these parts, and for several hours of every day the heat is more or less intense. It is therefore not unreasonable to suppose that temperature plays an important part in limiting the geographic distribution of lice and thus indirectly of typhus fever.

It is furthermore probable that temperature determines the exacerbations in Mexico by the effect of the summer heat on the number of lice.

The experiments of Ricketts and myself were continued from December, 1909, to the end of June, 1910. In the early months there appeared to be no difficulty in obtaining an ample supply of body lice for the work, but as the warmer spring months from

March on progressed the servants who were paid to collect lice became less prompt in delivering the required number. I was also told by several of the nurses at the General Hospital that the poor applicants were relatively freer from vermin during the hot period following the winter months than at any other time of the year.[1]

The coincidence between the decrease in typhus and the beginning of the hot season is remarkable, as reference to Chart I will indicate. It is of greater importance to my mind than the relation between the rains and typhus indicated on the same chart. As is shown, the typhus curve always begins to fall about the time the rains *commence*, but this is before precipitation has reached any effective amount. The typhus curve begins to drop in April, and yet until the end of May the roads remain dusty. The ditches are empty until June or July. Then, but not until then, is the influence of the rains manifested. Water becomes abundant, clothes are washed, and bathing may even be indulged in, with the result that a great destruction of lice occurs, a large proportion of the total number of infected insects is killed, and the typhus curve drops still further. When the rainfall of any given year is scanty, as for instance in 1900 and 1905 (see Chart II), the ditches are not filled, a smaller number of lice are destroyed, a greater number of infected lice are left alive, and the following year the exacerbation becomes a severe epidemic. This I believe to be the relation between the rain and typhus, its effect secondary and accessory to that of the heat, their combined effect being directed against the louse population.

It is not my intention to insist too strongly on this point, namely that the effect of heat and rain on typhus is accomplished by destruction of lice, and I recognize that other factors enter in, that the greater heat of the summer encourages better ventilation

[1] This matter is of sufficient importance to justify verification. The question could probably be settled in the course of a year or two by employing two or three reliable individuals, typhus immunes, to examine the clothing of all arrivals at some large hospital and to form by count as accurate an estimate as possible of the number of lice harbored by each individual. It would be difficult to make such an estimate absolutely accurate because of the minute size of the newly hatched lice, but even rough estimates if sufficiently numerous and extensive would, I believe, reveal, first, that more people harbor lice during the cold winter months than in the summer, and second, that the average number of lice per individual louse-carrier decreases in the hot months.

Nicolle reports that the relative number of lice in Tunis is very low during the non-typhus months of September, October, and December, whereas these insects abound in the spring and early summer when typhus is at its height.

of homes and less crowding, and that the richness of the harvests and the consequent nutrition and state of resistance of the poor is dependent on the amount of rain, but overcrowding, poor ventilation, famine, and destitution, although important accessory forces in determining the occurrence and spread of typhus fever, are not essential to its occurrence and spread, while the presence of body lice in particular is essential.

It should also be recognized that the effect of heat may be directed not so much against the life of the louse as against the duration of the infectivity of the louse, as is the case in plague in India. The infectivity of the flea is diminished or destroyed by the excessive heat of the Indian midsummer. Fleas thrive at this time, but are not infective. The possibility that similar sterilization of infected lice may be produced by the intense midday heat of the Mexican summer has not been investigated to date, but certain theoretical considerations make this seem highly probable. Chief among these is the following:

Travel between Mexico City and Veracruz is quite constant, and, as was mentioned before, typhus cases are not infrequently imported into Veracruz from the plateau. Opportunities are therefore numerous for spreading typhus from one city to the other and yet they have never resulted in the production of an epidemic in Veracruz. Indeed, I was informed by numerous physicians of that city that they had never known of a single case contracted from an imported typhus patient, although many of these were vermin-infested on their arrival, and no attempt was made toward isolation or disinfection. Lice are surely not killed quickly enough by the heat of Veracruz to safeguard the contacts of these patients, but sterilization of the lice may and seemingly must occur. Experiments designed to investigate this interesting problem have been planned and it is highly desirable that they be performed.

SUCCESS ATTENDING PROPHYLAXIS DIRECTED AGAINST INSECTS.

As a final argument supporting the theory of louse transmission is the successful result which has attended prophylactic measures directed toward the elimination of body vermin. In an epidemic which occurred in Aberdeen in 1906 insect transmission, particularly

transmission by the flea, was suspected by Hay, who gives the following reasons for arriving at this conclusion:

1. Every case of typhus examined in the hospital exhibited flea bites, these being carefully distinguished from petechiae.

2. Every case, however clean and free from body vermin himself, was found to have been in contact with vermin-infested patients at the probable time of infection.

3. There occurred no instances of contagion in families of perfectly cleanly habits, although typhus patients had lain in the house during the greater part of their illness and in two cases without attempt at isolation. One of these cases concerned a mother who slept with her child during his illness without catching the infection, a case similar to the one cited on a previous page.

4. Every nurse and wardmaid at the City Hospital who was infected was engaged in receiving and cleaning typhus patients and thus exposed to the vermin on the patients' clothing. None of the nurses who attended the patients in the wards and no physicians contracted the disease, although they were in constant proximity to the patients.

The prophylactic measures instituted by Hay were directed against the flea, but it will be seen that they are so designed as to be equally effective in destroying other body vermin such as lice.

When a patient was reported and removed from a house, the house was thoroughly fumigated with sulphur, in order to stupify all insects. The bedding, clothing, carpets, etc., were then removed to the disinfecting station, the woodwork, walls, and floors after a thorough spraying with formaldehyde were washed and the walls stripped of paper and limed. After such precautions no case of house infection occurred and the epidemic died out.

Hepper reports the successful combat of a little outbreak of typhus which sprang up in the prison hospital of Peshawar in India. In previous years the hospital had been visited by severe epidemics, and for this reason the place was rebuilt several years ago along lines designed to eliminate vermin. Iron beds and clay bunks were substituted for the wooden furniture used before. In spite of these precautions, after an interval of several years, typhus again appeared in the hospital. The iron beds were examined and

found to harbor bedbugs. These beds were then surrounded by leaves of sugar cane which being fired subjected them to a short but intense heat. The tile floor of the hospital was likewise covered with cane and fired, while the patients were removed to tents and given clean clothing and bedding. The epidemic was completely stamped out. The only other case which occurred was that of a patient who came down with the disease six days afterward and had undoubtedly been infected before the disinfection. No sick attendant of the typhus cases got the disease, which "was contrary to the usual experience, the sick attendants as a rule being very liable to become infected."

In this connection the experience of Robinson and Potts should again be referred to. Patients were bathed on admission to the Liverpool City Hospital and their clothes fumigated, with the result that no case of hospital infection was observed. The fact that this is the general experience in all modern and strictly clean hospitals is the strongest kind of an argument against the reputed "contagiousness" of typhus fever. Under cleanly conditions typhus is not contagious.

CONCLUSIONS.

1. Typhus is an insect-borne disease.

2. The disease is contagious only in so far as infected vermin are transmitted from host to host by contact and is not contagious under conditions in which vermin are excluded.

3. Three insects should be regarded with suspicion as possible conveyers of the infection. These are the flea, the bedbug, and the louse.

4. The epidemiology of typhus indicates the possibility that neither fleas nor bedbugs ordinarily play any great rôle in transmission.

5. The body louse (*Pediculus vestimenti*) stands incriminated, first by the experimental results of Nicolle, Compte, and Conseil in Tunis, and Ricketts and myself in Mexico, and again by the epidemiology of the disease.

6. The louse theory is in every way consistent with the etiology of Mexican typhus so far as this is understood and explains several

important phases of the epidemiology which were formerly obscure. Chief among these are, (*a*) the geographic limitation of typhus to the central tableland of Mexico, (*b*) the seasonal variation of the disease and the effect of temperature and rain on the epidemics in Mexico City.

7. Prophylactic sanitary measures directed against typhus fever should take into primary consideration the body louse.

V.

EXPERIMENTAL OBSERVATIONS ON TYPHUS FEVER AND ITS COMMUNICATION.

Inoculation experiments have been attempted with the blood of typhus fever patients in a wide range of animals. Mosler (quoted by Pie-Smith) injected fresh blood from patients into the veins of dogs without result, and numerous other negative experiments of the kind are reported in the European literature. Zulzer alone found that when he took blood while the disease was at its height and injected it into rabbits these died within two or three days. The symptoms were not, however, very characteristic of typhus, and the results have failed of confirmation by other investigators.

In Mexico extensive inoculation experiments undertaken by Director Gaviño of the Bacteriological Institute and his assistants failed to produce any evidence of infection in guinea-pigs, rabbits, white rats, and mice. The blood was taken from patients at different periods of the disease. Numerous other investigators have obtained similar results.

Experimental transmission from man to man has been attempted, but the results are not satisfactory. In 1876 Moczutkowski inoculated himself with blood from a typhus patient and 18 days later developed a fever and the typical symptoms of the disease. The experiment is reported in a publication of 1900. It is not very conclusive. The author claims to have had exanthematic typhus before when thirteen years old, and on several previous occasions attempted unsuccessfully to infect himself with blood. At the time of the experiment reported he was engaged in active work in the typhus ward, which exposed him presumably to the constant danger of infection by natural channels.

In 1907 M. Otero, a physician of San Luis Potosi, Mexico, made several attempts to infect human beings by inoculation. In three cases he obtained no result, but in a fourth he was successful. A volunteer was injected intravenously with 0.5 c.c. of blood taken from a patient in an early stage ot a typical typhus fever of moderate severity.

Yersin and Vassal in French Indo-China have recently announced the successful

infection of two men, native coolies, by the subcutaneous inoculation of 0.5 c.c. of typhus blood. This blood was drawn from a patient in the second day of illness. In respectively 14 and 21 days after the inoculation the two coolies developed fever which began acutely, persisted for 11 days, and reproduced with great clearness all of the symptoms of the natural disease excepting the eruption. No exanthem of any kind was visible. The authors discuss the diagnosis of the disease and differentiate it from relapsing fever, dengue, and kala-azar, but no mention is made in the report of any precautions taken to prevent the accidental infection of the two subjects.

The first successful animal experiments were performed by Nicolle of Tunis, who in 1909 transmitted typhus fever from a patient to a chimpanzee by the inoculation of blood. After a latent period of 24 days the animal developed a fever of seven days' duration, which the authors interpreted as typical of typhus. Death followed the consequent cachexia. An eruption appeared on the 17th day after the injection. This consisted of rose spots and was confined to the face. A similar eruption is reported by the authors in subsequent experiments, but has been denied in their later publications (*Compt. rend.*, July, 1910).

From the chimpanzee the infection was transmitted by blood inoculation to a monkey of the species *Macacus sinicus*. Previous attempts at direct infection of the macacus with human blood had failed,[1] but in experiments undertaken subsequent to the investigations on Mexican typhus, described below, successful infection directly from man to the macacus monkey has been obtained by the Tunis investigators. In these later attempts numerous monkeys have been inoculated. Several of these were of the species *Macacus sinicus*. Rhesus, sinicus, the inuus, and the cynomologus monkeys have been used. The quantity of blood injected has varied in amount from 0.5 c.c. to 10 c.c. and the injections have been made subcutaneously in some cases and intraperitoneally in others. The sinicus has been found more susceptible than the rhesus, although individuals of both species have been successfully infected. The authors claim that typhus blood is infectious at all stages of the disease even before the onset of fever and for several days after crisis.

In December, 1909, Anderson and Goldberger, working independently of Nicolle, succeeded in transmitting Mexican typhus directly to inferior monkeys from man. Two animals, one a *Macacus rhesus* and the other a *Cebus capuchinus*, were inoculated on successive days with large quantities (10 c.c. doses) of blood from typhus patients. Both animals suffered severe attacks of typhus which were clinically typical except for the absence of eruption. The incubation periods noted were 11 and six days respectively. Immunity tests given to these animals after their recovery were resisted completely. Passage was also successfully accomplished with blood taken from the

[1]Nicolle states in his more recent publications that his failure to infect the inferior monkeys directly with human blood in his earlier attempts is to be attributed to the use of insufficient blood. In this early attempt two monkeys, one a cynomologus and the other a sinicus, were injected, each receiving 1 c.c. of blood taken from different patients during the early part of severe fever. Neither of the animals manifested any discomfort following the injection, but it was found some months later that they had been immunized by the blood. They proved resistant to inoculations of infected blood from other monkeys. This result appears to be of the nature of a vaccination or active immunization. Such an interpretation is indeed made in the publication of April, 1910, *Ann. de l'Inst. Pasteur*, p. 259: "Une inoculation de sang humaine typhique au bonnet chinois ne l'infecte pas, mais le vaccine contre le virus de passage par bonnet chinois." It is however contradicted in a later report (*Compt. rend. de l'Acad. des Sci.*, August, 1910), in which the statement is made that a first attack of typhus fails to confer immunity if not sufficiently severe. "Une atteinte légère de la maladie expérimentale ne donne pas l'immunité."

animals at the height of their fever and the disease reproduced in other rhesus monkeys. A third passage failed.

McCampbell has also succeeded in giving the Mexican disease to monkeys by injections of blood from human patients.

Gaviño and Girard of Mexico City have succeeded in infecting a monkey of a species indigenous to Mexico, the *Ateles vellerosus*.

Prieto of Mexico City has recently reported the experimental infection of dogs with typhus fever, but to my knowledge his observations have not been confirmed by others.

PERSONAL INVESTIGATIONS.[1]

During the course of the investigations of Mexican typhus undertaken by Dr. Ricketts and myself twelve normal monkeys of the species *Macacus rhesus* were inoculated either with blood or serum from early cases of typhus. All proved susceptible to the inoculation excepting one (the animal receiving the smallest dose, No. 21), whose history follows shortly. Three other monkeys, likewise macacus, were injected with virulent monkey blood; in addition five monkeys, previously the subjects of insect experiments, proved susceptible to inoculations of human typhus blood. In all, 20 monkeys have reacted to the injection of virus in practically the same manner, and, as all were later reinoculated and proved immune to the subsequent reinoculation or "immunity test," I feel justified in concluding that they were infected with typhus by the original injection of blood. From these experiments the following conclusions may be drawn concerning the nature of typhus fever in the *Macacus rhesus:*

The monkey is not very susceptible to infection with typhus. First, the minimum infective dose has been found to lie between 0.2 c.c. and 1.0 c.c. Second, it has been found difficult if not impossible to maintain the infection by passage from monkey to monkey. Anderson and Goldberger, and McCampbell were all equally unsuccessful. All report a diminution in the severity of

[1] The following experiments were largely designed by Dr. Howard T. Ricketts, who died of typhus while engaged in this study. They were made in Mexico City during the winter and spring of 1910, were temporarily interrupted after the death of Dr. Ricketts, and were later completed in so far as was possible. Many of our results were unavoidably lost, and much work that had been planned was necessarily abandoned. The studies have not been completely reported in the preliminary communications published by Dr. Ricketts and myself, and it is the purpose of the present paper, first, to collect the substance of all of our investigations on transmission, the problem which is undoubtedly of the greatest practical interest in connection with the disease, and, second, to draw from these studies certain general conclusions. In the pursuance of these investigations we were greatly aided by the courtesy and kindness of the Mexican physicians, and by the numerous privileges granted us by the Mexican government.

the disease after the first passage, which is probably significant of an attenuation of the virus. Our own experience, although less conclusive on this point, will be discussed later.[1] It is undoubtedly safe to say that the monkey is less susceptible than man.

The incubation period after injection of the virus into a monkey occupies from six to 10 days, although it has been as short as four days and in two cases was protracted to 15 and 16 days respectively. This agrees fairly well with the incubation period observed in man. The duration of the fever extends from eight to 15 days, although in one or two mild cases it has been shorter (five days). Frequently after the first two or three days of high temperature a drop to normal is noticed which is followed by a return of fever. The course in man is almost always longer and except in sporadic cases the fever is relatively higher and more constantly sustained. No prodromal symptoms have been noticed in the monkey excepting an increased irritability, but during fever all of the animals have suffered to a greater or less extent from weakness, loss of appetite, occasional intestinal disturbances, and coughing. No eruption that could be interpreted as being caused by the disease has been observed on the skin or buccal mucosa, and in this respect Mexican typhus fever in the monkey differs from that in man, where a very characteristic petechial eruption is an almost invariable occurrence. Many of our monkeys during sickness showed congestion of the conjunctivae. Also a reddening of the face particularly at the corners of the eyes and the root of the nose was frequently noted, but in our opinion this should not be interpreted as an eruption, inasmuch as normal monkeys under our observation occasionally revealed the same reddening.

