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DEPARTMENT OF THE ARMY
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ON THE TRANSMISSION OF TYPHUS FEVER
Observations of a Group-Infection in the Laboratory

[Following is a translation of an article by W. Loffler and H. Mooser of the Medical Clinic and the Institute of Hygiene of the University of Zurich which appeared in the German-language periodical Schweizerische Medizinische Wochenschrift (Medical Weekly of Switzerland), No 28, 1942, pages 755-761.]

Effective combat -- above all prophylaxis -- of epidemic diseases must be based upon a knowledge of the modes of transmission.

Nicolle was of the belief that lice transmit typhus fever and he also developed proof of this fact. Until the day he died, he remained convinced that transmission was caused mainly by the bite of the typhus fever louse. To the many names which typhus fever already had, he proposed adding that of louse disease (Marad el Aml) in order to enlighten the Tunisian population. The thought of a connection between lice and typhus fever never occurred to those doctors who saw these two scourges of the armies exist side by side. Two examples which seem to be particularly noteworthy: Dr. Johannes Kupferschmied (1), who participated in the second Willmerger War as a military doctor with the Bern troops and who had a great deal of experience with typhus fever, wrote, "...the fevers ravage the army camps and fill the cemeteries,...the fever often attacks like an armored warrior and often causes more war dead than the armed enemy." (Cf. W. Rutimeyer [1].)

Concerning the clothing louse, which he apparently knew well, he wrote:

"An unpleasant burden on the army is the lice plague (Phthiriasis) with itching pains over the entire body. Smallest animals, with many feet, white with black spots on the back, invade the entire body by sections and inhabit every seam of the clothing. These are not the same lice as occur on the heads of children, rather they thrive on all of the hairy areas of of the skin and are unbelievably fruitful. Treatment of Phthiriasis is

simple and the itching stops when the lice disappear. Lice are gotten rid of by smoking the clothing with the smoke of the tobacco plant and by washing the body with bitter decoctents (the enzian flower); the best method of driving off the louse consists of bathing the entire body with warm water and heating the uniform in an oven. If this does not help, then certain results are obtained using quicksilver and pork fat mixed into an effective salve."

Nearly one hundred years later, in 1912, Heinrich Roos (2), a regimental doctor with the Wirtemburg contingent of the great army, related with striking geographic and timely similarity to our present day situation his experiences in the East. After having been astounded by his experience with the supposedly incurable plica Polonica (Weichselzopf) during the march forward, he now encountered typhus fever during the retreat:

"We reached Moschaisk at night on 28 October during a snow storm. With several others, I set myself up for the night in the ruins of a burned house. In the morning I went to the headquarters which was located in a half-burned house. Several staff officers of Count von Scheler were burying the remains of one of their comrades who had died of war typhus. This horrible disease began now to ravage our ranks..... Here some troops who had remained in Moscow reached us. These men had been able to rest there and looked well. Among them were also some convalescents and wounded from Moscow. One of General von Brauning's staff officers also met us and led me to a road ditch. There lay the body of the general who had just died of typhus. He succumbed to a disease which often leads to sudden death and which we called 'war typhus.'....He had become sick in Moscow and died in Moschaisk."

Later, Roos himself became ill with typhus fever. After the retreat he had entered the Russian service. He wrote:

"War typhus raged in the villages in a horrible manner. We prisoners of war had brought this disease to the area. I had been able to experience it myself in the camp at Tschernichnia. The number of cases had increased during the retreat. This disease was so severe that I can report, without exaggeration, that half of those who contracted it died. Among the prisoners, the mortality rate was even higher."

Dr. L. Brauer (3) of Hamburg saw many cases of typhus fever when serving as a consulting military doctor during the First World War. He told us personally that he had not become sick and this he believed due to the fact that he had always used caution while examining his patients. He always approached the bed <u>first</u> and did not allow the practice whereby the enlisted medic would smartly throw back the blankets from the patient in preparation for the doctor's examination. He assumed that this brusk military custom caused the lice on the blanket to be thrown into contact

with the doctor and that the sickness was transmitted in this manner. This procedure on his part, which he based upon Nicolle's theory, undoubtedly served as an effective prophylaxis by keeping the lice away from his person. There is here no proof of the fact that the bite of the louse is the only method of transmission, however, and even before the discovery of rickettsia there was plenty of cause for doubt that only the bite of the louse was responsible.

Jochmann (4) assumed that his own infection with typhus fever had been contracted during a visit to a camp of Russian prisoners of war where typhus fever was prevalent. During this visit, he was wearing tightly sealed clothing and after leaving the camp he immediately undressed and bathed thoroughly. He therefore viewed his infection as being caused by the crowded conditions prevailing in the camp. There was only very limited space between the mattresses, and thousands of lice marched about in squads and platoons in this area. In 1916, Jurgens (5) stated that "in spite of the lice theory, we stand at the beginning and not at the end of the question of typhus fever, and every individual must be left to adapt this theory to his own experiences."

