January 10, 1992

EPIDEMIC TYPHUS FEVER IN YUGOSLAVIA AND RUSSIA

Circumstances in Yugoslavia and several parts of the former Soviet Union are now approaching conditions predisposing to disastrous outbreaks of louse-borne typhus similar to those that occurred earlier in this century -- civil strife, either currently in progress or imminent; severe cold; fuel shortages; refugees crowding together; hunger in many places. Lice multiply very rapidly and spread throughout populations that are subjected to such circumstances.

Furthermore, there are thousands of individuals in Yugoslavia and parts of the former Soviet Union who had typhus years before, some of whom will develop a recrudescence of the disease (Brill-Zinsser Disease), infect the lice that feed upon them, and start epidemics among their louse-infested contacts. In the 1950s and early '60s this was demonstrated conclusively by Dr. Edward S. Murray and his associates in Yugoslavia.

The spread of typhus was sharply curtailed during World War II by well organized and coordinated measures against lice, early procurement of necessary supplies, vaccination of personnel, and rapid identification of the early cases followed promptly by delousing of their contacts. Since that time, however, lice over much of the world have developed varying degrees of resistance to insecticides. To the best of my knowledge no work is being done currently to produce effective anti-typhus vaccine in quantity. More information is needed as to the possible effects of doxycycline administered to typhus patients and to their contacts on the infectivity of the feces of their lice. Personnel need to be trained to detect typhus cases quickly and to delouse not only the patients but also their contacts. To combat typhus successfully there should be an organization (such as the United States of America Typhus Commission that was established by Executive Order of President Roosevelt in 1942) with authority to prepare plans and coordinate activities of several international agencies both civilian and military.

The purpose of this statement is to urge the appropriate organizations in the United States to recognize the imminence of the typhus threat and develop a coordinated plan with the World Health Organization and other international agencies for rapid and effective action to prevent the kind of disaster that struck Yugoslavia in 1915 and large parts of the former Soviet Union in 1919-22. A few statistics emphasize the magnitude of former disasters:--

Serbia, 1915-16: "more than 150,000 deaths from typhus in less than six months"; Russia, 1919-22:"..more than twenty-five million cases of typhus in the territories controlled by the Soviet Republic, with from two and one-half to three million deaths." Zinsser, "Rats, Lice, and History" pp. 297-99.

John C. Snyder, M.D., Staff Member,
International Health Division,
the Rockefeller Foundation, 1940-46,
Member, United States of America Typhus Commission, 1942-45

conditions of severe exposure. I was assigned to Naples, Italy, when typhus broke out in the air raid shelters and was spreading rapidly -- I was responsible for training the personnel of eight teams for case finding and delousing of patients and close contacts using power dusters and DDT powder. Later I was assigned by the office of preventive medicine in the US Army Medical Corps to enter several of the concentration camps as soon as they were liberated by the Allied Forces, to establish the extent of the typhus epidemics then in progress and to assist in the delousing and vaccinating. After the end of the war, as Professor of Microbiology at the Harvard School of Public Health, I worked with Dr. E.S. Murray to prove that patients with Brill's Disease did infect lice that fed upon them, and we published the first designation of recrudescent typhus as Brill-Zinsser Disease. Dr. Murray subsequently documented several outbreaks of typhus in different parts of Yugoslavia that began with a patient suffering from Brill-Zinsser Disease. I made one observation, in Teheran in February, 1943, (that I did not have a chance to publish because of the pressure to assist in the efforts of the Typhus Commission to control the outbreaks in various villages as well as in Cairo): the observation may be of some importance, however - - several head lice were removed from a seriously ill typhus patient and kept very carefully isolated from the body lice from the same patient; the head lice proved to be just as heavily infected with rickettsiae as did the body lice when these were tested in the Cairo laboratory two days after removal from the patient. Head lice in several countries including the United States of America and Great Britain have become prominent especially among children, and if that is also true in Yugoslavia and parts of the Commonwealth of Independent States, the typhus problem may have another dimension.

I hope the above will indicate why I am so keenly interested in the situation in Eastern Europe.