No micro-organisms which could be cultivated on the ordinary media have been found in the blood of typhus monkeys in any stage of the disease, although numerous cultures have been made from the heart blood of all animals suspected of having typhus. This result agrees with that reported by all other investigators of the subject and the failure to cultivate organisms thus constitutes a partial control of the fact that the monkey actually has typhus,

[1] In his latest publication Nicolle reports the successful transmission of the disease through nine generations of monkeys without any evidence of a diminution in virulence.

eliminating the possibility of certain other septicemiae which might cause an elevation of temperature.

The disease in the monkey terminates with only moderate abruptness, the temperature taking two or even three days to fall to normal. In this respect it resembles the termination of Mexican typhus in man, which has been repeatedly described as a "lysis" rather than a true "crisis." Recovery has been usually rapid, although certain animals later became cachectic and died from other causes. In only three cases (Monkeys 4, 6, and 22) has the disease ended fatally. The autopsy findings in the first two cases are given on pages 56 and 58. Monkey 22 was inoculated with virus which had been carried by passage through two other monkeys (Nos. 7 and 11). He showed no rise in temperature whatsoever as a result, but sickened perceptibly, becoming progressively weaker until his death, which occurred 14 days after inoculation. Before being made the subject of the experiment he was lively and seemingly in perfect health, and inasmuch as I have seen several cases of typhus in man that terminated fatally without showing any rise in temperature I think it highly probable that he died from typhus. Autopsy was made immediately after death. No definite anatomical changes that could be interpreted as the cause of death were found. Intense cerebral and intestinal congestion was present similar to that seen in previous cases, but as in human typhus the absence of local inflammation or other anatomical change was the more significant feature. Subsequently a monkey (No. 38) was killed on the fifth day of a severe course of fever. Again no distinctive changes were found; no enlargement of the spleen; the liver normal but for slight fatty infiltration; the kidneys showing only slight inflammation; the other organs normal except for great congestions of the vessels of the brain and of the abdominal viscera.

The technic employed in all of these experiments on transmission by the injection of virus was the following: Human blood was obtained from patients at the general hospital. Patients were selected who were typical cases at the height of their febrile courses, that is between the sixth and tenth days of fever. The arm of the patient was scrubbed and the anticubital space cleansed and

disinfected. The median basilic vein was then punctured with a sterile needle, and the required amount of blood extracted by means of sterile syringes or side-necked flasks. These latter were provided with cotton-stoppered aspirating tubes, the needle being attached by a short piece of rubber tubing to the side neck. The flasks contained glass beads, and the blood was immediately defibrinated by shaking. As little time as possible was allowed to pass before making the injections. Usually this amounted to three or four hours, as the distance between the hospital and the laboratory was great. Monkey blood was as a rule aspirated from the heart.

Various quantities of blood were used in different experiments. Where the amount of material was not great the peritoneal route was chosen for injection; in other cases a portion was introduced into the peritoneal cavity and the remainder beneath the skin.

Several flasks, each containing from 50 to 100 c.c. of broth, were inoculated with every specimen of blood used, this serving as a control against the presence of micro-organisms other than those of typhus. In most cases a Widal test was also made.

Before injection the blood was diluted with two or three times its volume of salt solution on theoretical grounds, and because experience with Rocky Mountain spotted fever suggested that dilution of the virus might favor infection. Dilution is known to render less effective specific antibodies which may be destructive to the virus, and there can be little doubt that blood drawn from typhus patients on the eighth day of the disease contains germicidal antibodies, particularly since the disease is one which clinically is known to cause the development of distinct immunity. Dilution may also favor infection through the peritoneal route by affording better conditions for rapid absorption or dissemination of the micro-organisms. In experiments with spotted fever it was occasionally noted that smaller doses of virus would cause infection when larger doses of the same material would not, the injections being intraperitoneal. Small doses, as 0.01 c.c., would be usually diluted with 2 or 3 c.c. of salt solution, whereas larger doses, as 5 c.c., would be diluted to a much less degree or not at all.

The animal experiments on typhus fever were confined to the

Macacus rhesus monkey. This animal is normally healthier, is far less ferocious, and is more easily handled than the capuchin, the sinicus, and other varieties of Macacus. Also it was deemed advisable to restrict the experiments to one species of animal in order that the final results could be better compared with one another, and the rhesus was chosen because it could be more easily obtained than other monkeys. The animal has its disadvantages. It normally runs a rather high temperature, and the variations between the morning and afternoon temperatures of uninfected and apparently healthy monkeys are often considerable. The morning temperatures of healthy controls have habitually been from 0.8 to 1.8 or 2 degrees lower than those of the afternoon. The former is commonly below 101° and may lie between 99° and 100° for several days in succession; whereas in the afternoon (from 3 to 4 o'clock) it commonly is found at some point between 102° and 103° or even 104°. The comparatively cold nights and the warmer days of Mexico City may have had some influence on the more extreme variations. We attempted to eliminate this factor as much as possible by warming the room in which the animals were kept from the hours of 5 P.M. to 9 A.M., the temperature at night being about 15° C. Furthermore from the experience of Nicolle with European typhus the rhesus appears to be less susceptible to typhus than are certain other species. Nevertheless, in spite of these difficulties the results obtained in Mexican typhus with the rhesus are definite and easily interpretable.

TRANSMISSION FROM MAN TO THE MACACUS BY INJECTION.

On January 11 a quantity of blood was drawn from the median basilic vein of José Hernandez, a patient in the Hospital General (Mexico City), on the eighth day of his sickness. The fever and condition of the patient were typical for an attack of typhus of this duration, the attack being one of moderate severity. Although the skin was quite dark, the spots, not yet petechial, could be seen over the abdomen, chest, axillary skin, arms, legs, and back, and the conjunctivae were reddened characteristically. The spleen showed little or no enlargement on percussion, and it could not be palpated. After the blood was drawn the patient passed through a typical "crisis," which occupied about three days, and recovered.[1]

Two cubic centimeters of the blood of the patient planted in 50 c.c. of broth

[1]Both the onset and the crisis of the typhus fever of Mexico are said to be less abrupt than in the classical European typhus. This has been contended by prominent Mexican authorities, and has appeared in their literature, for a number of years.

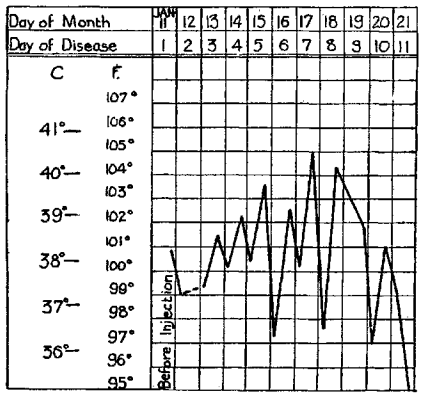
remained free from discoverable micro-organisms, which corresponds with the usual results of cultivation experiments with typhus blood.

Blood inoculation experiment.—Inoculations of 1, 5, and 10 c.c. of defibrinated blood were made respectively into Monkeys 5, 6, and 7. No. 5 died five days after its inoculation, showing a consolidation of the lungs, and since it had had no fever, it was discarded from the experiment. In addition, Monkey 4 received 8 c.c. of the serum from the same blood.

The blood after defibrination stood at room temperature (15° to 20° C.) and in diffuse light for from six to seven hours before injection.

The 5 c.c. of blood which Monkey 6, weighing 2,010 gms., received was diluted to 15 c.c. with sterile physiologic salt solution and the entire amount introduced intraperitoneally. Its temperature on successive days was as recorded on curve No. 1.

CURVE 1.



TEMPERATURE OF MONKEY NO. 6 AFTER INOCULATION.

On January 17, six days after inoculation, the animal ate little and sat "huddled up" with hairs more or less erect. This condition continued and on the 19th there was increased secretion from the conjunctivae and the animal coughed moderately. The illness appeared more severe on the 20th; there was no resistance to manipulation; emaciation; moderate diarrhea. On the 21st, when the temperature became subnormal, the animal was still somewhat responsive until about the middle of the afternoon, when its condition grew rapidly worse, and at 9 o'clock it was moribund.

The autopsy, which was performed at once, showed nothing distinctive and very little that appeared abnormal. The lymph glands generally were moderately enlarged, but were not congested or hemorrhagic. Those of the axilla and groin were the seat of old pigmentation. The lungs were pink, and showed no inflammation or other alteration except for a slight amount of atelectasis at the upper border of the left lower lobe. The pleurae were free from signs of inflammation. Moderate swelling of both the kidneys and liver was present, but they were not degenerated. The spleen was rather firm but not distinctly enlarged. No evidence of infection was found in the peritoneal cavity. The meninges and cerebral cortex were free from congestion, edema, or other signs of inflammation.

A broth flask culture from the heart's blood and agar slants from the viscera remained sterile.

Monkey 7, a male weighing 2,150 gms., received 10 c.c. of the same defibrinated blood, made up to 20 c.c. with salt solution. One-half the quantity was injected intraperitoneally, the other half subcutaneously. Its temperature on successive days is given in curve No. 2.

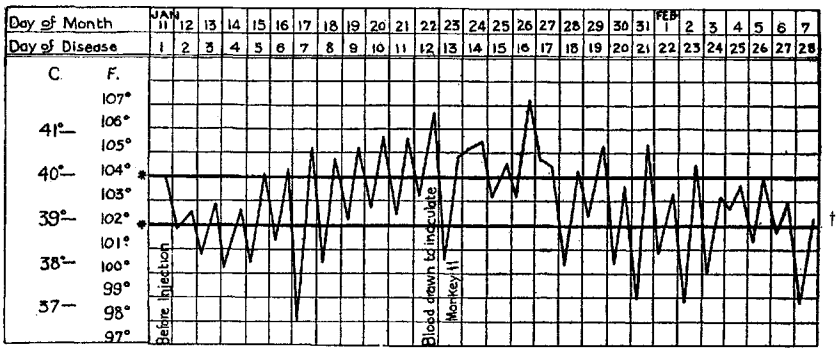
The animal first began to appear sick on the 16th, the second day of fever. On the 17th it made little resistance to manipulation and from this on it appeared dis-

tinctly ill and ate little. It developed no marked diarrhea, although the stools became rather soft. While the temperature became high the animal at no time lost its responsiveness. The conjunctivae were not noticeably reddened, and a distinct eruption could not be identified. After a rather long and severe course, the animal recovered.

Monkey 4, weighing 1,800 gms., received 8 c.c. of serum of the same blood; the serum was obtained by defibrination and centrifugation. This quantity was diluted to 25 c.c. with salt solution, one-half being injected intraperitoneally, the other half subcutaneously. The temperature on successive days was as recorded in curve No. 3.

On the 17th, the first day of distinct fever, the animal, which had hitherto appeared vigorous and healthy, looked sick, unkempt, its hairs stood up, and it "huddled up"

CURVE 2.



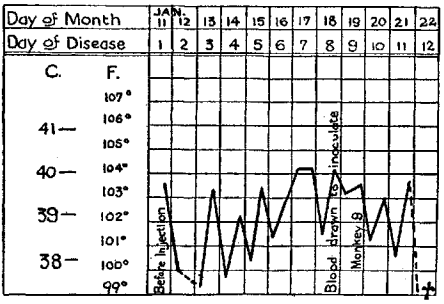
TEMPERATURE OF MONKEY NO. 7 AFTER INOCULATION.

* The heavy horizontal lines indicate the normal limits of P.M. temperatures. The A.M. temperatures should be lower.

† Remained below 103.6° F. until February 21. Death from peritonitis.

even in the sun. This condition continued, food was refused, and emaciation developed. On the 20th a moderate diarrhea appeared and continued until death. On the afternoon of the 22d it became soporose, and died at about 6 o'clock. An eruption which could be referred positively to the infection, or bearing a resemblance to that of typhus fever, could not be identified. An "eruption" which did appear on the skin of the lower chest and the upper portion of the abdominal skin probably was accidental. On the 18th, the second day of fever, the monkey had been bled from the heart, for cultivation and other experiments. A small amount of blood escaped through the skin when the needle was withdrawn, and at autopsy it was found that some subcutaneous hemorrhage had occurred and that the blood had "diffused" posteriorly in the form of a rather narrow band, fol-

CURVE 3.



TEMPERATURE OF MONKEY NO. 4 AFTER INOCULATION.

lowing the median line. The "eruption" was roughly median although it extended about an inch beyond the visible limit of the subcutaneous extravasation. In character, it was at first pink, that of the early rose spot, and seemed to disappear on pressure. It appeared two days after the heart had been punctured and on the fourth day of fever. On the following day and subsequently it became darker, more or less cyanotic in color, and could not be effaced by pressure. The spots were rather ill-defined, and appeared to consist of collections of minute punctiform hemorrhages. A similar condition could not be identified on other parts of the body, and in view of the subcutaneous hemorrhage which complicated the situation, it seems probable that the eruption had its source in the latter rather than as a manifestation of typhus fever.

At the autopsy, the lungs were found of a normal pink color; there were no signs of inflammation. On the visceral pleura, particularly of the left lung, were a number of small, circular, dark-red hemorrhages from 0.5 to 1.5 mm. in diameter. The pleural cavities were normal; the heart normal; no inflammation of the valves or pericardium. The liver was apparently somewhat enlarged, pale, as if fatty, but showed little or no congestion; the lobules were well marked; anterior border distinctly rounded. The spleen was about 1.5 cm. longer than that of Monkey 6, and perhaps a few millimeters broader; was distinctly enlarged, bluish-red in color, and of rather firm consistence; contained no hemorrhages.

The kidneys were perhaps a little enlarged and moderately congested; cortex and pyramids of a homogeneous normal color; striations normal; the cortex had a relation to the medulla of about one to one.

The mucous membrane of the colon was much reddened, and perhaps even hemorrhagic; the colon contained a large amount of glairy mucus but no blood or feces. The mucous membrane of the ileum appeared normal, and the ileum contained nothing but a slightly viscous, yellowish fluid; there was a short intussusception, with no inflammatory or obstructive signs of the parts involved. The duodenum contained bile-stained mucus, the mucosa being normal. The stomach contained some undigested banana and mucus.

The lymphatic nodes everywhere seemed more or less enlarged but were not congested or hemorrhagic. Those of the groin and axilla were almost black from some previous pigmentation.

The meninges showed a good deal of congestion and edema, the fluid being perfectly clear. The cerebral cortex appeared normal. Other parts of the central nervous system were not examined.

Cultures, as in the case of No. 6, remained sterile, including those from the meninges.

As a basis for interpreting these experiments, we have for consideration: the existence of an incubation period which was approximately the same in all three animals, and during which they remained healthy; the occurrence of illness and fever followed by the death of two of the animals; the sudden onset of fever and illness, and the rapid defervescence in the animal which recovered; the negative outcome of cultures; and the more or less negative

findings at autopsy, corresponding with the condition in typhus in man.

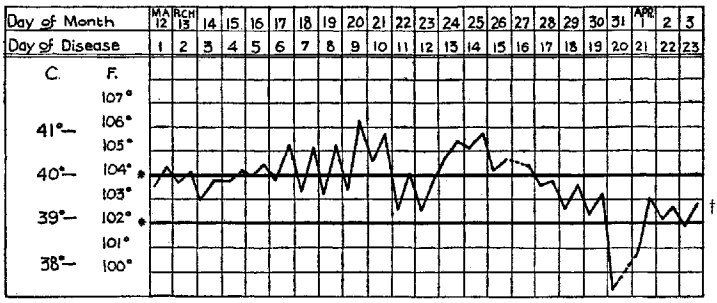
Later investigations have never failed to confirm the results obtained in these early experiments.

Monkey 3 was infected with typhus blood serum. This animal was to all intents and purposes a normal animal, although he had been previously the subject of another experiment (to be described). His temperature curve will be found on p. 67 (curve No. 13).