Earlier authors, such as Naunyn (6), saw "that both the severity and the contagiousness of this disease prevail in full measure when the patients lie crowded together in close rooms, particularly in military hospitals," and Curschmann (7) pointed to the importance of large, well ventilated rooms for the treatment or prevention of typhus fever.

In a richly documented study made in 1916, Wolter (8) came to the conclusion that the mystery of the contagion of typhus fever lay in the fact that "one only contracted the infection there where the miasmatic conditions of typhus fever have been imparted to the atmosphere of a room" and that the clothing and effects of the patients are guilty of imparting the cause of the disease to the atmosphere. This author, who is otherwise rather rambling and erring, apparently hit upon the correct solution in this case.

Clinical observers have always spoken of typhus fever as a very contagious disease, but with the proviso that its contagiousness always dropped suddenly and drastically inside of well arranged hospitals. This seems to be in sharp contrast with earlier observations, for years ago it was in the hospitals where typhus fever raged in the most severe fashion. But hospitals such as those in use during the wars of Napoleon usually did not even meet the most rudimentary requirements for sanitation. It is no coincidence that during later wars, such as World War I, a particularly high rate of typhus fever was reported from prisoner of war camps and that the rate of sickness among guard and kitchen personnel was also high. Typhus fever was bred in many military hospitals, just as was puerperal fever (childbed fever) in maternity institutions prior to the time of Semmelweis.

Since the discovery of the causative agent of typhus fever, we have come much closer to the solution to the question of the mode of transmission of this disease. After identifying rickettsia as the causative agent of typhus fever, Arkwright and Bacot (9) (died of typhus fever) were the first to show that the saliva glands of lice did not contain rickettsia and that therefore the louse could hardly cause infection directly through its bite.

Infectiousness of the feces: These same authors, on the other hand, showed that the feces of lice, the infectiousness of which had been demonstrated by Nicolle, could remain infectious for at least eleven days. They therefore believed that the infection was not caused by the saliva of the louse, but rather at best by the contamination of the outer part of the proboscis. Then Miss Fejgin (10) and Starzyk (11), working in Weigl's laboratory, were able to show that the feces of lice remain infectious for a very long time under laboratory conditions. The feces of fleas dried in a vacuum remain infectious up to 355 days and 651 days according to Blanc and Baltazard (13). These same authors proved that experimental animals could still be infected with 1/100 mg of such feces, even 1/1000 mg if it were administered intraperitoneal. Blanc and others therefore assume that, during the periods between epidemics, the typhus fever virus [sic] exists in unused clothing and in the louse feces deposited there.

Already in 1929, Sparrow and Lumbroso (17) caused infections in experimental animals through dropping infectious material into the nose and eyes. These experiments were conducted using a classical typhus fever strain. Later Nicolle and Sparrow demonstrated the same behavior with a murine strain of typhus fever.

Sparrow and Marechal (19) also caused infections in humans by placing infectious material in the eyelid sack and in the nose. They used a murine strain which was very non-pathogenic for humans, however. Based upon earlier experiments, Sparrow then assumed that infections contracted via nasal and conjunctival routes ("natural ways," as Sparrow [20] called them) were less severe than when contracted through sub-cutaneous innoculation. She wrote:

"Il est possible que le virus, en suspension etendue, introduit dans l'organisme par les voies naturelles d'une maniere qui ne lese pas les cellules, recontre, de la part de celles-ci, plus ou moins specialisees dans la luttre contre les agents pathogenes venus de l'exterieur, une resistance plus grand qui elimine une partie des microorganismes pour n'en laisser penetrer qu'une quantite infime, voisine de la dose minima infectante."

[It is possible that virus in a diluted suspension introduced into the organism via natural methods, and in a manner which does not in-

volve injury to cells, meets in these areas which are more or less specialized in countering pathogenic agents coming from the outside with a resistance which eliminates a part of the microorganisms by allowing only a minute amount to penetrate, similar to a dose minimum for infection.]

Only through the experimental work of Castanela (21) was the mode of transmission via air first brought into its proper light, in that Castaneda was able to demonstrate with experimental animals that the bronchial and alveolar epithelia not only had no resistance to the entry of the causative agent, but also constituted an ideal primary breeding ground for them.

Dyer (22), in agreement with the observations of Arkwright and Bacot (9), showed that fleas infected with murine virus did not infect guinea pigs when they were allowed to sting through mull gauze. He did succeed in infecting guinea pigs by rubbing the feces of fleas and mashed fleas on the skin.

Mooser and Castaneda (23) have proved by histology that, also in the case of the flea, the virus is never found in the salivary glands, but only in the intestine and in the Malpighian corpuscles (kidney-like organs) [sic].

These observations and determinations demonstrate that the infection does not result from the bite of the louse or flea as such. Only the feces are infectious, and infections of animals and humans occurred through placing infectious organ emulsions + lice feces in the eyelid sack of the eye and into the nose (Sparrow).