Sincerely yours,

John C. Snyder, M.D

Please return to JCS

HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

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please refer to : R7/370/1
e rappeler la référence:

Dr John C. Snyder
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Etats-Unis d'Amérique

2 April 1992

Dear Dr Snyder,

Thank you for your letter of 15 February 1992 concerning the control of rickettsial diseases in countries of East Europe and the historical aspects of Rickettsiology.

Please accept our apologies for the delay in replying to you. This is due to the fact that, in the meantime, we have been in contact with the Public Health Authorities in the countries in question. Recently our colleagues in Yugoslavia informed us that the last case of epidemic typhus recorded in that country was in 1971. Also, a limited number of cases of Brill-Zinsser disease has been noted over the last several years. For example, 13 cases were noted in Bosnia and Herzegovina in 1991. However, as there is no "Pediculosis vestimenti", there is no immediate risk of an outbreak of epidemic typhus from persons with Brill-Zinsser disease.

Your recommendations on the activities to be undertaken for a better control of epidemic typhus were discussed at a recent WHO HQ/EURO meeting on joint strategies for prevention and control of communicable diseases in selected countries of the Commonwealth of Independent States and Central and Eastern Europe. In accordance with the recommendations of the meeting, copies of your letter were dispatched to the Directors of WHO Collaborating Centres in Czechoslovakia and the Federation of Russia so that they may consider your proposals.

I take this opportunity to inform you that the report on the current status of the WHO Project on Global Surveillance of Rickettsial Diseases is being prepared for publication in one of the WHO editions. As soon as the manuscript is finalized and approved a copy will be sent to you.

With kind regards,

Yours sincerely,

Y. Pervikov

Dr Y. Pervikov
Medical Officer

Viral and Rickettsial Infections of Man, 4th Edition 1965
Edited by Horsfall, Jr.
(First edition of 6 was edited by Thomas M Rivers, MD Director of Rockefeller Inst Medical Research.)

JOHN C. SNYDER, M.D.
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The Typhus Fevers

Several human infections are induced by micro-organisms called "rickettsiae" which have been tentatively placed in the family *Rickettsiaceae* (Pinkerton, 1936). These micro-organisms are intermediate in characteristics between bacteria and viruses. They are readily visible in microscopic preparations as pleomorphic cocco-bacillary forms, multiply only within certain cells of susceptible species, and are found in various arthropods in nature. On the basis of clinical features, epidemiologic aspects, serologic and immunologic characteristics, the rickettsial diseases of man are divided into the five groups listed below.

1. Typhus group (discussed in this chapter)
   a. Classic epidemic (louse-borne) typhus
   b. Murine (flea-borne) typhus
   c. Brill's disease
2. Spotted-fever group (Chapter 33)
3. Scrub typhus (Tsutsugamushi disease) (Chapter 34)
4. Q fever (Chapter 35)
5. Trench fever (Chapter 36)

CLASSIC EPIDEMIC TYPHUS (LOUSE-BORNE)

(SYNONYMS: Jail fever, camp fever, war fever, famine fever, ship fever, hospital fever, petechial fever, morbus hungaricus, *typhus historique, typhus exanthematique, dermotypho, tabardillo, typhus exantematico, Fleckfieber*)

INTRODUCTION

Typhus fever is an acute, infectious disease characterized by sustained high fever, severe headache, generalized macular or maculopapular rash, and termination by rapid lysis in 14 to 18 days. Case-fatality rate in epidemics is about 20 per cent. The etiologic agent was named *Rickettsia prowazeki* in honor of two investigators, Dr. Howard Taylor Ricketts, an American, and Dr. S. von Prowazek, an Austrian, who died of typhus fever in the course of their studies of its etiology (da Rocha-Lima, 1916).