Monkey 18 was infected with the serum from fresh typhus blood. The temperatures and the details of the inoculation appear on p. 69 (curve No. 15).

Monkey 20, a normal animal, was used to test the virulence of blood employed for other experiments. He thus served as a control for the immunity tests given to Monkeys 1, 3, 13, 25, 24, and 12. All of these animals, together with No. 20, were injected on March 12 with fresh blood taken from a patient (No. 37) in the eighth or ninth day of fever. The blood was defibrinated and diluted with salt solution in the proportions 1 to 2. Each animal received 12 c.c. of the mixture, half subcutaneously

CURVE 4.



TEMPERATURE OF MONKEY NO. 20 AFTER INOCULATION.

* The heavy horizontal lines indicate the normal limits of P.M. temperatures.

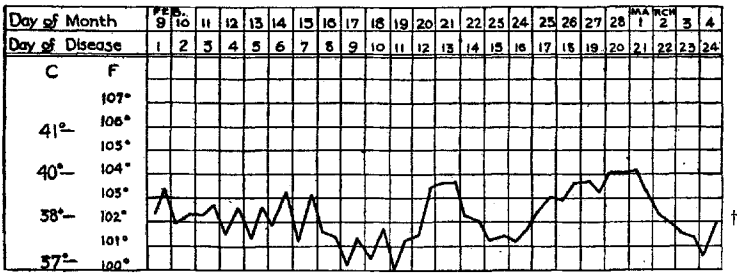
† The temperature of monkey No. 20 had been taken twice daily since February 3 and from that date until March 12 it had remained constantly within the normal limits. During this time the animal was in perfect health.

and half intraperitoneally. The temperature of Monkey 20 on the successive days following the inoculation is plotted on curve No. 4. The course of fever was typical of typhus—an incubation period of five days, a sustained pyrexia of 11 or 12 days, followed by a rapid and complete convalescence. The animal normally ran a rather high evening temperature. Thus on the day of the inoculation 104.3° is recorded, but on this day, in spite of his temperature, he seemed in perfect health. He was well nourished and active, his coat was smooth and glossy, his eyes bright, and his appetite excellent. Quite a different animal was seen on March 21, that is, on the fifth day after the beginning of fever, and from this date until the 27th the monkey was obviously very sick, sitting huddled and unresponsive in his cage, and at times even behaving as if delirious. Broth inoculated with his heart blood on March 25 remained sterile. Recovery was rapid after the subsidence of fever, and by April 9

the animal seemed as well nourished and active as he was before his sickness. He was inoculated again on this date with 4 c.c. of human blood, the virulence of which was controlled by Monkeys 19, 21, and 33. To this second inoculation No. 20 manifested complete immunity, remaining in perfect health until June 16, when observations were discontinued. During this entire period his temperature remained below the limits of possible normal.

Monkey 24 was injected with fresh typhus blood on February 9. After an incubation period of 10 days an elevation of 2° F. is noted (see curve No. 5), and following this date for a period of 10 days the thermal elevation is maintained with the exception of a drop on the 23d and 24th. On the morning of the last day a temperature of 104.1° is recorded, which is at least two degrees higher than the maximum normal limit of *morning* temperatures for the macacus monkey. On the following day

CURVE 5.



TEMPERATURE OF MONKEY NO. 24 AFTER INOCULATION.

† Continued below 102.5° for the following 26 days.

the temperature fell and remained from then on unusually low. In view of the fact that the temperature of this animal before the beginning of the experiment was constantly lower than the average, the thermal elevation, coming as it does 10 days after inoculation and persisting for 10 days, should probably be interpreted as typhus. Cases of mild and abortive typhus occur in man, particularly in children, and the animal in question was one of the youngest of our collection. A bad diarrhea developed about the time of the inoculation, which grew progressively worse. On the 15th he was very weak. On the 21st emaciation and weakness were extreme. On the 25th the conjunctivae were inflamed. The animal was reinoculated on March 12 with blood, the virulence of which was controlled by the injection of monkey No. 20. He resisted this immunity test without the slightest rise in temperature, but continued to grow progressively weaker and died on March 30 as the result of cachexia caused by a persistent diarrhea.

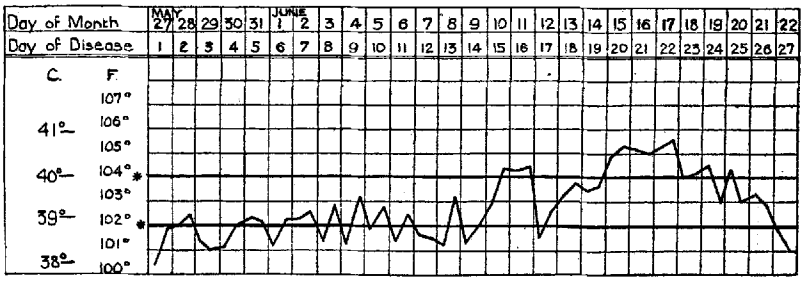
Monkey 43 was the subject of an experiment on the protective power of the serum of convalescents. The serum was found not to protect, and the monkey that was injected with a mixture of serum and virus succumbed 14 days later to a typical course of typhus fever. His temperature is plotted on curve No. 6.

Monkey 44 was inoculated on May 27 to control the virulence of blood being used for other experiments. The animal received 3.5 c.c. of defibrinated blood diluted just before injection with twice its volume of physiologic salt solution. The injection was intraperitoneal. The blood used was drawn at 10:00 A.M. from patient

No. 58 at the general hospital, who was in the seventh or eighth day of a typical typhus fever. The injection was made at 2:00 P.M. The temperatures of the animal appear on curve No. 7.

The reaction exhibited by Monkey 44 was in every respect typical of the course of typhus fever in the macacus. On May 30 the animal had diarrhea and was unusu-

CURVE 6.

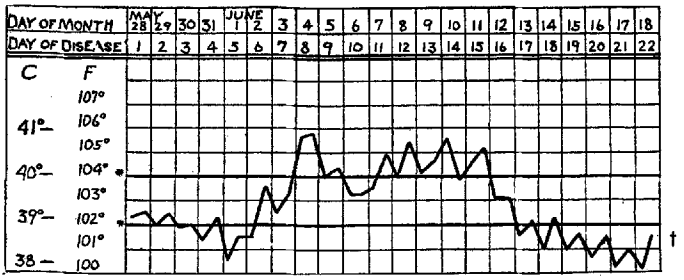


TEMPERATURE OF MONKEY NO. 43 AFTER INOCULATION.

* The heavy horizontal lines indicate the normal limits of P.M. temperatures.

ally irritable. A leukocyte count made on June 1 showed 22,900. By June 5 he was very sick. Broth inoculated from the heart blood on the 5th remained sterile. Smears from the blood revealed the bipolar bacillus described by Ricketts and myself in a previous paper. On this day the leukocytosis equalled 19,650. On June 7 the monkey was still very sick. He sat huddled in his cage, showed little interest in the arrival of his food, and ate nothing. On the 9th he was obviously thinner, and his coat seemed unusually dry and ruffled. The conjunctivae were inflamed. Broth cultures inoculated on the 13th remained sterile. Convalescence was complete and rapid.

CURVE 7.



TEMPERATURE OF MONKEY NO. 44 AFTER INOCULATION.

* The heavy lines indicate the normal limits of P.M. temperatures of the *Macacus rhesus* monkey. A.M. temperatures may be normally much lower.

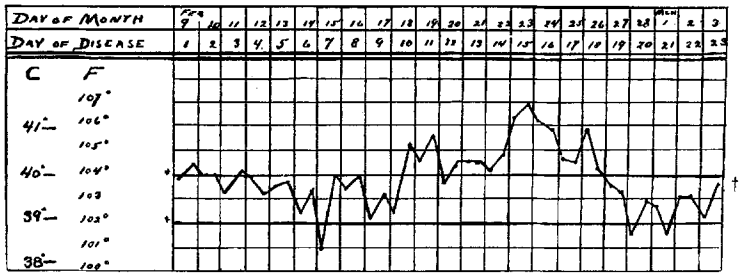
† Remained below 102° until June 21, when observations were discontinued.

THE MINIMUM INFECTIVE DOSE OF TYPHUS BLOOD.

Experiments designed to determine the minimum dose of virulent typhus blood required to infect the macacus monkey were undertaken.

Monkey 25 was inoculated intraperitoneally with 1 c.c. of defibrinated blood obtained from a typhus patient (No. 27) in the eleventh day of fever. The virus was diluted with 5 c.c. of physiologic salt solution before injection. After an incubation period of nine days No. 25 developed a high fever which continued for nine days. On February 21, the first day of fever, the animal began to appear sick, and the following day he was very dejected, sitting huddled in one corner of his cage, shivering, weak, and offering little or no resistance to manipulation. This condition continued until the end of his sickness. His recovery was rapid and complete, and he resisted successfully a subsequent immunity test. The temperatures of this animal during his sickness are recorded in curve No. 8.

CURVE 8.



TEMPERATURE OF MONKEY NO. 25 AFTER INOCULATION.

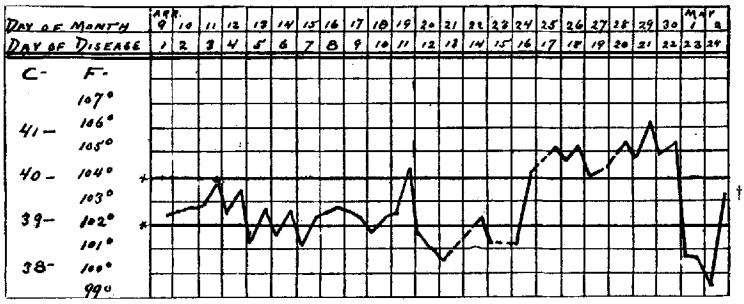
* The heavy horizontal lines at 102° and 104° indicate the normal limits of variation of P.M. temperatures of the species *Macacus rhesus*. The A.M. temperatures may be lower.

† Remained below 103.9° F., 40° C., as long as under observation.

No. 25 was undoubtedly infected by this inoculation of 1 c.c. of typhus blood.

On February 18 Monkey 21 received an intraperitoneal injection of 0.2 c.c. of virulent typhus blood obtained six hours previously from a patient (No. 30) in the sixth day of a typical typhus fever. The blood was defibrinated immediately after it was drawn and was diluted before injection with 2 c.c. of physiologic salt solution. Monkey 21 was apparently not affected by this dose of virus and continued in perfect

CURVE 9.



TEMPERATURE OF MONKEY NO. 21 AFTER SECOND INOCULATION.

* The heavy horizontal lines at 102° and 104° indicate the normal limits of variation of the P.M. temperatures of monkeys of the species *Macacus rhesus*. The A.M. temperatures may be much lower.

† Remained below 103° F., 39.4° C., for the following 30 days.

health and without the slightest elevation of temperature for the following 30 days. A control monkey (No. 18) which had been inoculated with larger quantities of the same virus developed a typical typhus.

No. 21 was later (on April 8) given an immunity test which consisted of the intraperitoneal injection of 3.5 c.c. of virulent typhus blood from Patient 48. To this test he proved susceptible and after an incubation period of 15 days developed a high fever and a typical course of typhus (see curve No. 9).

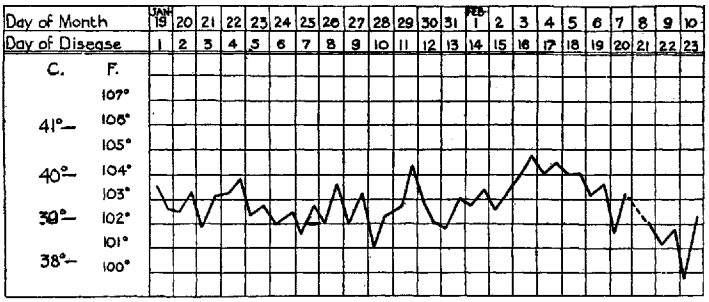
These experiments seem to indicate that the minimum infective dose of blood for the monkey lies between 0.2 c.c. and 1 c.c.

TRANSMISSION FROM MONKEY TO MONKEY BY INJECTION.

Attempts were made to maintain the infection in the monkey by passage from animal to animal.

Monkey 9 was injected intraperitoneally with 5 c.c. of fresh blood drawn from the heart of Monkey 4 on January 18, 1910, that is on the second day of the fever of No. 4 (see curve No. 3). The blood was not diluted. After an incubation period

CURVE 10.



TEMPERATURE OF MONKEY NO. 9 AFTER INOCULATION WITH BLOOD FROM MONKEY NO. 4.

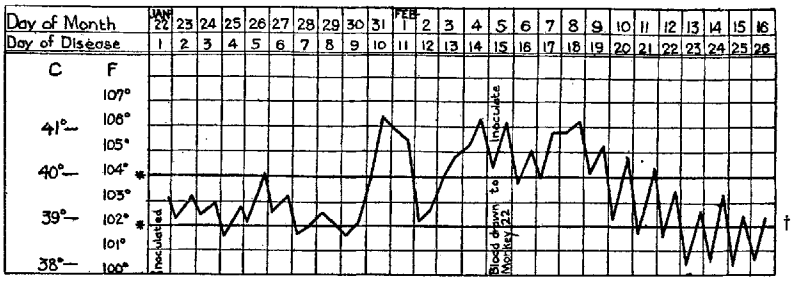
of 10 days No. 9 developed a fever of slight severity which lasted for 9 or 10 days. During this period he was noticeably sick. An immunity test was given 12 days after his recovery. This consisted in the injection of fresh blood from a human typhus patient and was controlled by the reaction obtained with the same virus in Monkey 18 (see curve No. 15). He proved absolutely immune, the temperature remaining below 102.9° F. while under observation.

Monkey 11 was inoculated on January 22 with 5 c.c. of the heart blood of Monkey 7, drawn on the fourth day of the fever of this animal. The blood was diluted with 10 c.c. of salt solution and injected partly intraperitoneally and partly subcutaneously. The change of temperature of the animal taken on successive days following the injection appears on curve No. 11.

On the day of the inoculation Monkey 11 was well and active. By January 31 it was noticed that he was quieter than usual. His face seemed somewhat mottled and was quite red. By February 4 the animal was very sick. Broth inoculated on this date remained sterile. On the 5th 7 c.c. of blood was drawn from the heart,

5 c.c. of which was used to inoculate Monkey 22. Broth cultures made with the remainder remained sterile. On the 7th the animal was still more depressed, sitting huddled in the cage, the coat ruffled and dry. On the 7th, 8th, and 9th he was tied down and lice of Group 9 were fed on his abdominal skin. These lice were employed in experiments detailed a little later. The duration of the fever of Monkey

CURVE 11.



TEMPERATURE OF MONKEY NO. 11 AFTER INOCULATION WITH THE HEART BLOOD OF MONKEY NO. 7.

* The heavy horizontal lines indicate the normal limits of P.M. temperatures.

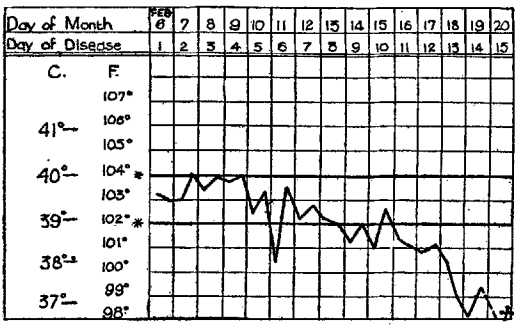
† Remained below 103.4° F. until March 9, when animal was used for an experiment on spotted fever.

11 was 12 days. By February 1 he was recovering rapidly and later resisted an inoculation of human blood which caused in a control (Monkey 21) a typical course of fever. We may therefore conclude that Monkey 11 had been infected with typhus by the injection of blood from Monkey 4.

Monkey 22, inoculated with 5 c.c. of the blood drawn from the heart of No. 11 on February 5, namely, on the sixth day of the fever of that animal, exhibited a peculiar reaction.

On the date of inoculation he appeared to be a perfectly normal animal, strong, healthy, and well nourished, and for the first five days following the injection he seemed to be in good health although his temperature was somewhat elevated, but after this date he sickened rapidly, losing weight progressively, eating poorly. By the 15th his fur was ruffled and dry, he sat huddled and inattentive in his cage, and on the 17th he was so weak that he could hardly support himself on his legs. Now for the first time he had a little diarrhea. His weakness increased and on the morning of the 20th he was found dead, yet during all this time he had no fever, his temperature falling gradually to below normal (see curve No. 12).