Natural methods of infection therefore would be assumed to include the following:

1. Scratches, whereby feces deposited on the skin and the content of the intestine of crushed lice enter the wound.

2. Innoculation via the bite of the louse, whereby the feces contaminating the exterior of the sucking apparatus enter the body.

3. Transmission of the feces into the eyelid tissue after crushing a louse with the fingers (carriers of lice habitually crush them between their fingernails).

4. Breathing in the dust of lice excretion.

Mooser, Varela and Pils (24) demonstrated for the first time that the human who is inapparently infected could not constitute the reservoir for the virus, since lice are not infected from an inapparent case. The epidemicological unimportance of inapparent infections for the sustaining

of the causative agent during inter-epidemic periods has also recently been recognized by Polish authors. It is for this reason that Blanc now assumes that the feces of lice constitute the reservoir for the virus from which new epidemics develop. It remains to be investigated as to whether the feces of lice can stay infectious under natural conditions as do the feces of fleas when dried in a laboratory. It also remains to be explained why typhus fever regularly breaks out in endemic areas during the colder seasons of the year. One would have to assume that all of the clothing put away in the spring would have to be taken out and worn again for the first time during the next winter (winter equipment). The lice contained therein would be long since dead, but the feces which had dried in place would still be virulent and persons not immune would be infected via the atmosphere.

As regards proof of the fact that the murine virus acts the same way as the classic typhus fever virus in human lice, being therefore just as likely as is the classic virus to cause lice-caused epidemics, it must be considered that in many areas the typhus fever virus is hosted by rodents, and that rodents therefore constitute the reservoir for epidemic typhus fever. That the murine virus can actually cause widespread epidemics propagated by lice was shown in Mexico (Mooser, Vareda and Pilz).

After the French authors [see note] had for years, sometimes with lively polemic, rejected the claims that the murine virus was transmitted by the human louse and that the classic virus was transmitted by the flea, Blanc and Baltazard (13) were also able, in 1940, to demonstrate how easily rat fleas could be infected with the classic virus. Blanc, however, considered this rather late discovery as an especially important personal accomplishment (Nouveaux faits experimentaux) (14). The only actual accomplishment of Blanc and Baltazard was that they demonstrated that the feces of the flea remained infectious for a much longer time than Bacot and the Polish authors had assumed for the feces of lice. Blanc, as already mentioned, then arrived at the opinion that the feces of lice form the virus reservoir from which epidemics develop after long epidemic-free periods. [Note: Ch. Nicolle and P. Giroud, Archives Inst. Pasteur (Archives of the Pasteur Institute), Tunis, 1935, 24, 47.]

Surprisingly, he discounts the flea of humans as a possible virus reservoir, despite the fact that Mooser demonstrated that the human flea acts in the same manner in relation to the classic typhus fever virus as does the rat flea to the murine virus. Blanc wrote of the human flea: "il ne reste jamais sur l'homme, emettant ses dejections loin de l'homme." (it never stays on humans, dropping its excretions far from man). How it was that he imagined the transmission of the murine typhus fever of rats to humans via the fleas of rats is then puzzling, since infection can occur only through the feces. It seems that the fleas in Casablanca are much more hygienic than elsewhere, where they deposit their feces in the clothing of humans. Anyone who has lived in the warmer regions is well

aware of the so-called "flea dirt" in underwear.

The mode of infection in numerous cases of humans having been infected in laboratories with murine and classic typhus fever virus has never been completely explained. It has been worthy of note, for instance, that contraction of the classic typhus fever has occurred only in cases where work was carried on with lice. As long as work was limited to that involving experimental animals, there have been no cases of such sickness. On the other hand, sickness has invariably occurred in all laboratories after the researchers began to work with murine strains, even when no lice were present. Nicolle, who warned especially of the danger of the murine strains as opposed to the classic strains, was of the opinion that the fleas of the experimental animals played a role. This could not be the case, however, since the fleas of rats transmit the classic typhus fever just as easily as the murine. Mooser explained the high contagiousness of the murine virus under laboratory conditions with the very large amounts of the causative agent in the endothelial lining of the tunica vaginalis of guinea pigs and the peritoneal cavity of rats, the only tissues of the experimental animals where, as in the case of lice, the causative agent can be demonstrated by means of direct smears. Mooser in his case assumed that a skin wound served as the place of entry.

Since the observations of nasal and conjunctival infections of animals (Mme. Sparrow), the possibility of conjunctival and nasal infection in these laboratory cases in humans has come to be considered more and more. Eyer and associates (27) [Translator's note: this article translated by USJPRS under CSO: R-3425-D] blamed the numerous cases of infection in their laboratory at Krakau upon the respiration of the dust-like excretions of lice. Experiments by Mme. Sparrow (29) have actually shown that practically unbelievable amounts of infectious materials are contained in the feces of lice. She pointed out that in a single louse intestine there is contained up to 100 billion infectious doses for rats. In that the clothing of typhus fever sufferers contain very great amounts of lice and their feces, the transmission via such feces according to the above statement must be very easy.