CURVE 12.



TEMPERATURE OF MONKEY NO. 22 AFTER INOCULATION WITH BLOOD OF MONKEY NO. 11.

* The heavy horizontal lines indicate the normal limits of P.M. temperatures.

The autopsy findings in this monkey were largely negative, revealing nothing that would account for his death. The body was greatly emaciated. Axillary and inguinal lymph glands were rather large and congested. The abdominal cavity was free from fluid or sign of inflammation. The thoracic cavity contained no fluid, and the lungs and pleura were perfectly normal. The pericardial cavity held a normal amount of clear amber fluid. The heart was unaltered. The liver was enlarged and showed marked fatty changes. The spleen was of normal size, color, and consistency. The kidneys were markedly icteric, somewhat congested, and of normal size. The stomach was distended with gas, but contained no food. The intestines were empty except for bile-stained mucus. Throughout the entire length of the alimentary canal there was no sign of inflammation. The meninges contained a rather large amount of clear fluid, the brain bulging, but there was no cellular exudate. The superficial vessels of the brain were moderately hyperemic. Flasks containing 40 c.c. each of broth were inoculated with 2 c.c. of heart blood drawn at autopsy, and remained sterile. Cultures from the meninges showed a few colonies of staphylococci. The technic of opening the head was crude, however, and as there was no macroscopic evidence of meningitis these growths were judged to be contaminations.

There seems to be nothing to account for the death of Monkey 22 except his injection with typhus blood, and the autopsy rather supports such an interpretation. Afebrile cases of typhus are not uncommon in the literature, and I have myself observed such cases among the patients at the General Hospital of Mexico. One patient who entered the hospital on May 27 in a delirium ran the following evening temperatures for the next nine days: 98.0°, 98.2°, 97.4°, 98.0°, 96.8°, 97.2°, 97.4°, 96.8°, 97.2° F. Death occurred on the following day. The autopsy revealed nothing which could point to any other cause of death than typhus, and the eruption observed during the course of the disease was typical.

In view of the absence of any contrary evidence at the autopsy of Monkey 22 I am inclined to believe that the animal died of typhus fever, and that the atypical course of the disease in his case

is to be attributed to an extreme susceptibility. Unfortunately no attempt was made to continue the passage.

INFECTIVITY OF BLOOD SERUM AND THE FILTERABILITY OF THE VIRUS.

From the above experiments it is evident that the virus of typhus must exist in the blood, and the next question to present itself was whether the virus was simply an intracellular organism or whether it existed free in the blood serum, that is whether blood serum separated from the blood cells would prove infectious. It also became desirable to determine the approximate size of the micro-organism, and these two purposes were served by the following group of experiments.

Blood serum separated by centrifugation was found to be infectious, nearly if not quite as much so as the whole blood, and it was determined that it lost its infectivity on being filtered through a stone filter of fine porosity, a Berkefeld candle.

In the investigation of diseases of unknown etiology filtration experiments of this kind, designed to throw light on the relative size of unknown micro-organisms, have come to be recognized as routine procedures. The filters used are of different porosities. Porcelain filters, known under the names of Chamberland, Reichel, and Pukall, are of rather unequal porosity and will allow particles of about 30 microns to pass, as has been determined by experimentation with suspensions of particles of known size, as, for instance, colloidal gold solutions. The Berkefeld filters used in our experiments are made from siliceous earth and have been found to hold back even the smallest of the known visible bacteria. By the use of this filter one can therefore determine whether or not an unknown virus is of sufficient size to permit of its observation with an oil immersion lens. If it is ultramicroscopic in size it is likely to pass through the pores of the filter and the collected filtrate will still be infectious. If on the other hand it is stopped by the filter it is reasonable to infer that it is large enough to permit of microscopic observation. Accordingly the following experiments were made:

Of the same blood used to inoculate Monkeys 7, 6, and 5, 34 c.c. were centrifugated until the corpuscles occupied approximately the lower three-fifths of the column. The overlying serum was drawn off and replaced by an equal amount of sterile salt solution. The corpuscles were thoroughly mixed or washed with the latter and again centrifugated moderately, after which the overlying fluid was added to the first portion. This was repeated again and the three fluid portions then combined. It seemed probable that through this procedure one might obtain a larger quantity of micro-organisms in the fluid than by resorting to a single more vigorous centrifugation. This seemed better also than to attempt to filter the uncentrifugated blood, which indeed is an almost impossible task with moderate pressures.

It seems sufficiently accurate to consider that the defibrinated blood consisted of about equal parts of serum and corpuscles and that we obtained the equivalent of about 17 c.c. of serum by this washing process.

For the purpose of filtration the serum was diluted to 51 c.c. by means of salt solution, and this quantity was divided into two equal portions, one to be filtered and the other to be injected without filtration.

The first portion was passed through a small Berkefeld candle, and with the threefold dilution it filtered readily. The filter was washed by passing through it an additional 5 c.c. of salt solution, this filtrate being added to the first.

The interval between the drawing of the blood from the patient and the injections was from six to seven hours, as in the preceding experiments.

The total quantity of each portion was approximately 25 c.c., of which one-half was injected intraperitoneally, the other half subcutaneously, after suitable preparation of the skin.

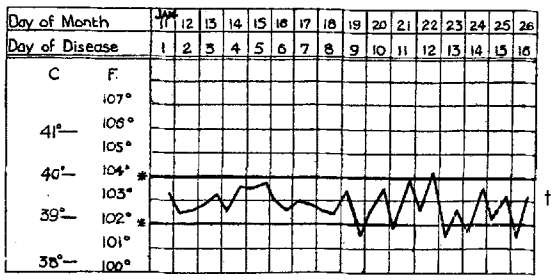
The result of the injection of the unfiltered serum into Monkey 4 was given in an earlier part of this paper, it being our conclusion that the animal became infected with and died of typhus fever.

No. 3, which received the filtered serum, exhibited on successive days the temperatures as recorded on curve No. 13.

In spite of rather high morning temperatures, the animal remained in apparently perfect health, which is in distinct contrast with the course shown by No. 4 (see curve No. 3). As stated previously, the latter, after an incubation period of about six days, developed fever, grew sick, and died eleven days after inoculation, with findings which are in harmony with those of typhus fever.

We may therefore conclude that the virus did not pass through the filter employed, or if it did, that it did not pass through in a quantity sufficient to produce recognizable infection.

CURVE 13.



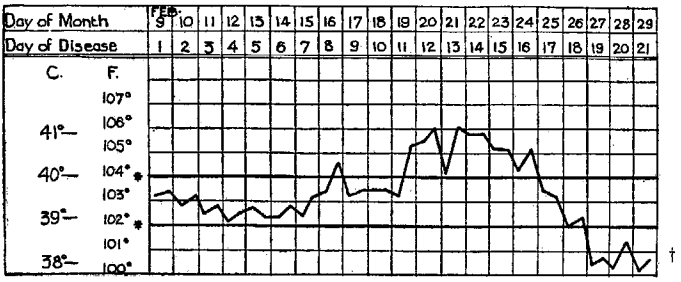
TEMPERATURE OF MONKEY NO. 3 AFTER INOCULATION OF FILTERED SERUM.

*The heavy horizontal lines indicate the normal limits of P.M. temperatures.

†Remained below 103.6° F. until immunity test was made on February 9.

The immunity test confirmed this conclusion. This test, which was given about one month following the "filtration experiment," consisted of the intraperitoneal injection of 7 c.c. of diluted defibrinated blood drawn from a human patient on the tenth or eleventh day of his fever. No. 3, which had tolerated the filtered serum without visible disturbance, showed a course of high fever lasting 11 days, and preceded by an incubation period of seven days, as the result of the immunity test (see curve No. 14).

CURVE 14.



TEMPERATURE OF MONKEY NO. 3 AFTER IMMUNITY TEST.

* The heavy horizontal lines indicate the normal range of P.M. temperatures.
† Remained below 103.6° F. as long as under observation.

Anderson and Goldberger subsequently reported a similar result in a similar experiment.

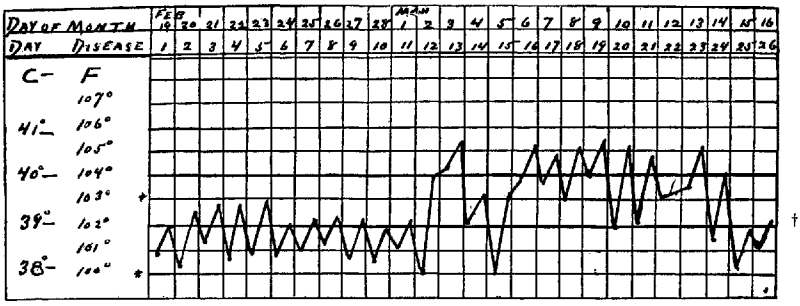
Our experiment was repeated in about the same way, and in the main the earlier results were corroborated. The causal organism of typhus does not pass through the filter in sufficient numbers to provoke a febrile reaction in the monkey.

Two normal monkeys (Nos. 18 and 19) were inoculated with serum from the blood of a typhus patient (No. 30), the former receiving the pure serum, the latter a portion of the same which had previously passed through a Berkefeld candle. The dose of serum in each case was 7.5 c.c., diluted with 22.5 c.c. of physiologic salt solution, one-half of the entire volume being injected subcutaneously and the remainder intraperitoneally. The accompanying temperature curves (Nos. 15 and 16) of the two monkeys indicate the result: No. 18 ran a severe course of typhus, while No. 19 who had received the filtered serum showed at no time during the following 49 days any indication of discomfort.

Thus far the results are the same as those obtained in the previous experiment, but on April 8 an immunity test, consisting of the injection of 4 c.c. of virulent typhus blood, was given to

both of these animals. No. 18 proved immune, as was to be expected, but, whereas before the animal which had received the injection of filtered serum had proved *susceptible* to a subsequent immunity test, No. 19 was found to be immune. The blood used for the test of Nos. 18 and 19 was obtained from a patient (No. 48) who at the time was in the eighth day of fever. The eruption

CURVE 15.

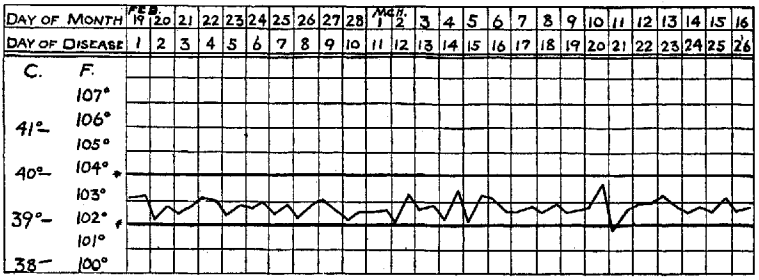


TEMPERATURE OF MONKEY NO. 18 AFTER INOCULATION OF UNFILTERED SERUM.

* Normal limits of variation of temperature of monkey No. 18 as long as under observation indicated by heavy horizontal lines.

† Continued below 103° F., 39.4° C., as long as under observation.

CURVE 16.



TEMPERATURE OF MONKEY NO. 19 AFTER INOCULATION OF FILTERED SERUM.

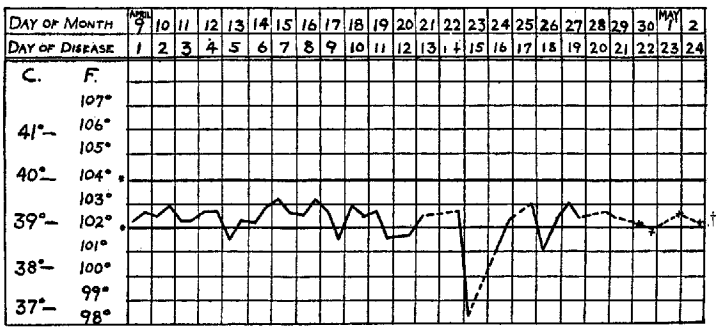
* The heavy horizontal lines at 102° and 104° indicate the normal limits of variation of the P.M. temperatures of monkeys of the species *Macacus rhesus*. A.M. temperatures may be lower.

was profuse and petechial and the subsequent history entirely characteristic of typhus. Other monkeys inoculated with this same material, e.g., monkey No. 21, whose temperature curve is given above, and No. 33, whose history follows, reacted in the usual manner with a distinct febrile reaction.

The refractiveness of monkey No. 19 to this inoculation of

blood may be explained by one or more of several different hypotheses: The animal may have been naturally immune to typhus. If such is the case, however, he is the first normal monkey with which we have had to deal that has shown such an absolute immunity when inoculated with over 1 c.c. of virulent blood. A second possibility is that the animal was immunized by the filtered serum. The filtrations in the two experiments were probably not identical: thus different filters were used and, although both were new and of the same pattern and size, individual filters are subject to variations in porosity; and again the suction pressure was not controlled. Hence it is quite possible that in the second experiment substances

CURVE 17.



TEMPERATURE OF MONKEY NO. 19 AFTER IMMUNITY TEST.

* The heavy horizontal lines at 102° and 104° indicate the normal limits of P.M. temperatures of the *Macacus rhesus* monkey. A.M. temperatures may be lower.

† Remained below 103° F., 39.4° C., for the following 44 days.

filtered through which on the previous occasion had been held back, and that these substances produced the immunization of No. 19.

Such immunization could have been accomplished either by micro-organisms sufficiently small to pass the filter, by fragments of organisms, or by toxins. The serum used on the two occasions came from different patients and these patients were not in the same stage of the disease at the time their blood was drawn. It is possible that the serum of the one was richer in micro-organisms than that of the other, this difference alone accounting for the diverse results obtained in the two experiments. Or the microbe of typhus may pass through several different stages of growth in

a pleomorphic development and, whereas the first serum contained only larger, non-filterable forms, the second had a proportion of minute spores or segments.

On the other hand it is conceivable that certain toxins or fragments of micro-organisms passed the filter and that the amount of these in the first case was sufficient to immunize. The subject deserves more attention since a means of vaccination is suggested which might prove of practical value, and I regret that circumstances made it impossible for me to repeat these particular experiments.[1]

EXPERIMENTAL STUDIES ON INSECT TRANSMISSION.

This investigation included a series of researches bearing on the relation of the body louse to Mexican typhus fever. A preliminary report on the subject appeared in *Jour. Am. Med. Assn.*, April 16, 1910, and at that time in commenting upon the results obtained, emphasis was laid on the following considerations:

The first of these relates to the method of diagnosis of typhus fever in the monkey. As stated, every normal macacus inoculated with a dose of typhus blood equaling 1 c.c. or more has reacted with a well marked course of fever and characteristic clinical symptoms. Furthermore every monkey who has once had typhus whether the attack was severe or mild has proved immune to a later inoculation or immunity test. Reference to the protocols of the experiments with direct inoculation of typhus blood given above will reveal how uniformly all of these animals resisted their immunity tests. It follows therefore that the immunity test constitutes a reliable and accurate method of determining whether or not a course of fever was due to infection with typhus. Such a test consists in a second injection of virulent blood after the subsidence of fever. The virulence of the blood must of course be controlled by the injection of an equal quantity of the same blood into a normal monkey.

The degree of susceptibility of the monkey is another important consideration. As I have shown the macacus is relatively insus-

[1] Nicolle in his latest paper reports that in one instance the serum obtained from infected blood by allowing the clot to separate spontaneously proved immunizing for a *Macacus inuus*. Although his other experiments were negative, he argues that this one positive result is sufficient to demonstrate the filterability of the typhus microbe. This conclusion does not seem to me to be justifiable.

ceptible to typhus and can only be infected by the injection of a large quantity of virus. Also it appears, from the experience of Nicolle, Anderson and Goldberger, and McCampbell, that the infection dies out in the monkey and cannot be maintained by passage.[1]

From these considerations it might appear a priori that the monkey is not sufficiently susceptible for satisfactory results from insect experiments. The question arises, however, as to whether he may not react to the bites of infected insects by an infection of a mild type which will not be accompanied by a high fever, but which might nevertheless be recognized by later giving the animal an immunity test. If he proves immune to a dose of blood of known infectiousness it is to be presumed that he owes his immunity to his previous exposure to the insects.[2]

Such has indeed been our experience. In none of our insect experiments were we able to provoke in the monkey a very characteristic febrile reaction, although slight fever was observed in nearly every case, but when a monkey is exposed to the bites of infected lice he is thereby immunized to typhus fever so that he proves refractive when later injected with virulent blood. The same result has been obtained repeatedly. The animals show some slight indispostion and an insignificant thermal elevation after their exposure to the lice, an abortive attack too mild to permit of positive diagnosis, but in almost all cases they are later found to be immune. Therefore I believe that it may be concluded that the monkeys are infected by the bites of the lice.

Thirteen monkeys have been made the subjects of experiments as to louse transmission. Of these eight were subjected to the bite of lice previously infected by feedings on man (typhus patients). All save three were infected and the results of two of these unsuc-

[1] Nicolle in subsequent experiments, which are reported in a recent publication of the *Annals of the Pasteur Institute* (Vol. XXIV, No. 1, January 25, 1911), has apparently accomplished passage through nine generations. In this series five species of ape were used, three chimpanzees, three sinicus, one cynomologus, one inuus, a second sinicus, and another cynomologus. No diminution in the activity of the virus was observed.

[2] The possibility of the occurrence of mild attacks of infectious diseases which establish immunity cannot be denied, as has been shown in experiments on guinea-pigs with Rocky Mountain spotted fever. In the case of two of our typhus monkeys inoculated by the intraperitoneal injection of blood only a very slight elevation of temperature was obtained, a reaction which we were unwilling to diagnose as typhu fever before we had given immunity tests. In both cases, however (Monkeys 9 and 24), when such tests were given the animals were found to be refractive, while controls (Monkeys 18 and 20) exhibited severe fever.

cessful attempts suggest only that certain biological conditions were not observed, as will be discussed later; the third failure seemed to be due to the use of too few insects. In one case, that of Monkey 39, a decided febrile reaction followed the exposure of the animal to the lice. Two monkeys have been infected by lice which had fed previously on infected monkeys, and two scarification experiments, performed with the intestinal contents of infected lice, resulted in positive transmission.

Monkey 39 was infected by 17 lice, while a negative result was obtained with 10 lice on Monkey 37, and it therefore appears that the minimum number of lice required to infect monkeys lies somewhere between these two figures. The failure to infect with a smaller number may be due to either or both of two possibilities: first, that the monkey is relatively insusceptible as compared to man, and, second, that when any given group of lice are fed on a typhus patient only a small fraction are thereby rendered "infectious," i.e., able to infect a second host. It is probable that if experiments on man could be performed they would reveal that one truly infected louse could alone give the disease to man, and I realize that our results may be criticized on the grounds that the use of such a large number of lice in these experiments does not reproduce the natural condition of infection in man, the transmission obtained being purely mechanical and accidental. This objection is met, first, by an experiment described below which indicates that the young of infected lice although themselves never directly exposed to infection are able to immunize, i.e., infect a second host, and, second, by the results of certain investigations which seem to show that reproduction of the virus actually occurs in the body of the louse. Thus in one of the scarification experiments, the protocols of which follow, a monkey was immunized by the subcutaneous inoculation of six lice which had been infected by three full feedings on typhus patients. The total amount of blood ingested by each louse during these three feedings could not, on the most liberal estimate, have exceeded 0.01 c.c., the total amount of blood ingested by the six lice being, therefore, well within 0.06 c.c., an amount insufficient, even in the case of the most infectious blood, to cause any reaction on the part of the

monkey. In the experiment reported above 0.2 c.c. of blood produced no effect on Monkey 21. Even the 17 lice that infected Monkey 39 would contain in their entire bodies less than this amount of material and the conclusion that the micro-organism actually proliferates in the body of the louse seems justified.

In these experiments the greatest possible precautions were taken to avoid accidental infection of our animals. Monkeys were imported from districts free from typhus and by means of baths and frequent application of insect powder were kept free from all body parasites. Each infected animal was isolated in a separate cage, which was cleaned frequently, and, in order to control the possibility of accidental contagion, normal animals were confined in cages with the diseased. The temperatures of these controls were taken twice daily, and in no case did any one of them develop typhus. All monkeys which were thus exposed proved susceptible to later inoculations, the result tending to disprove contagiousness.

THE TRANSMISSION OF TYPHUS FROM MAN TO MONKEY BY THE BITES OF INFECTED LICE.

Group 3, *Pediculus vestimenti*, was infected as follows: January 5 they fed for thirty minutes on E.S., on the tenth or eleventh day of his sickness;[1] January 6, on J.V., tenth day of sickness; January 7, on C.T., ninth day of sickness; January 8, on the same patient.

On January 9, 45 lice were alive, and 40 fed on Monkey 1 for about an hour; January 10, 334 were alive, and 23 fed on the monkey; January 11 they were not fed; January 12, 19 fed; January 13, 13 fed; January 14, 11 fed; January 15, 9 fed. The feedings were not carried further.

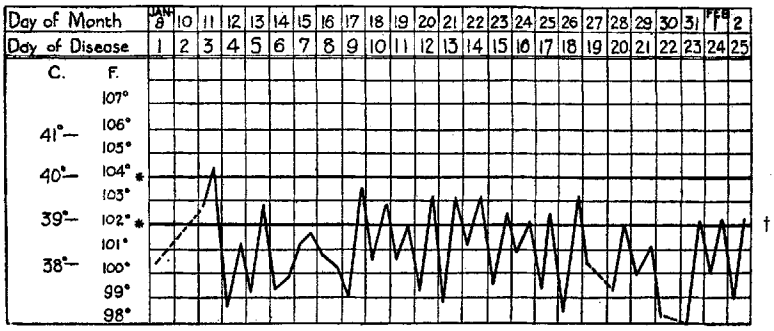
The temperature of the monkey on successive days was as shown in curve No. 18.

It will be noted that in the afternoons of January 17, 20, 21, and 22, the temperature lay between 103.2° and 103.6°, the first rise being eight days after the lice began to feed, or having the 20th in mind, the interval was 10 days. Inasmuch as the animal's temperature was constantly below 102.5° for a period of 31 days later, it is not improbable that the slight elevation referred to represented a mild infection, although no other signs were apparent.

[1] The technic employed in feeding this and nearly all other groups of lice was the following: The anterior cubital skin of the patient's arm, or the abdominal skin of the monkey, in some cases the more vascular face of the monkey, was shaved, cleaned, and dried. The lice lived between feedings in a pill box or test tube which was securely closed. From this receptacle they were taken one by one and placed on the host. They seldom refused to attach themselves promptly to the skin, and, once attached, a large number (50 to 100) could be watched at one time. While the insects fed, the peristalsis of the sucking organ and the stomach gradually filling with blood could be distinctly seen. At the end of an hour or less many would be satisfied and as they detached themselves from the skin they were removed and placed again in confinement. After careful trial of this and other methods, such as keeping the lice beneath inverted bottles, we decided that the danger of losing infected lice was less by this technic than by any other. The lice were carefully counted before and after feeding.

The belief that the animal had suffered from typhus was corroborated by an immunity test consisting of 7 c.c. of defibrinated blood from Patient 27, given February 8. For 19 days thereafter, the morning temperature lay between 99.0° and 102.0°, and in the afternoon between 101.5° and 102.8° (see curve No. 19). This immunity test was controlled by inoculations of 4 c.c. of the same blood[1] into No. 3, and 1 c.c. into No. 25.

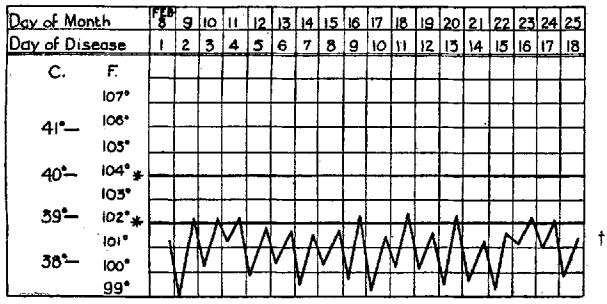
CURVE 18.



TEMPERATURE OF MONKEY NO. 1 AFTER BEING BITTEN BY INFECTED LICE.

* The heavy horizontal lines indicate the normal limits of P.M. temperatures.
† Did not rise above 102.4° F. thereafter.

CURVE 19.



TEMPERATURE OF MONKEY NO. 1 AFTER IMMUNITY TEST.

* The heavy horizontal lines indicate the normal limits of P.M. temperatures.
† Remained low while under observation.

No. 3, after an incubation period of seven days, and No. 25, of nine days, developed fever, which in both animals lasted for ten days, going as high as 106° in the former and 106.8° in the latter (see curves No. 14 and 8).

The immunity of Monkey No. 2 was again tested a month later, March 11, with the same result, whereas Control 20, after an incubation period of five or six days, passed through the usual course of high fever. The first immunity test, however, is

[1] No. 3 had been injected previously with filtered serum without becoming infected; hence this injection constituted an immunity test for No. 3.

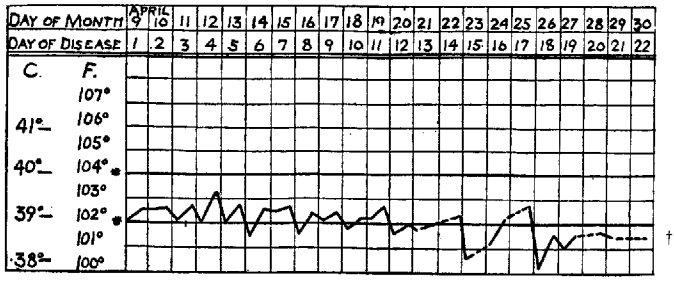
the one which indicates, and it would seem conclusively, that No. 1 was infected by the lice.

Group 11 (*Pediculus vestimenti*) was infected by two full feedings on typhus patient (No. 30) in the seventh and eighth days of his sickness.

On February 21, the day following the last feeding of the group on the infected host, 50 lice were alive and 37 fed on the shaved face of the normal *Macacus rhesus* (Monkey 28) for about one hour. February 22, 45 were alive and 29 or 30 fed on the monkey; February 23, 37 remained alive and 30 fed; February 24, 25 fed; February 25, 23 fed; February 26, 12 fed.

Monkey 28 remained to all appearances in perfect health during the following three weeks. On one day only, March 15, 10 days after the first feeding of the lice, did his temperature rise above 103° F. (39.4° C.), and the temperature of 103.4° F. (39.7° C.) noted on this occasion is well within the normal afternoon variation of the monkey.

CURVE 20.



TEMPERATURE OF MONKEY NO. 28 AFTER IMMUNITY TEST.

* The heavy horizontal lines at 102° and 104° indicate the normal limits of the P.M. temperatures of monkeys of the species *Macacus rhesus*. A.M. temperatures may be lower.

† Remained below 103° F., 39.4° C., for the following 46 days.

On April 8, nearly a month later, he was given an immunity test consisting of the injection of 4 c.c. of blood from a typhus patient (No. 48), recently drawn and defibrinated. To this injection he proved absolutely refractive, continuing in excellent health until June 22, when observations were discontinued. During the entire period his temperature never mounted above 103° F. (39.4° C.), although controls inoculated with the same material developed typhus of moderate severity (see curve No. 20).

This resistance to the immunity test seems to indicate that Monkey 28 was infected by the lice of Group 11.

TRANSMISSION OF TYPHUS TO THE MONKEY BY LICE TAKEN FROM THE GARMENTS OF TYPHUS PATIENTS.

Lice (*Pediculus vestimenti*) were collected on the morning of March 4 from the garments of patient No. 34 on his entrance into the typhus ward of the general hospital. The patient could not tell how long he had been ill, but from his eruption appeared to

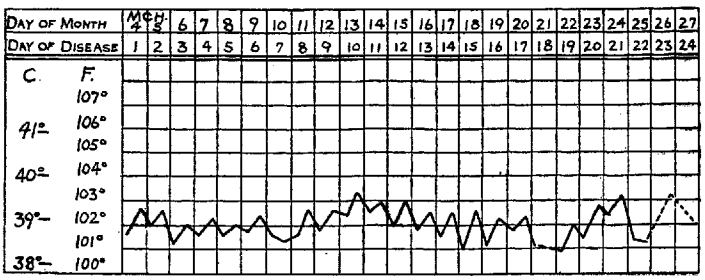
be in the eighth or ninth day of his sickness. He subsequently completed a typical typhus course of moderate severity.

The monkey used for this experiment (No. 17) had been the subject a short time before of a similar experiment, but on that occasion the lice placed upon him apparently all died without feeding. The animal had been washed with green soap, and enough of the soap seems to have remained on the skin to kill the lice. In the second attempt he was clothed in a heavy canvas jacket, which contained a plaited lining of soft wool. The adult lice were placed between the jacket and the skin and the animal confined in a "louse-proof" cage, a cage that had been previously enveloped in muslin to prevent the lice from being forcibly thrown out and that was placed on a square piece of oil-cloth bordered by a strip of eight-inch sticky fly-paper. The method in feeding the lice followed on this occasion was designed for the purpose of raising young lice. In this we were only partly successful.

The lice were placed on the monkey on the afternoon of March 4. On March 8 the jacket was removed and examined; only 12 living lice and 13 dead ones were to be seen, the remainder having probably died and fallen to the bottom of the cage. The live lice had all gorged themselves with blood. Some 200 eggs were also observed, and the jacket was replaced on the animal. On the 14th it was again examined and found to contain no adults, but about a dozen young lice of the second generation. All of these were gorged with blood.

The temperature of the monkey after the first exposure to the lice is given in curve No. 21. It will be noted that a very slight elevation of temperature occurs between March 12 and 15, following an incubation period of nine days since the first exposure of the animal to infection. On March 13 the animal seemed unusually irritable, but at no time was he weaker than usual or otherwise indisposed.

CURVE 21.

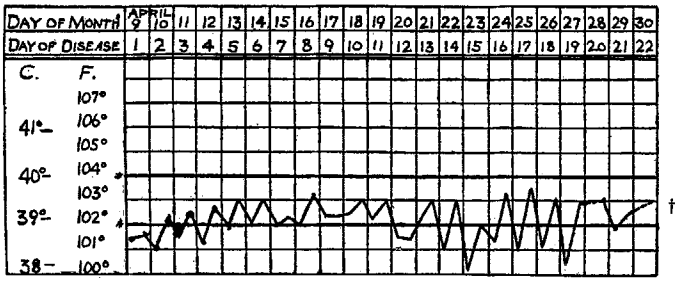


TEMPERATURE OF MONKEY NO. 17 AFTER BEING BITTEN BY LICE TAKEN FROM CLOTHES OF TYPHUS PATIENTS.

† Remained below 103° F., 39.4° C., for the following 6 days, when observation was discontinued.

On April 8, one month later, Monkey 17 was given an immunity test consisting of 4 c.c. of typhus blood from Patient 48. He resisted the inoculation absolutely, his temperature remaining normal for the following two months. Curve No. 22 records his temperature for the 22 days succeeding his immunity test. Only on two days, April 24 and 25, does the curve rise above 103° F. (39.4° C.), and the slight elevation 103.3° F. (39.6° C.) is not above normal for monkeys. The controls, Monkeys 21 and 33, inoculated with the same blood, ran fevers lasting from six to 10 days and reaching elevations of 106.3° F. (41.3° C.) and 104.9° F. (40.5° C.) respectively.

CURVE 22.



TEMPERATURE OF MONKEY NO. 17 AFTER IMMUNITY TEST.

* The heavy horizontal lines at 102° and 104° indicate the normal limits of the P.M. temperatures of monkeys of the species *Macacus rhesus*. A.M. temperatures may be lower.

† Remained below 103° F., 39.4° C., for the following 46 days.

TRANSMISSION OF TYPHUS FROM MONKEY TO MONKEY BY LICE.

Monkey 7 was infected by the injection of blood from man, as described above.

Group 5, *Pediculus vestimenti*, was infected by three feedings on Monkey 7, on the sixth, seventh, and eighth days of its fever. Thereafter, the lice were fed for eight successive days on Monkey 12, their number gradually decreasing from 81 on the first day to nine on the last day of feeding.

The temperature of No. 12 was irregular and rather high prior to the experiment, although the animal was active and well nourished.