In their reports it is not stated as to whether Eyer and associates came upon the importance of the inspiration of lice excretion dust through intuition. They make no reference to the comprehensive experiments of Sparrow and Castaneda. The statement of Eyer and associates to the effect that the concentration of excretion dust in room atmosphere must have been very great in order to have caused a clinically manifested typhus fever in persons who had been immunized must be noted. This could be right. The mild "attacks" at the start of their work with lice were certainly not caused by typhus fever infection, however. Persons who have been immunized and then suffer a mild typhus fever do not become sick again a short time later when exposed to a clinically severe typhus

fever. This is contradicted mainly by the observations of French authors in Tunis and Morocco who, after even the mildest hint of an infection or even a purely inapparent infection following immunization with live murine virus, always observed an absolute immunity against subsequent infection with the classic virus. The results of the numerous experiments with animals also speak against the correctness of the opinion of Eyer and associates.

The reports of Ciuca and Ionesco-Mihaesti (28) bring the first observations of frequent laboratory infection with the classic typhus fever virus in the absence of lice. They worked with the method of Castaneda, meaning that they caused pneumonia in mice by dropping the virus in the nose. They explain some of their infections as having been caused through these droplets. The innoculation from mouse to mouse was done with emulsions of pneumatic lungs. Such lungs contain great amounts of virus, also in the case of strains of classic typhus fever, as shown by Durand and Sparrow (32). Dilutions to 10^{-12} still cause infection in guinea pigs. The presence of the classic virus in laboratories is therefore very dangerous, even in the absence of lice, since a method has been found which produces infections which are at least as strong as those of the intestine or feces of lice.

The very contagious disease described as typhus fever by Murchison, which then later was for a long time declared to be absolutely not contagious, becomes, with knowledge of the meaning of lice feces, again a highly contagious disease, but only as long as the feces of lice are present in the clothing of the patient, where they can so readily become dry and dusty. The Wolter "typhus fever miasma" can be seen in these lice feces. This issues not from "infested" land but rather from the "infested" clothing of the patient, however.

Head lice. Most epidemiologists are of the opinion that the head louse plays no role in the transmission of typhus fever. This opinion is certainly erroneous. The head lice act in relation to typhus fever identically with body lice. One of us often took infected lice from the head of a typhus fever patient. In view of recent knowledge concerning the importance of feces, the head lice-infested mane of a convalescent must, when shaken, be an ideal instrument for dispensing the dust of feces in the immediate area surrounding its bearer (Weichselsopf, df. introduction).

Our Observations

These deal with the infection of six persons which occurred in connection with attempts to obtain a typhus fever vaccine. The first attempts were carried out by one of the authors together with a laboratory assistant. Emulsions of typhus fever pneumonic lungs were dropped into the noses of rats and mice under ether. (Used here was a Mexican murine

strain which had been isolated from a patient in 1936/37. Since then the strain had been cultured in guinea pigs and maintained its characteristics fully since it was isolated.) At this time it occurred that, upon expiration, especially in the rats, but also with mice, the albumen-rich lung emulsions caused large bubbles to be created, which then burst. Infectious material was thus vaporized in the air of the room. For this reason it was ordered that the experiments would no longer be conducted while wearing only rubber gloves and aprons, but that gas masks would also be worn.

This was done. But the laboratory assistant (L. A., Case I) became ill shortly after the first experiments. The work was then stopped, but this caused an interruption in a series of therapeutic experiments which had already started, which was most unfortunate. After some hesitation, therefore, permission was granted to continue with the innoculations using gas masks. In the course of one experiment, 60 mice were innoculated nasally within half an hour. Shortly thereafter, all three persons who had taken part became ill, one after another. The gas masks had been worn only as long as the innoculations lasted and the participants removed them immediately thereafter, but remained in the room.

In addition, two female laboratory assistants, Miss Hu. and Miss He., became ill. Miss He. (Case V) had nothing to do with either the innoculation or the feeding, nor had she had any contact at all with the experimental animals. She entered the operations room for a very brief period of time after nasal innoculations had been conducted, but after everything had been cleaned and replaced. In this case, therefore, the infection can only be explained by a vaporization of the virus, as had seemed to be the case for the others who had become sick. Miss Hu. was never present during actual innoculations. Twice daily she had fed a sulfonamide preparation, as a part of chemotherapy experiments, to mice which had been nasally innoculated and at least once she entered the room in which animals had been innoculated very recently.

A Brief Description of Our Cases of Illness

Case I. (Illustration 1.) Clinical history, Vol 92, entry L. A., 34 years of age, laboratory assistant, male, helped with the first experiments (cf. above).

> 13 March 1941. First day of illness, in the morning sudden headache and increase of temperature. The next day the patient felt fine and was able to return to work ("crochet" of temperature, according to Nicolle).
>
> Third day of illness, renewed severe headache and on
>
> Fourth day of illness, admitted as typhus fever. General feeling

of exhaustion, pressure sensitivity in the calves. Scattered papules between the shoulder blades (papulous pre-exanthema described by the Mexican clinician Escalona). Striking bradycardia. SR [sedimentation rate?] not increased at first. Leukopenia with Li displacement and lymphopenia; eosinopelia.