Its temperature continued as in curve No. 23.

A definite course of fever cannot be made out positively. If present, it would appear to lie between January 30 and February 5 or 6, a period of seven or eight days, and the incubation period would be seven or eight days. On February 2 the animal was manifestly ill, in contrast to its former active condition, and this condition continued for four or five days. On February 9, however, it was again active and appeared well. At this time an immunity test was given; the temperature is given in curve No. 24.

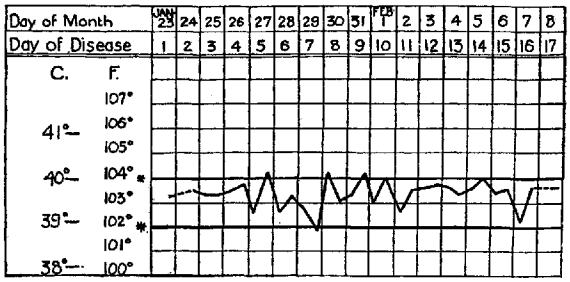
The controls were Nos. 3, 24, and 25, already cited. A second immunity test resulted in the same way, No. 20 (see above) being the control. During neither of the immunity tests did the animal show any sign of illness.

No. 25 is a particularly good control for No. 12, since, like the latter, its temperature was naturally high and irregular. The course of fever was as shown in curve No. 8.

In our opinion, the result justified the conclusion that No. 12 was infected by the lice of Group 5.

Lice of louse Group 10 (*Pediculus vestimenti*) were collected partly from the garments of two *non-typhus* patients at the General Hospital of Mexico City, partly from pupils at a neighboring school, and partly from the clothes of a healthy workman employed temporarily at the laboratory. When obtained the lice were presumably normal. They were infected as follows: From February 12 to 16 they were allowed to feed daily on Monkey 22, which had been inoculated seven days before with blood from Monkey 11, the latter animal being in the sixth day of a typical course of typhus

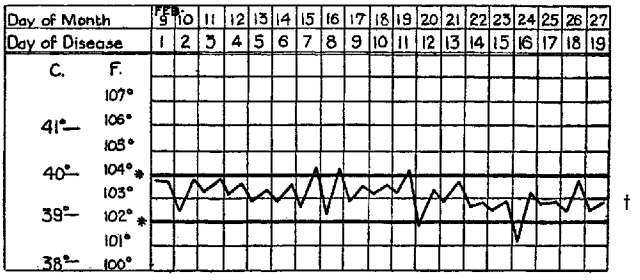
CURVE 23.



TEMPERATURE OF MONKEY NO. 12 AFTER BEING BITTEN BY INFECTED LICE.

* The heavy horizontal lines indicate the normal limits of afternoon temperatures.
† Received immunity test.

CURVE 24.



TEMPERATURE OF MONKEY NO. 12 AFTER IMMUNITY TEST.

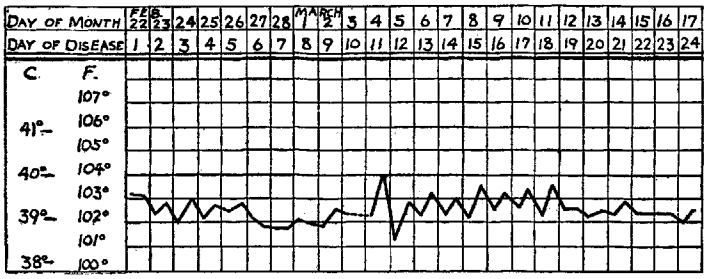
* The heavy horizontal lines indicate the normal limits of afternoon temperatures.
† Continued below 103.9° F. while under observation.

fever at the time the blood was taken. As was mentioned above, this monkey (No. 22) at no time developed fever, but, although normal when inoculated, became progressively thinner and weaker and died fourteen days later, showing no positive anatomical lesions to account for his death excepting intense meningeal congestion, edema, and pronounced hyperemia of the abdominal and subcutaneous vessels, findings highly suggestive of typhus. At the time, however, we were not satisfied with the infection of this animal and hence on February 17 the lice were fed on Monkey 3, which had been inoculated eight days before with blood from a human case of typhus

and was beginning to show an elevation of temperature. No. 3 ran a typical and severe course of typhus. On February 18 the lice were not fed, but on February 19 and 20 they were placed on Monkey 25 during the second and third days of his sickness. This animal had been inoculated with human typhus blood and contracted a severe course of typhus fever of nine days' duration. His history and a curve of his temperature are given on p. 68 (curve No. 14).

After their last feeding on an infected host the lice were allowed to rest for 24 hours and were then placed on the shaved skin of the face of Monkey 29, a normal *Macacus rhesus*. The feedings on this animal were as follows: February 22, 27 fed; February 23, 18 fed; February 24, 15 fed; February 25, 7 fed; February 26, 1 fed.

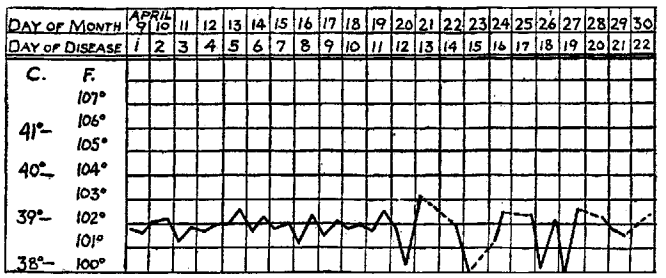
CURVE 25.



TEMPERATURE OF MONKEY NO. 29 AFTER BEING BITTEN BY INFECTED LICE.

† Remained below 103.1° F., 39.5° C., for the following 15 days.

CURVE 26.



TEMPERATURE OF MONKEY NO. 29 AFTER IMMUNITY TEST.

† Remained below 103° F., 39.4° C., for the following 28 days.

The temperatures of Monkey 29 are recorded in curve No. 25. The slight elevation between March 4 and March 11, coming as it does after an incubation period of 10 days, beginning rather abruptly and followed by constant lower temperatures, is suggestive of typhus, but more significant is the fact that the animal resisted absolutely an immunity test given on April 9, one month later. This test consisted in his inoculation with 4 c.c. of defibri-

nated typhus blood from Patient 48. Controls, Monkeys 21 and 33, previously discussed, were injected with the same material and became infected with typical typhus, while Monkey 29 showed absolutely no elevation of temperature or other sign of discomfort (see curve No. 26). I believe that we were justified in concluding that this animal was infected by the lice of Group 10 with a mild attack of typhus.

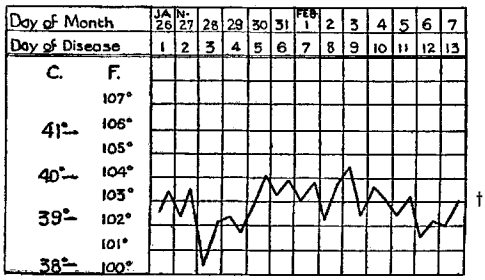
INFECTION OF THE MONKEY BY INOCULATION WITH THE ORGANS OF LICE.

A first experiment, which consisted of the subcutaneous injection of the intestinal contents of infected lice, resulted in death in less than twenty-four hours, from septicemia.

A second experiment was performed as follows: As the lice of Group 5 were feeding on Monkey 12, a small quantity of feces was collected from a number of the lice as it was extruded, and placed in a sterile test-glass. To this material the abdominal contents of three lice were added and the mass was triturated in sterile salt solution. This was done three days after the last feeding of the lice on the infected Monkey 7.

Twelve small incisions, each less than one-eighth inch in length, and extending through the entire depth of the skin, were made in the abdominal skin on Monkey 13. The emulsion of feces and abdominal contents was then instilled into these incisions, which thereafter were massaged by means of a sterile probe. The incisions healed promptly and without suppuration. The temperature of No. 13 was as shown in curve No. 27.

CURVE 27.



TEMPERATURE OF MONKEY NO. 13 AFTER INFECTION WITH ABDOMINAL CONTENTS OF INFECTED LICE.

† Continued low as long as under observation.

As appears on the curve the temperature rose on the fifth day after inoculation and remained above the normal for this animal for five or six days. During this period the animal became passive and was not inclined to run about, although it was not seriously ill at any time.

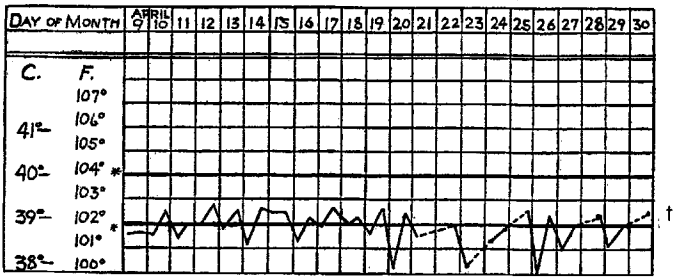
As a consequence of an immunity test given on February 9, the animal showed no febrile reaction whatever and appeared perfectly well, whereas the controls (Nos. 3, 24, and 25) reacted with severe fever, as stated above. A second immunity test, given a month later, gave the same results, the control in this instance being No. 20 (see above).

In our judgment, this experiment proved the existence of the virus of typhus fever in the abdominal contents of the louse for at least three days after feeding on infected blood.

INFECTIVITY OF THE INTESTINAL CONTENTS OF THE LOUSE.

Lice of Group 17 (*Pediculus vestimenti*) were infected by three successive daily feedings on a typhus patient (No. 31) during the eighth, ninth, and tenth days of his sickness. After a rest of 48 hours, during which time they were kept at a temperature of 11 to 12 degrees C., the intestinal contents of six full-grown members of the group were dissected out and introduced beneath the skin of Monkey 32 in the following manner. Care was taken not to rupture the organs during dissection, and until the moment of

CURVE 28.



TEMPERATURE OF MONKEY NO. 32 AFTER IMMUNITY TEST.

* The heavy horizontal lines at 102° and 104° indicate the normal limits of the P.M. temperatures of monkeys of the species *Macacus rhesus*. A.M. temperatures may be lower.

† Remained below 103° F., 39.4° C., for the following 46 days.

injection they were kept intact in a small amount of physiologic salt solution. Twelve incisions, each two to three mm. in length and extending through the entire depth of the dermis, were cut in the abdominal skin of Monkey 32; the six intestinal canals were then ruptured, emulsified in a small amount of salt solution and introduced into these cuts, the material being forced under the skin beyond the edges of the incisions by means of sterile forceps. The wounded surface was then carefully dressed and subsequently healed with little or no suppuration.

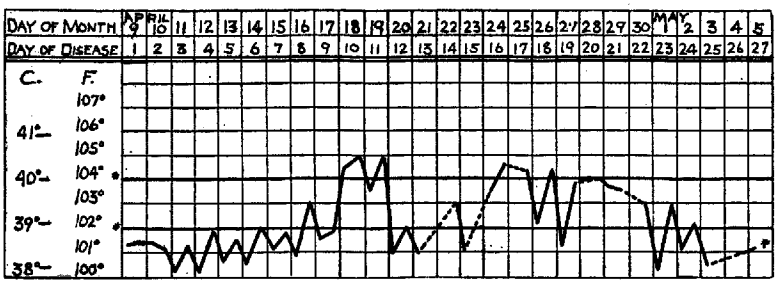
We were unable to observe that Monkey 32 was affected in the least by this operation, for his temperature remained perfectly

normal and he seemed constantly in good health. However, when a later immunity test was given him he was found to be absolutely refractive. This test consisted in the injection of the animal with 4 c.c. of virulent typhus blood, recently drawn from Patient 48. The controls, Monkeys 21 and 33, as mentioned before, which were inoculated with this same material, developed typhus, and the insusceptibility of Monkey 32 is apparently due to his previous inoculation with the intestinal contents of the lice.

AN EXPERIMENT WITH THE HEAD CONTENTS OF INFECTED LICE.

The following experiment was undertaken with a view to testing the infectiousness of the salivary glands of the louse which we thought lay in the head of the insect. We found later that the

CURVE 29.



TEMPERATURE OF MONKEY NO. 33 AFTER IMMUNITY TEST.

* The heavy horizontal lines at 102° and 104° indicate the normal limits of variation of the P.M. temperatures of monkeys of the species *Macacus rhesus*. A.M. temperatures may be lower.

† Continued beneath 102° F., 38.9° C., until June 22, 1910, at which date observations were discontinued.

head contains little or no glandular material. According to Landois, the salivary glands of *Pediculus pubis*, a member of the same genus as *Pediculus vestimenti* and a very close relative, are confined to the thorax, and we observed glandular structures in the thorax of *P. vestimenti* which resemble the salivary glands of *P. pubis* described by Landois. Powlowski describes, in the head of *P. capitis* and *P. vestimenti*, a minute gland which opens into the junction of the mouth and the pharynx, but the chief salivary glands of *P. vestimenti*, as is the case with most of the insects, would seem to lie in the thorax, and hence an injection of the head contents of infected lice is not a test of the infectiousness of these

glands. As might have been expected, the result of this experiment was negative, and the chief reason for reporting the protocols is that the animal (Monkey 33) by proving susceptible to his immunity test served as a control for the other scarification experiments.

Lice of louse Group 13 (*Pediculus vestimenti*) were infected by a feeding on a typhus patient, No. 32, in the ninth day of his sickness, and by two successive feedings on Patient 33 on the fifth and sixth days respectively of his fever. The group was then allowed to rest for three days.

The head contents of 21 of these lice were dissected out, emulsified in salt solution, and injected hypodermically into Monkey 33. No effect whatsoever was produced in the monkey by the inoculation and a month later, on April 9, he proved susceptible to an immunity test consisting of the injection of 4 c.c. of virulent typhus blood recently drawn from a patient (No. 48). The temperatures of the monkey following his inoculation are recorded on the accompanying curve No. 29. His sickness, although not severe, was quite characteristic of typhus.

A month later Monkey 33 was given a second immunity test and on this occasion proved to be absolutely immune.

DURATION OF THE INFECTIVITY OF THE LOUSE.

The following experiment was performed with the purpose of determining how long lice remain infective after feeding on an infected host, with the hope that thereby some further light might be thrown on the question as to whether transmission by the louse was purely mechanical and accidental or whether it involved the ability of the micro-organism of typhus to live for any length of time within the body of the louse.

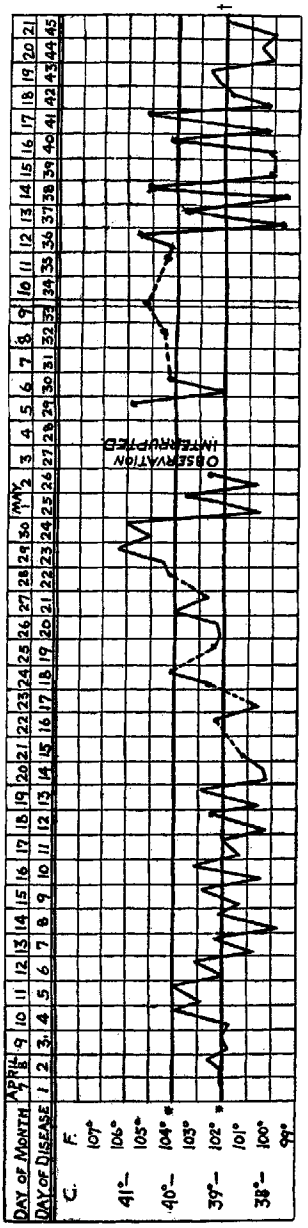
Group 17 (*Pediculus vestimenti*) was infected by feeding for three days, March 29, 30, and 31, on typhus patients (Nos. 41 and 45); on the former during the sixth and seventh days of a severe course of fever. On April 1, 145 of the group were alive and 60 of them were fed on a normal monkey (No. 38). On April 2 and 3, 60 lice were again fed on No. 38, those lice which had not fed on the previous day being chosen from the group.

On April 4, 60 lice were placed on a second normal monkey (No. 36). On April 5 only 58 remained alive; these were all fed on No. 36 and again on April 6, 40 fed on this animal.

On April 7, seven days having elapsed since their last contact with an infected host, 15 lice were fed on Monkey 39. On April 8, these 15 fed again. On April 9 only seven of the group were alive, six feeding on Monkey 39.