Sixth day of illness, spleen becomes palpable, symptoms definitely severe. Often somnolent, but can be aroused, never actually delirious. Appearance of the typical, small-spotted exanthema. It is very dense and covers the entire body, including forearms, backs of the hands and palms of the hands, only the face is spared. The exanthema leaves a post-pigmentation and shows a petechial development. Very severe sensitivity to pressure in the calf muscles.

Eighth day. General condition still critical. "Status typhosus." Blood pressure 100/55.

Tenth day. Bronchialpneumonic symptoms prevailing. Massive amounts of type XXI pneumococcus in the sputum. SR 4/16 mm, increasing pulse with decreasing temperature. Weil-Felix positive 1:50,000.

Eleventh day. Extreme weakness. Pulse 128, dicrotic, blood pressure 115/50, extremely severe pressure sensitivity in calves, patient's tendon reflex completely diminished.

Twelfth day. Exanthema clearly petechial in places; in the evening the patient feels somewhat fresher, gradual recession of the pneumonia with Cibazol (total 37 grams). Finally spurting diuresis following previous slight ankle edema. With the pneumonia there occurred a neutrophile leukocytosis and a sharp increase in SR until far into the convalescence.

Twenty-second day. Since a light subfebrile temperature still persisted, a mild administration of Cibazol (10 grams) was given, whereupon the fever promptly vanished, exanthema disappearing.

Twenty-fifth day. SR 50/60.

Twenty-seventh day. Feeling better. Light areas on the lungs by x-ray examination. No longer sensitive to pressure on the calves, patient's tendon reflex positive, SR still 23/35 mm.

Case II. (Illustration 2.) V. G., Dr. of Medicine, male, 28 years of age. Became sick on 20 March 1941. Admitted on 22 March (3rd day). Temperature 39.2°C, pulse 120, SR 5/15 mm. Occasional roseola-like, papular efflorescence between the shoulder blades. General feeling of weakness, headache, spleen not yet enlarged. Blood pressure 140/80. No pro-

nounced bradycardia. Blood: relative leukopenia with lymphopenia, cf. curve. High febrile temperature until 9th day. Lytic decline, no fever after 13th day. Spleen becomes palpable on 6th day and remains so until after discharge. The exanthema increases, spreads over the entire back, decreases about the 14th day and becomes slightly petchial. Post-pigmentation. Urine: Diazo reaction continuously negative. Weil-Felix positive 1:100,000. During entire period of illness patient feels tired. Headache, pain in calves; overall progression of case classified as medium-severe.

Case III. (Illustration 3.) H. E., 24 year old male animal caretaker. No injury of any kind. Has worked at the Institute for one year. Participated in animal experiments.

First day (27 March 1941). Slight feverous feeling. After a short period of feeling well on next day ("crochet") there followed on 29 March, the

Third day, headache and pain in limbs, also coughing and increase in temperature.

Fifth day (31 March). Admitted to the clinic. Generally depressed feeling, headache, sensorium free. Very scattered papular efflorescence between the shoulder blades which can be squeezed off. Severe symptoms developed already on the evening of day of admission. Course of temperature (see chart) highly febrile over period of 13 days, remittent, then gradual decline to normal within five days. Continuous relative bradycardia. On the 10th day, the spleen becomes definitely palpable and at the same time the exanthema becomes somewhat more defined on the back. Blood pressure 95/60. Blood: persistent moderate lymphopenia, but always short of lymphocytosis. SR initially 37 mm in the first hour, one week later 20 mm, one more week later 50 mm. Weil-Felix 1:200. The reaction has no diagnostic importance in this case since the patient received 100 cc of convalescent blood on two occasions at the start of illness. During the entire period of sickness, a slight, diffused bronchial condition persisted in both lungs. Toward the end, colibacilluria with another increase in temperature. Very fleeting, temporary thrombophebitis of the left calf veins. Blood pressure 110/70.

Case IV. (Illustration 4.) G. A., Professor Doctor of Medicine, male, 45 years of age. Previously had malaria, otherwise healthy. Became ill with chills on 28 March 1941, more chills on 4th and 5th day. Severe, clearly typhus case with moderate psychomotor excitation. Appearance of a sparse, typical papular exanthema on the back and loins. From the start, coughing and mild bronchitis findings. Spleen palpable

on 4th day. Blood cultures sterile. No plasmodium maleriae in blood. Sixth day moderate bronchopneumonia in lower right fold. Eigth day small bronchopneumonic center lower left. Diminished bronchopneumonia after Cibazol, but no effect on temperature. Blood: Leukopenia 4000, stab culture 53, segment culture 24.5, eosinopenia 1.5, baso 1.5, mono 19.5, lympho 13, plasma 1. Slight toxic transformation. Weil-Felix 1:1600. Torturous thirst, high volume of urine with rich lateritious sedimentation, otherwise no finding, irregular-lytic drop in fever with persistent severe diffused bronchitis with mild asthmatic characteristics.