In the case of the first two monkeys it was impossible to recognize during the following three weeks either elevation of temperature above normal or other sign of sickness, nor was either of the two protected by the lice against later immunity tests, both reacting with fever of moderate severity to subsequent inoculations of typhus blood. Monkey 39, however, following an incubation period of 17 days began to show irregular elevations of temperature which, on April 29, reached a height of

CURVE 30.

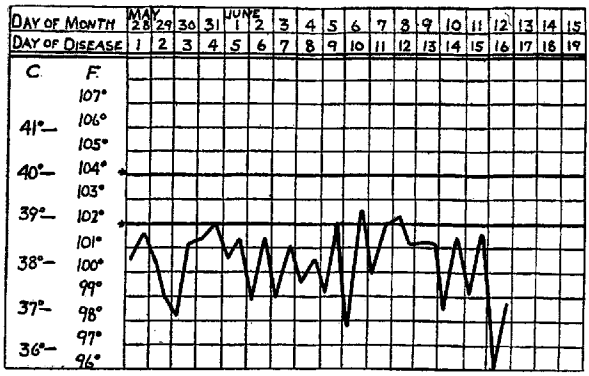


TEMPERATURE OF MONKEY NO. 39 AFTER BEING BITTEN BY INFECTED LICE.

* The heavy lines indicate the normal limits of the P.M. temperatures of the *Macacus rhesus* monkey. A.M. temperatures may be lower.
† Remained below 103.2° F., 39.5° C., as long as under observation.

106.3° F. (41.3° C.). On April 26 the animal was noticeably growing thinner and from then on he sat huddled and inattentive in his cage, his fur ruffled and dry. Broth cultures made from the heart blood on May 30 remained sterile. On the morning of May 1 the temperature dropped to normal and shortly thereafter observations of the animal had to be discontinued. Subsequently the temperatures of this monkey were taken irregularly but from May 5 to 17 they reveal a great irregularity. The nature of the curve during this period, showing as it does large daily variations, is suggestive of some extraneous infection, possibly streptococcic or pneumococcic, but as no cultures were made from the blood at this time the curve is impossible of interpretation (see curve No. 30). The eventual recovery of the animal was very slow, and he remained always thin and unhappy. On May 28, however, his condition seemed slightly improved and on this date he was given an immunity test consisting of 3.5 c.c. of typhus blood from Patient 58 (see curve No. 31). He proved to be absolutely immune, manifesting no febrile reaction, while the control animal (Monkey 44) ran a severe course of fever. Monkey 39 died subsequently, June 15, the post mortem showing acute intestinal and pulmonary tuberculosis.

CURVE 31.



TEMPERATURE OF MONKEY NO. 39 AFTER IMMUNITY TEST.

* The heavy lines indicate the normal limits of P.M. temperatures of the *Macacus rhesus* monkey. A.M. temperatures may be normally much lower.

In view of the resistance shown by No. 39 to the immunity test it seems practically certain that he was immunized by the lice and at least highly probable that the fever occurring between April 23 and May 1 was due to his infection with typhus, certain unsatisfactory conditions in the experiment notwithstanding. That he was sufficiently susceptible to react to an infection by lice with no high fever may be explained by the fact that he was an old monkey, his teeth being hollowed, worn, and decayed. It is known that age plays a large factor in the susceptibility of man to typhus.

Why Monkeys 36 and 38 were not infected or at least immunized

by the lice may likewise be explained by individual variation in susceptibility due to age. They were both quite young and exceptionally healthy animals. It is conceivable also that the infectivity of the louse increases progressively after his infection, due either to the greater proliferation of the organisms, an increase in virulence of the micro-organisms while in the louse, or possibly to their migration to the salivary glands; and hence the result of this experiment points to biological changes of the virus in the louse.[1]

HEREDITARY TRANSMISSION OF THE INFECTIVITY OF THE LOUSE.

This experiment was undertaken with a view to determine whether the young of infected lice were themselves infective, that is, able to give the disease to a host on which they feed. The adult louse contains in its ovaries many mature eggs. These eggs are covered with a compact shell which we thought might prove impermeable to micro-organisms; hence it was decided to rear young lice to maturity on the bodies of typhus patients so that if the eggs were susceptible to infection at any stage of their development they would have every opportunity of being infected within the ovary.

On March 29, 140 adult lice of Group 17 (*Pediculus vestimenti*), 70 males and 70 females, were placed in a stocking on the leg of a typhus patient (No. 41). The stocking was sealed above with adhesive tape to prevent the escape of any of the insects. Two days later 1,000 eggs were found adhering to the fibers of the cloth. The lice were removed and replaced on the patient in a fresh stocking, while the

[1] Attention was called above (p. 40) to the early experiments of Nicolle, Compte, and Conseil on the transmission of typhus by the louse. In Nicolle's latest paper the following results are reported: typhus transmitted from a chimpanzee and a sinicus monkey to four monkeys by lice which had been in contact with their infecting hosts for one to 12 days before, one to six days and five to seven days before, respectively. On the contrary negative results were obtained, that is, neither a febrile reaction nor immunization, on three monkeys bitten by lice which had been in contact with their infecting hosts one to four days before and eight to 12 days before respectively. From this Nicolle concludes that the bite of the louse is not infective before the fifth or sixth day after its contact with its infecting host, and that it is not infective after the seventh day. This observation, it is claimed, supports the theory of the protozoic etiology of typhus fever.

Our experiments, reported above, seem to confirm the first of these observations, namely that the louse is not infective until five or six days have passed since its last contact with its infecting host, but it does not seem justifiable to me to conclude from a single negative experiment on a single animal, as Nicolle does, that the louse is not infective after the seventh day. This observation should first be confirmed by further experiments. Nor do I believe that these observations necessarily support the theory of a protozoic etiology of typhus fever and a life cycle of the micro-organism in the body of the louse, as Nicolle affirms. It is quite as reasonable to consider that a certain lapse of time is necessary for multiplication of the organism to occur in the body of the louse before it is present in sufficient numbers to render the bite of the insect infective.

stocking containing the eggs was put on the patient's other leg. Approximately 800 more eggs were subsequently laid by this generation of lice.

By April 6 many of the eggs began to hatch and by the 15th of the same month about 500 young lice had been collected. These were placed in a fresh stocking which was kept constantly on the leg of a patient in an early stage of fever. For this purpose Patients 47, 49, 52, and 53 were used. Many of the young lice died, but approximately 250 of them reached maturity and laid eggs.

When a sufficiently large number of these eggs of the second generation, presumably infected, had been obtained, all of the adult lice were removed and placed in a new stocking on the same patient. The stocking containing the eggs was then sealed and incubated between the sheet and the mattress of a patient in an early stage of convalescence.

Monkey 42, of the species *Macacus rhesus*, which served for this experiment had been quite recently imported into Mexico from a district free from typhus. As the eggs hatched the young lice were collected and placed on this normal monkey in the following manner: The animal's skin was shaved over the entire abdomen, and a piece of finely woven linen, two by three inches, was tightly secured to the skin by means of a border of two-inch adhesive tape. One edge of the cloth being left unattached, the open end of a tube containing the young lice was inserted beneath this edge, and the lice poured into the pocket formed between the cloth and the skin. The mouth of the pocket was then sealed with tape, and the animal clothed with a heavy canvas jacket in order to prevent interference with the lice.

Thus, on April 28, 50 young lice were placed on the monkey. On April 30, 30 more were added. At this time it was noted that the lice of April 28 had fed, their bodies being gorged with blood. On May 2, 25 additional lice were collected from the stocking and placed on the monkey, whereby in all 105 lice, the offspring of infected lice but themselves never directly infected, were given the opportunity of feeding on Monkey 42.

Unfortunately the temperature of this animal could not be taken regularly during the following three or four weeks, nor was he under very close observation during this period. On May 26, however, he appeared to be in good health. But more important is the fact that he proved resistant to an immunity test. This test, consisting in the intraperitoneal inoculation of 3.5 c.c. of virulent typhus blood from a typhus patient (No. 58), was given on May 27, a month after his exposure to the lice. For the following three weeks Monkey 42 remained in perfect health, although controls inoculated with the same quantity of the same material all contracted typhus of moderate severity, their temperatures maintaining an elevation of 105° to 105.7° F. (40.5° to 41° C.) for a period of 10 or 12 days.

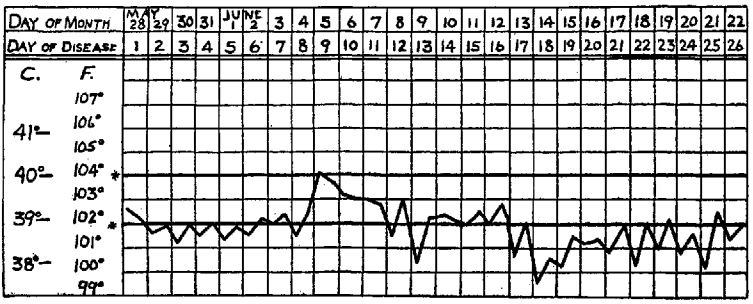
Curve No. 32 shows the temperatures of Monkey 42 on the successive days following the inoculation; curve No. 7 shows those of the control Monkey 44 (see p. 61).

The slight elevation of temperature shown by Monkey 42 on June 5 and June 6 may or may not be an effect of the virus. In any case it is extremely mild and the animal may be said to have been far less susceptible to an injection of typhus blood than the control Monkey 44 or than all normal animals have been found to be.

I appreciate that the result of one experiment does not constitute decisive proof, but the definiteness of the result justifies, in

my opinion, the conclusion that Monkey 42 owed his immunity to his previous infection by the young lice of Group 17, and that hereditary transmission of the infectivity of the louse is established to the extent of reasonable probability.

CURVE 32.



TEMPERATURE OF MONKEY NO. 42 AFTER IMMUNITY TEST.

* The heavy lines indicate the normal limits of P.M. temperatures of the *Macacus rhesus* monkey. The A.M temperatures may be much lower.

INFECTIVITY OF THE FLEA AND THE BEDBUG.

I have referred on a previous page to certain theoretical considerations which are opposed to the theory that the bedbug and the flea are influential in spreading typhus. It is impossible to explain certain epidemiological characteristics of the disease by assuming that either of these insects is the sole agent in carrying the infection and yet either or both of them may play a rôle subsidiary to that of the louse, and under certain circumstances act as carrier. In order to throw further light upon this question the following experiments were devised:

Infectivity of the Bedbug.—A group of about 50 bedbugs was fed on three successive days on typhus patients at the general hospital. The bugs were confined beneath a wide-mouthed glass bottle inverted over the skin of the patient. In this way 10 or 12 could be handled at one time. All were given the opportunity of gorging themselves with blood.

On April 2, two days after their last feeding on a typhus-stricken host, they were placed on the shaven abdomen of a monkey (No. 38) and allowed to feed. On April 3 they were again placed on the monkey. On April 4 they were not fed. On April 5, 28 bugs fed well on the animal; April 6, 16 bugs fed lightly; April 7, 17 bugs fed lightly; April 12, 29 bugs fed well, gorging themselves with blood.

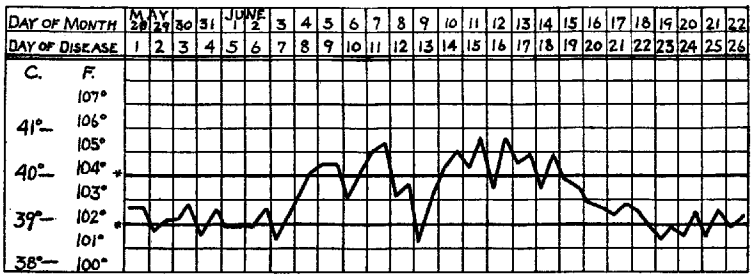
The animal showed absolutely no rise in temperature and continued in excellent health during the following 32 days. Unfortunately he died from an accident before

an immunity test could be given him, and hence the experiment cannot be taken as proof of the noninfectivity of the bedbug. The possibility that the bedbug is better able to transmit typhus than the louse does, however, seem to be eliminated insomuch as both the period of feeding on the infected host and the period of feeding on the monkey were considerably in excess of the feedings of the louse in certain of our experiments.

Infectivity of the Flea.—Human fleas of Flea-Group 2 were infected on typhus patients at the general hospital in the following manner: One or two fleas were confined in each of several long and narrow tubes. These tubes were made of 6 mm. glass tubing, were sealed at one end, and cut sufficiently long (20 cms.) to prevent the escape of the flea by jumping. For this purpose also they were slightly bent in the middle. The fleas were fed by inverting this tube over the skin of the patient.

Subsequent to their last feeding the fleas were allowed to rest for about 60 hours. The entire bodies of 10 of the group were then emulsified in physiologic salt solution

CURVE 33.



TEMPERATURE OF MONKEY NO. 41 AFTER IMMUNITY TEST.

* The heavy horizontal lines indicate the normal limits of the P.M. temperatures of the *Macacus rhesus* monkey. A.M. temperatures may be lower.

and rubbed into scarifications in the abdominal skin of a normal monkey (No. 41), the technic employed in this procedure being the same as that used in the scarification experiment performed with the intestinal contents of lice and described above. The wounds healed with but little suppuration. The animal's temperature was taken daily for the following 34 days and during this time he remained in perfect health.

On May 27 this monkey was given an immunity test, receiving an inoculation of 3.5 c.c. of typhus blood from Patient 58. After an incubation period of seven days he began to run a fever which lasted for 12 days, his temperature being recorded in curve No. 33. On June 4, a leukocyte count was made which showed 30,350. The animal was very irritable and his coat dry and ruffled. On June 5, he had diarrhea, huddled in his cage, and was less active in resisting manipulation and until the 14th of the month he seemed very sick. His subsequent recovery was rapid and complete.

In brief, No. 41 had not been infected by the fleas, as is shown by the fact that he was not immune to a subsequent inoculation of typhus blood.

These results seem to strengthen our position as to the unimportance of the flea and the bedbug in the transmission of Mexican typhus fever.

SUMMARY OF EXPERIMENTAL OBSERVATIONS ON TYPHUS FEVER.

1. A limited number of observations are on record of successful infection of human beings by inoculation of blood from typhus patients.

2. Various species of ape have been found to be susceptible to typhus fever. None of the other laboratory animals thus far tested have been susceptible.

3. In our personal investigations all normal monkeys of the species *Macacus rhesus* have been successfully infected by the inoculation of 1 c.c. or more of virulent typhus blood from man. The blood should be drawn not later than the tenth day of fever and should be diluted with physiologic salt solution before injection. The minimum infective dose lies between 0.2 c.c. and 1 c.c. of defibrinated blood.

4. The course of typhus fever in the macacus after blood inoculation is sufficiently characteristic to enable positive diagnosis and accurate interpretation. The disease runs a course similar to that observed in man. After an incubation period commonly lasting from six to 10 days there occurs a high febrile reaction which continues from eight to 15 days. The long incubation period, the absence of cultivable organisms in the blood and of anatomical lesions are characteristic.

A general leukocytosis is observed quite frequently in the monkey, as in man, and a relative increase in the number of large mononuclears is a constant finding. The temperature falls by lysis, taking two or three days to return to normal. Convalescence is as a rule rapid and complete. One attack of the disease confers absolute immunity, and an immunity test may therefore be relied on to illuminate the diagnosis of doubtful cases in monkeys.

5. We have succeeded in carrying the disease in the monkey through three passages.

6. The serum from the blood of typhus patients is infective.

7. The virus of typhus is apparently non-filterable, blood serum losing its infectivity on passing through a Berkefeld filter. In one experiment, however, a monkey was seemingly vaccinated by an inoculation of filtered blood serum. This result would seem to

indicate that toxins, bacterial fragments, or micro-organisms sufficient to immunize may pass through the pores of a filter.

8. Typhus has been transmitted to monkeys by the *bite* of lice in seven out of 10 experiments. In addition two monkeys were infected with typhus by the introduction into cutaneous scarifications of the intestinal contents of infected lice.

9. The minimum number of lice found necessary to infect a monkey was 17.

10. A monkey was infected and immunized by the subcutaneous introduction of the intestinal contents of six adult lice. The material thus injected proved considerably more infectious than an equal amount of typhus blood, for it has been shown by experiment that more than 0.2 c.c. of blood are required to immunize a monkey, whereas, by the most liberal estimate, these six adult lice did not ingest more than 0.06 c.c. of blood during their three feedings on a typhus host. The conclusion is indicated that the infectiousness of the virus is enhanced within the louse. This may occur by multiplication of the causal organism, or by an increase in its virulence, or by both.

11. In the one experiment attempted, a monkey was immunized, i.e., infected, by the bite of the young of infected lice. As these lice of the second generation had never been themselves directly exposed to infection, hereditary transmission of the infectivity of the louse is indicated.

12. Experiments performed with the bedbug and the flea failed to give any evidence that either of these insects can transmit typhus and support theoretical objections to their consideration as carriers of the disease.

VI.

PROPHYLAXIS.

It seems appropriate to conclude a paper on the transmission of a disease with a discussion of the prophylactic measures which are indicated by the conclusions reached in the course of the study. In this discussion I wish to confine my remarks to the problem of the control and elimination of typhus fever in Mexico City where I am personally familiar with the conditions which favor its con-

tinuation, although I have no doubt that in general my remarks will apply equally well to other cities. I feel firmly convinced that the institution and strict enforcement of the following hygienic measures in Mexico would result in a great reduction in the death rate from typhus, in the control of the epidemic exacerbations which now occur annually in that city, and ultimately in the absolute extinction of the disease.

There is no evidence leading to the suspicion that typhus is ever acquired through the alimentary canal, either in drinking water or as a contamination of food, and measures designed to purify the food and drink of the community will have no direct effect on the amount of typhus fever. In clean surroundings typhus is not "catching," and the disease does not belong to the category of infections commonly spoken of as contagious. Its reputed "contagiousness" has been shown to be entirely dependent upon the presence of infected vermin. Three insects (flea, bedbug, and louse) are open to the suspicion of being typhus carriers, and in the case of the louse sufficient evidence has been adduced to prove that this insect is the chief agent in the transmission of typhus fever.

Prophylaxis should therefore be directed toward limiting the activity first of the louse and then of the bedbug and the flea. Such prophylaxis should contemplate: (1) the general destruction of lice wherever or by whatever means this is possible; (2) the extermination of all insects, fleas, bugs, or lice found on the bodies, clothing, or bedding of persons suspected of having typhus or of the contacts of such typhus suspects; (3) the adoption by individuals exposed to the disease of precautions to minimize the danger of their being bitten by infected vermin.

1. *The general destruction of lice.*—A problem similar to that so successfully met in the campaign against yellow fever confronts us, but the task of exterminating lice will probably be found to be more difficult than was the elimination of the yellow fever mosquitoes. It will even be considered by some as visionary to hope to eliminate lice from the poor population of the Mexican plateau. The harboring of body vermin by them is regarded as perfectly normal and natural, and the antipathy which the Mexican Indian

exhibits to water and the bath can only be overcome by a long and painstaking process of education. The poverty and misery of the great mass of the poor increase the difficulty of inspiring in them any inclination for cleanliness. Nevertheless, despite the discouraging outlook, such education should be undertaken, and I feel that a great deal would be accomplished simply by giving them the opportunity of keeping clean. Public baths and free wash-houses for the lavage of clothes should be erected. The squalor and filth of the poor is chiefly due to the fact that they have no water. For six months of the year the ditches around the city are dry, and in certain districts water must be bought from "aguadores," men who cart it about the streets, at a price which prohibits its use for washing. The fact that the people do make use of the opportunity to clean their clothes when the ditches contain water in the rainy season encourages me to believe that they would use the wash-houses were they provided.

In the public baths there should be facilities for the sterilization of the clothes of the bathers. A short exposure to steam would probably suffice to kill all the lice. In any case care must be taken to prevent promiscuous interchange of parasites between the divested clothing of various individuals.

The establishment of public wash-houses for clothes is in my opinion of greater importance than the baths. In these wash-houses there should be provided tubs for the use of women who bring their washing, and if practicable a general sterilization of all the soiled clothing should be performed. Such sterilization would be best accomplished by heated steam.

In that part of the population, a not inconsiderable proportion, which is under the immediate supervision of the government, personal cleanliness and *absolute* freedom from body parasites may be enforced. I speak of the inmates of hospitals, orphan and correctional schools, and institutions for the poor and incapacitated, the prisons, and army barracks. Mention has been made of the importance of Belem as a distributing center for typhus. Its inmates come from all sections of the city and return to their respective sections when they leave the prison. They have abundant opportunity to pick up infected lice while in the prison

and they disseminate the infection throughout the town. The enforced cleanliness of the prisoners would do away with this condition. The efficacy of a cleanly and sanitary prison administration in eliminating typhus is seen in the case of the Mexican penitentiary. Typhus has on numerous occasions raged in the city around the walls of the penitentiary, but owing to the enforced disinfection of all entrants and the strict cleanliness of the inmates no case of the disease has ever occurred within the walls of that institution.

The presence of lice on persons in the wards of hospitals is inexcusable and may easily be avoided by the bathing and disinfection of the bodies and clothing of all entrants before their admission to the hospital wards. Visitors to the sick should be excluded from the hospital if from their general appearance of uncleanliness it is suspected that they harbor lice. Other insects such as bedbugs should be exterminated whenever they are seen in hospitals and other institutions, and in all of these institutions frequent bathing and the use of clean clothes should be enforced. The harboring of lice by soldiers in the army should be made a punishable offense, and the army barracks be kept free from vermin. Finally, the cleanliness of all the pupils in the public schools should be insisted on. The parents of children found harboring lice should be amenable to fine. The spread of typhus from the schools, which are distributing centers of no small importance, would thus be limited. Prisons, hospitals, charitable institutions, armies, and army barracks, and finally schools, all of which places are now considered to be distributing centers for typhus, could thus be rendered harmless, and the disease would be confined to isolated sections of the city, where it could be fought case by case.

2. *The extermination of insects found on typhus patients or on the contacts of such patients.*—Every case of typhus fever arising in the city should immediately be reported to the department of health. Such cases should be visited promptly by sanitary inspectors, and unless the house and surroundings of the patient are clean and above the suspicion of being infested with vermin, the patient and all of his contacts should be removed to the typhus hospital. If the case occurs in the family of people of cleanly habits, where the

presence of body lice and bedbugs can be excluded, there should be no objection to the treatment of the patient at his home. In this case the house should be quarantined and kept under the strict observation of sanitary inspectors.

At the hospital a separate entrance pavilion should be provided for the reception of typhus patients and their contacts. Here the patient should be stripped and bathed before he is admitted to the wards. The contacts should likewise be bathed and their clothes disinfected. Heat disinfection (steam) will probably recommend itself for the sterilization of the clothing.

In the meantime the house or rooms from which the patient has been removed are to be disinfected, all rugs, bedding, hangings, etc., to be taken to a disinfecting station. The house should then be fumigated with sulphur, the walls repapered or lime washed, and the woodwork and floors washed with soap and disinfectants.

The contacts should be kept at the entrance pavilion of the hospital and provided for until the disinfection of their home has been completed, when they may be allowed to return. After their disinfection they may be considered as harmless and permitted to resume their occupations. They should, however, be kept under observation by the health department for a period of 21 days for fear that some of them were infected before and may develop fever. The incubation period of typhus in man is usually estimated at from seven to 14 days (Parkes) and probably does not exceed 21 days.

3. *Precautions designed to minimize the danger of those exposed to infection.*—So far as is possible typhus immunes should be employed in those occupations which constantly expose to infection, such as the reception at the hospital of typhus patients, their disinfection, and the cleansing of the clothing of patients and their contacts. Sanitary inspectors whose duty it is to fumigate the rooms occupied by patients are unduly exposed and should also be chosen from among immunes. The nurses and attendants in typhus wards should be immune, although these are in relatively little danger if the wards and patients are kept scrupulously clean and free from vermin. Visitors should be excluded from the typhus wards lest

they bring in insects and thus favor the spread of typhus from the patients to such nurses or physicians as are susceptible.

Other individuals, physicians, and students whose duties take them in contact with typhus patients, particularly if these are visited in filthy, vermin-infested surroundings, should observe the following precautions: Superfluous clothing which is liable to brush against the furniture, the bedding, or the clothing of the patient, or which sweeps the floor, is to be discarded. The skirts of nurses should be sufficiently short to be out of danger of touching the floor. Trousers are to be rolled above the shoe tops and coats should be removed. Loose gowns, besides being valueless as far as protecting against the contagium of typhus is concerned, are actually dangerous, as they sweep up any lice that happen to be within a wide radius. The sleeves should be rolled well above the elbows, so that occasional vermin which accidentally crawl onto the hands may be more readily discovered before they find concealment in the clothing. Eucalyptus oil is believed to be unpleasant to insects, and Hay recommends smearing neck, wrists, ankles, and shoe tops with a solution of eucalyptus in olive oil. Finally, frequent change of clothing is advised, and minute attention should be paid to personal cleanliness.

In conclusion I should like to add a word concerning the quarantine against typhus at the United States border. The northern states of Mexico—Nuevo Leon, Coahuila, Chihuahua, and Sonora —which border the Rio Grande are free from typhus for the same reason that the coast states are spared, namely because the greater heat of these regions is incompatible with the transmission of the disease (see pp. 42–43), and it may be presumed on the same ground that Texas, New Mexico, and Arizona incur no serious danger from the importation of typhus. Their climate is also too warm for typhus fever. The same is not true of our more northern states, whose cooler climatic conditions more nearly approach those of the Mexican central plateau. Body lice are far from uncommon among certain classes of our larger northern cities, and other predisposing factors—crowding, squalor, misery, hunger, and want—are never absent in the poorer districts. Should these conditions

become aggravated by industrial unrest, or in the emergency of the outbreak of war, such districts if infected might easily become centers of typhus. It is to our interest that they have no opportunity of becoming infected, and this can only be assured by preventing immigration of *lice-carrying* individuals from other typhus centers.

All patients suffering from typhus fever as well as their contacts should of course be quarantined at the border, as is done now. But more important than this is the necessity of fumigating the clothes and baggage of such immigrants as from their appearance may be suspected of harboring body lice.

At present the immigrating Mexican laborer comes chiefly from the border states and is therefore not apt to harbor *infected* lice, furthermore he rarely travels farther north than Texas or Arizona, but let there be any considerable migration from such hotbeds of typhus as Mexico City or San Luis Potosi directly to our northern cities without the quarantine regulations suggested, and typhus fever, now unknown in the United States, would in all probability gain a foothold.

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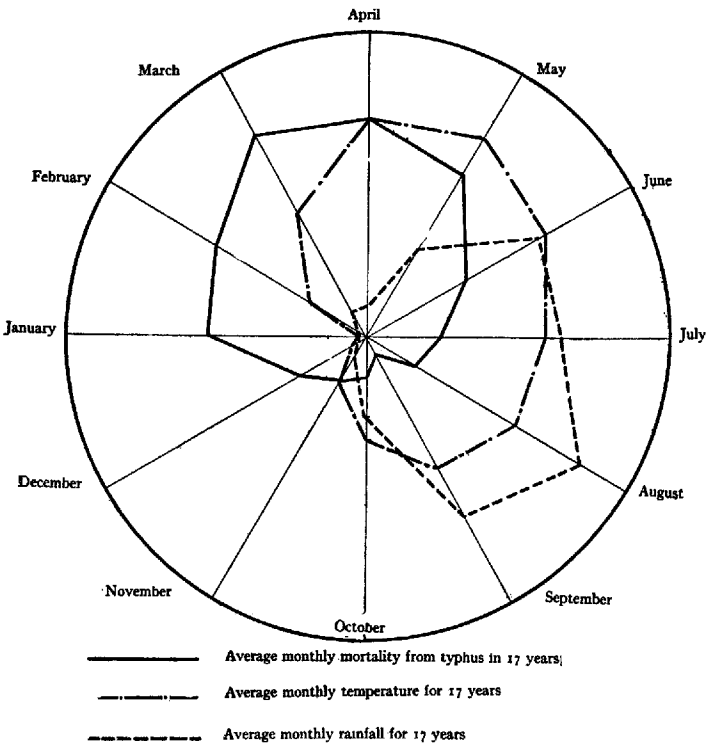
CHART 1.

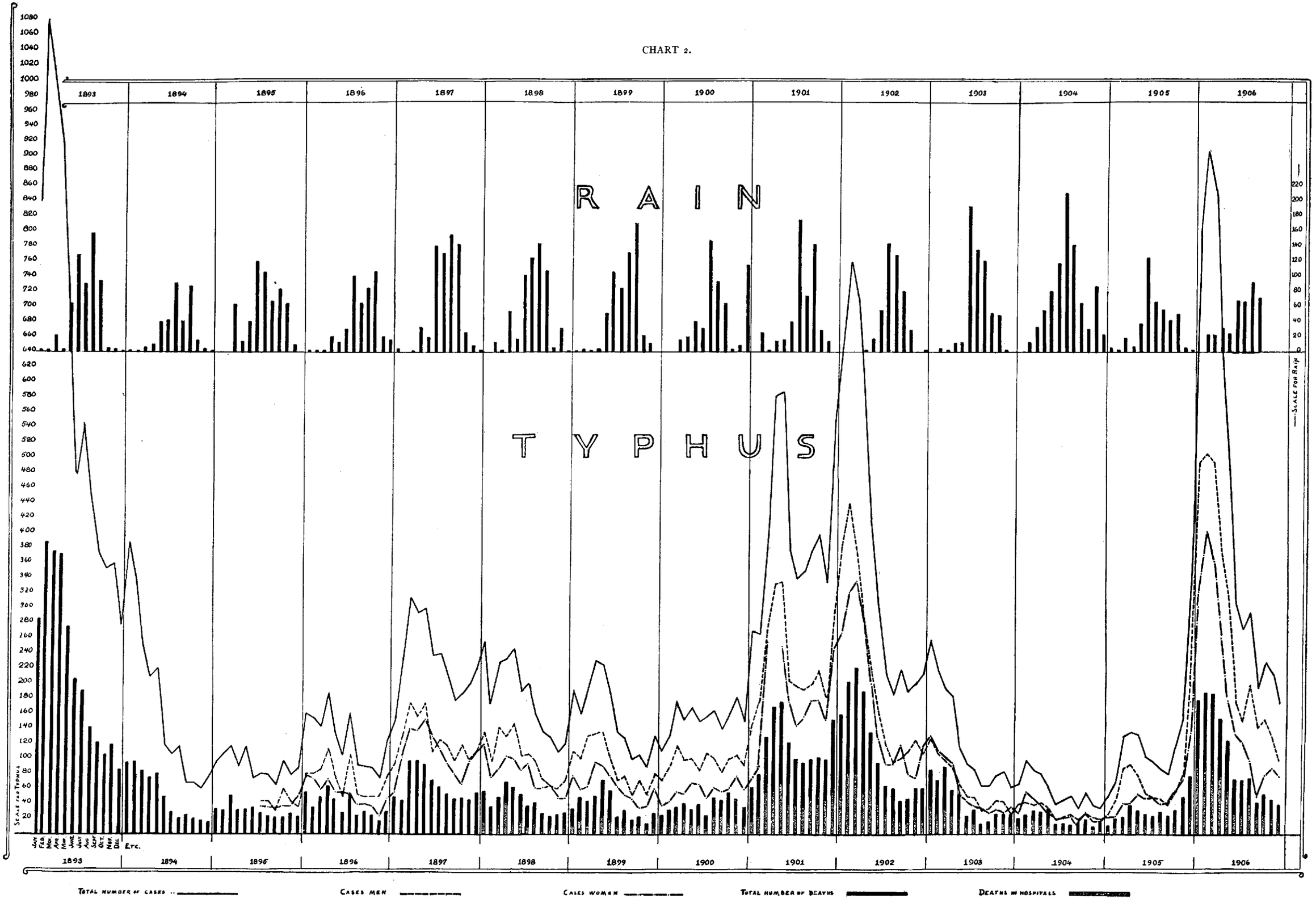
TYPHUS TEMPERATURE AND RAINFALL IN MEXICO CITY.



(After José Terrés, *Etiologia del Tabardillo*)

0.5 centimeter of radius = 10 deaths beginning with 30 at the center.
= 1 degree Centigrade of temperature beginning with 12.
= 20 mm. of rain.

CHART 2.



Drawn from chart in possession of the Consiio Superior de Salubridad of Mexico.

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