Case V. (Illustration 5.) He. R., female, 32 years of age, laboratory technician. This case is worthy of special interest because the patient was not actually a participant in the experiments. She had nothing to do with the animals, but explained that she had entered the room once after innoculations had been conducted but after everything was cleaned and replaced.

29 March 1941. Felt ill for first time, after two persons who had been involved in the experiments had become sick. Mild coughing. Temperature drops somewhat on 3rd day ("crochet"), later to rise to 39.5°C in the next few days.

Fifth day. Appearance of exanthema. Blood pressure 130/80.

Sixth day. Admission to the clinic. Very definite medium coarse-spotted, scattered exanthema over entire back and also on abdomen. The efflorescence are slightly raised and at this time can all be squeezed off. The extremities and face remain free. No increase in periferal circulation. Sensorium completely free. Spleen 8 cm not palpable. SR somewhat high initially. Leukopenia with lymphopenia with no great monocytosis. Weil-Felix positive 1:1600. Widal typhoid and paratyphoid tests negative. Tachycardia, running parallel with the temperature, continuing into the convalescent period. Heart tones pure. Flat "T" hooks in electrocardiogram. Temporary sensitivity to pressure in the calves.

Sixteenth day. Lytic temperature decline reaches normal this day. In contrast to the others, this patient had no particular complaints -- no actual headache, no pains in the limbs, also no somnolence. Blood pressure 110/70.

Case VI. (Illustration 6.) Hu., female, 24 years of age, laboratory technician. Patient was never present during innoculations. Twice daily she had fed innoculated mice, and while so engaged had always worn tight rubber gloves which reached to the shoulders and fit snuggly to the rubber apron.

Became ill on 7 April with symptoms similar to influenza, but with mild reactions. On the 4th day, a few roseola appeared. Rather intense headache for three days. On the 8th day onset of critical fever decrease. Illness of realtively short duration. Weil-Felix positive 1:100.

This illness would undoubtedly have been diagnosed as influenza in the absence of a particular interest in typhus fever. The mild course of the sickness is probably due to the fact that the patient had been immunized twice against typhus fever, first on 28 March, the second time on 5 April and with vaccine prepared from the same strain which caused the infection.

Case VII. M. H., Professor Doctor of Medicine. This one person of those participating in the animal experiments and exposed to an equally strong environment suffered only a fleeting, very slight, influenza-like indisposition during the time period in question. This apparent immunity is believed traceable to having survived typhus fever 14 years ago which was caused by the same strain of rickettsia.

Therapy in individual cases will not be discussed here. There is no specific to report. Sulfapyridine and Sulfathiazole, which were administered immediately in each case, failed completely. Only against the pneumonic complications did they prove to have any effect. Otherwise the therapy was the usual for fever diseases. In the more severe cases, stimulants were initially necessary.

Concerning Diagnosis

From H. Fracastoro, who differentiated typhus fever from other fevers for the first time in 1546, we quote here a few lines of his unsurpassable description. In his second book Von den Kontagien (On the Contagious Diseases), he writes about "the fevers, which are called lenticular, puncticular or peticular":

"There are fevers which occupy a more or less middle position between the true pest fevers and the non-pestilent, because many die of them, many do not.

"Like all pestilent fevers, they are at first mild, being so slight during the invasion period that the sick person hardly feels the need to visit a doctor and causing the doctor to erroneously expect the ailment to pass quickly....

"About the 4th or 7th day, red, often purplish spots break out on the arms, the back and on the chest, similar to flea bites, sometimes larger and pea-sized, whence the name [Fleckfieber, literal translation, 'spotted fever'].

"In the case of some patients there is somnolence, with others, insomnia, sometimes the two alternate in a single patient.

"The condition persists in some cases for seven days, in others for 14 days or longer."

In our situation, the diagnosis was oriented to typhus fever from the start. Only the patients themselves had doubts, and actually each for himself, about this diagnosis and at first believed himself to have influenza.

The various symptoms, if we discount the exanthema, were also initially those which accompany any severe fever ailment. In the absence of an epidemic and given no special circumstances, the diagnosis is therefore initially very uncertain until the specific reactions, such as the Weil-Felix-Reaction or the outbreak of typhus fever in experimental animals into which blood of the patient has been injected, bring certainty. The "status typhosis" was very pronounced in three of our cases -- in two cases (I, III) the severity exceeded that of a severe abdominal typhus; in Case IV, which was also severe, excitation (nervousness) was the prevailing symptom. The two female patients, also Case V which incidentally was not particularly mild, continued completely free in their sensorium.

Our cases were all characterized by exanthema. In Case I, it affected not only the trunk, as usually described, but also the extremities, to include the palms and soles of the feet. All cases showed a positive Weil-Felix-Reaction. In the first few days, the feverous sickness could hardly be distinguished from influenza so long as the sensorium remained free, no psychomotoric excitation existed and only the fever -- in one case (no.II) was accompanied only by chills and only a slight catarrh of the bronchial passage could be ascertained (status typhosis). In the more severe cases, these symptoms were accompanied by a clearly palpable spleen on the 4th-10th days, somewhat resembling the swelling present with undulant fever (Bang). In our Case IV, which began with chills and increasing swelling of the spleen, we first thought of the possibility of a malarial recividation, since the patient had suffered a severe tertian several years before.

The exanthema, which was expected in every case and sought for twice daily in detailed examinations, occurred in each case, but, with the exception of Case I, it was never a prevailing symptom. Although even when it was very slight, as in Case VI, it did not escape us because we looked for it, yet it is easy to imagine that it might not be found by every observer if he did not thoroughly search for it in every case of feverous sickness which lasts for a longer period of time. If the "roseolen" are not found, then the specific agglutination will probably also be omitted and a false diagnosis could occur.

As regards the progression of temperature, it was characteristic to a certain degree that the first increase was often followed by a brief drop (1-2 times in 24 hours), which was then followed by a continued increase -- in our Cases I, II and V. These temperature peaks (called "crochet" by Nicolle) are typical for typhus fever and can be found in the description of the patient. This is of little help in diagnosis. As to height and duration of fever, we refer the reader to the charts, each of which is quite typical in its way.

The behavior of the white corpuscles was monitored at all times and details are again to be seen in the charts: for the most part, there was leukopenia with left-displacement, presence of eosinophiles and lymphopenia. The complications such as pneumonia (Case I), cystitis and phlebitis (Case II) are characterized by the usual neutrophil leukocytes. Within the realm of the typical symptoms, our observations provided us with an idea of the wide variations between a typically severe case (Case I) to the inapparent case in Case VII.

Discussion

In that all of our cases were infected by relatively small amounts of virus taken in through the respiratory system (as we assume must have been the case), it is very noteworthy, in view of previous observations, that all who were'nt immune suffered a typically clinical case of typhus fever. In earlier experiments by Mooser (30) on humans with sub-cutaneous innoculation with large doses of virus of the murine strain which is now used again, only half the cases came down with a clinically diagnosable typhus fever. It therefore seems that the infection via subcutaneous methods is not as facilitated as through inspiration of the virus.

The pneumonic lungs of mice which were used in the Institute of Hygiene contained great amounts of virus. Peritoneal infection of white mice was still possible after dilution to $1:10^{-8}$ - 10^{-10} of suspensions of these lungs (31) (see also Durand and Sparrow, 32). An inapparent infection of mice was possible with 10^{-12} lungs. Here it must be considered, however, that these lung emulsions were not centrifuged and that the dose used might have a cm^3 of the greatest dilution or then again could have contained a cell fully loaded with rickettsia.

Our observations could be said to have experimentally shown that the typhus fever virus can cause typhus fever in humans upon being inspired. This is particularly understandable because bronchial and alveolar epithelial cells are very highly receptive places for the rickettsia to settle (Castaneda) (21). From here the further infection of the organism takes place through bursting of the infected cells and entry into the blood stream. It is noteworthy that the lower respiratory tract shows symptoms similar to influenza throughout the typhus fever infection.

Furthermore, in all of our cases, "complications" occurred which involved the respiratory tract. Possibly, however, these are actually not complications but rather are reactions at the point of entry of the virus. The almost obligatory participation of the respiratory tract in cases of typhus fever may indicate that, even under normal conditions, the organs of respiration often serve as the point of entry for the causative agent.

Influenza-like symptoms occurred in four of our cases at the very start (first or second day) of the illness, or days before the appearance of the exanthema, so that they cannot be explained as due to the exanthema or as a hypostasis. These initial lung symptoms are probably to be differentiated from the bronchopneumonic symptoms which occurred later in two of our cases. Typhus fever presents itself, as in our cases, as a sickness resembling influenza and text books refer especially to this similarity in a differential-diagnostic connection. Our cases started with coughing so that even the doctors among them believed themselves to have gotten influenza and at first could not be easily convinced that it was typhus fever at all.

Even though the transmission of typhus fever via the organs of respiration was proven experimentally in experiments on animals and humans by Mme. Sparrow and the observations of Castaneda, yet the transmission of typhus fever from human to human by means of coughing vapor does not necessarily follow. The respiratory tract may well be the point of entry but not the point of exit of the virus. Our observations should not be interpreted as saying that the authors are convinced that the transmission of typhus fever takes place from person to person through coughing vapors. Even in our cases which were partly very severe and required extensive care, there were no cases of secondary infection, as is the case when typhus fever occurs under natural conditions.

The case of Miss Hu. (Case VI) is worthy of special note in that the patient had been immunized against typhus fever. The first immunization took place 12 days before her sickness, on 28 March. The second immunization was on 5 April. These immunizations were carried out with a vaccine prepared from lungs bearing the same strain of murine typhus fever which caused her illness. She suffered a mild case of typhus fever, some roseola on the abdomen and back on the 5th day, some dry coughing, always feeling well in the morning with a rise in temperature evenings. She did not require hospitalization.

Research workers have become sick in all laboratories in which work has been carried on with typhus fever virus, and usually up to 100% of them; thus a higher percentage than with any other infectious agent, if we discount tularemia. The causative agent of typhus fever is therefore one of the most dangerous microbes to handle. It is certainly not erroneous to assume that a causative agent which brought about an infectiousness

in the laboratory surpassed by no other known agent could also be transmitted in basically the same way under natural conditions. To be especially pointed out in this connection is the fact that, in the case of typhus fever, the severity of the sickness is in direct proportion to the amount of the infected rickettsia taken in by the individual. This is clearly shown by the experiments of French authors on both humans and animals.

In view of the fact that, in a laboratory in which lice -- or typhus fever in any form -- are used, nearly all workers can become sick regardless of immunization, one must assume that an immunization does not provide protection against massive doses of inspired causative agents as are present in a laboratory. The observations of Mooser and Leemann (3) also vouch for this. They showed that mice which had become immune by having survived one infection could resist powerful doses of virus injected intraperitoneal, but that these same mice promptly became sick with typhus fever -- showing no difference from non-immunized mice -- when given an equal dose of virus in the pulmonary region via the nose.

The fact that humans are imparted a high degree of protection by having survived typhus fever once, however, is demonstrated by the fact that of seven persons who had participated in the nasal innoculation, six of them became sick with a typical case of typhus fever while the seventh, who had been exposed to the same atmosphere as the other six, suffered only a slight three-day indisposition. From this we must assume that humans are imparted an effective immunization for some time after having survived a typhus fever infection which entered through any point. It is also to be assumed that an immunization with a modern vaccine is effective against the type of exposure which may occur under natural conditions for at least a certain period of time. The observations made in Weigl's laboratory and the experiences of Eyer and associates seem to argue that such an immunization is not effective against massive doses introduced via the respiratory organs, however, In actuality, every immunized person who has worked with lice feces for longer periods of time has become sick with typhus fever.

However, in view of the fact that there are extremely large numbers of lice and there is an extraordinary amount of virus in their feces, caution is also to be recommended for persons who have been immunized. Members of delousing teams should, in addition to an immunization, be provided with a gas mask.

The feces of lice can be transformed into dust particles just as tobacco can. When handling lice-infested garments and by throwing back the blankets of typhus fever patients who have not been deloused, not only lice but also the feces of lice are thrown against the visitor. Thus the numerous cases in which persons who made no contact with lice have become sick during periods of epidemics (Jochmann and many others).

The recommendations of Bauer are therefore more applicable now than before. Typhus fever has again become an actual disease. For this reason, the cases observed by us are of particular interest, because they make a definite contribution to knowledge of the mechanics of infection.

Advances in the field of medicine, particularly those in the dangerous areas such as typhus fever, claim many victims. The history of typhus fever is overly rich with these. Our cases turned out favorably and left no damaging effects. Workers who carry on research in spite of this certain but unseen danger -- research which not only has a scientific interest but an eminently practical importance as in the case of typhus fever -- deserve the highest praise. Europe, and with it we ourselves, are threatened with this pestilence today, and knowledge of its nature and manner of propagation forms the basis for combating it. Let us consider the words of Johannes von Muller: "Courage in the face of obsolete evils is easy. Only the enlightened take proper measures in time. From him who waits for an emergency, only panicky, over-hasty action can be expected." Prophylactic measures are needed, and therefore further research in this area. Clinical observations have long since passed the point of diminishing returns. In 1882 Haeser (33) wrote of the typhus fever epidemics at the start of the 18th century: "As widespread as was the disease, as common the opportunity for observation, there is little to report concerning material advances in scientific insight."

Summary

Six cases of laboratory infections with murine typhus fever were described. Percutaneous infections can be eliminated in all six cases. The respiratory tract comes into question, however, as the point of entry for the infection, namely, through vaporized virus in the room.

In one case (He., Case V), this was the only possibility of infection. This patient never came into contact with infectious material, but only on one occasion entered the locality where nasal innoculations had been carried out a short time previously.

The opinion is expressed that the catarrhal symptoms in the respiratory tract which characterize the onset of the sickness are a specific symptom, pointing to the point of entry of the infection.

Our cases, some of which required close and continuous care, led to no further infections, as is also the case in most clinics. They were thus indicated as being non-contagious. An infection by means of vapor from human to human is therefore not likely. This agrees with all previous observations concerning the non-contagiousness of deloused patients.

Immunizations with vaccine do not provide certain protection against sickness, but are credited with having given the illness a mild character in Case VI. Surviving a case of typhus fever apparently provides better protection, even in the face of massive contamination in the laboratory.

In view of the fact that many immunized persons have become sick with typhus fever and the fact that immunized animals can be infected via the nasal method, it is recommended that members of delousing teams, who are exposed to particularly massive infectiousness, be equipped with gas masks in addition to their immunizations and protective clothing.

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