HISTORY

Although typhus fever has probably afflicted mankind since ancient times, it has not been definitely identified in the numerous records of epidemics which occurred before the sixteenth century. Zinsser believed that the account of an illness in the Italian monastery near Salerno which occurred in 1083 may have referred to typhus fever (Zinsser, 1935). However, the description by Fracastorius (1546) is the earliest medical record which is sufficiently clear to identify typhus fever as a separate entity. The word typhus is derived from the Greek, *typhos,* meaning smoky or hazy. Although the term had been used by Hippocrates to depict a "confused state of intellect with a tendency to stupor," it was not actually applied to typhus fever until

skin lesions. Bronchopneumonia, myocardial changes and petechial hemorrhages in the subcutaneous tissues and brain are the principal features which may be observed. Rarely, symmetrical gangrene of the extremities and thrombosis of a large blood vessel may be present. The microscopic pathology of typhus is quite characteristic. Rickettsiae multiply inside endothelial cells lining small blood vessels. Affected cells become swollen and proliferation occurs as shown by numerous mitotic figures. Thrombosis results from injury caused by rickettsial growth. Accumulation of polymorphonuclear leukocytes, macrophages and lymphoid cells around such lesions in capillaries, arterioles or venules gives rise to distinctive histologic appearance sometimes referred to as Fraenkel's nodules (Fig. 37). Early stages in the development of these lesions have been studied by skin biopsies (Wolbach, Todd and Palfrey, 1922). Rickettsiae can be demonstrated by careful technic in some of the endothelial cells. Vascular lesions are most numerous in the skin, central nervous system and myocardium, but are scattered widely throughout different organs of the body. Necrotic areas of the skin appear to be associated with thrombosis of capillaries, small arteries, and veins beginning in the corium. Symmetrical gangrene of the extremities may be due to nerve lesions instead of thrombosis of large vessels. Lesions in the respiratory tract are similar to those in terminal bronchopneumonic processes in various diseases and are not distinctive of typhus. (References which describe the pathology of typhus: Ceelen, 1919; Wolbach, Todd and Palfrey, 1922; Wolbach, 1948).

Experimental Infection; Host Range

Classic epidemic typhus is a disease which occurs as a natural infection of man, the human body louse, *Pediculus humanus corporis,* and the human head louse, *Pediculus humanus capitis*. The rôle of the human body louse in the transmission of typhus, although previously suspected (Otto, 1909), was first demonstrated experimentally by Nicolle, Comte and Conseil (1909). Their observations were promptly confirmed (Ricketts and Wilder, 1910a; Anderson and Goldberger, 1912). The human body louse spends its entire existence in the clothes of man. Eggs are laid in the seams of the undergarments. After about eight days, the eggs hatch and the nymphs in the course of two weeks go through three moults to become adults. The insects crawl about on the clothes, leaving the garments only to take a blood meal from their host. Lice cannot fly or jump but they have been observed to crawl for several yards. Each louse takes four to six blood meals a day from its host under natural conditions. Human blood constitutes their only food. *R. prowazeki* is present in the blood of patients suffering from typhus during the febrile period of the disease. The body louse becomes infected by imbibing a blood meal containing rickettsiae, which then enter cells lining the intestinal tract of the louse. All stages of lice, whether newly hatched lymphs or fully developed adults, are susceptible to infection with *R. prowazeki*. After a few days the rickettsiae have multiplied so profusely that the cells containing them are swollen and may burst. The organisms may then be passed in the feces of the louse or may enter uninvolved cells lining the intestinal tract. Ordinarily, rickettsiae appear in the feces of a typhus-infected louse about three to five days after the first infective meal. The louse usually succumbs to the infection after seven to ten days, but it is important to note that 24 days may elapse before all cells of the mid-intestine become full of rickettsiae.

Lice have been extensively used in typhus research. For this purpose a colony of normal stock lice is maintained by feeding on healthy human subjects twice daily. The lice are confined in a small capsule covered with bolting silk which is strapped to the

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leg or arm. Sometimes it is more convenient to store the capsule in an incubator between feedings. If the temperature is lower than 30° C., or higher than 32° C., rickettsiae may fail to develop; at temperatures above 37° C. the louse colony fares poorly. An ingenious technic was developed for the experimental infection of lice by means of a glass capillary inserted into the insect's rectum (Weigl, 1920). Lice thus infected develop typhus which is similar in every respect to the infection acquired by feeding. Although lice ordinarily do not thrive if nourished on other species than man, it has been possible to infect and to nourish them on rabbits, thereby permitting a wider range of experiments with these insects (Snyder and Wheeler, 1945). Russian workers have claimed successful results by feeding lice through a variety of membranes (Pshenichnov, 1943).

The presence of rickettsiae in the feces of lice or in the intestinal tract of a louse may be demonstrated by means of smear preparations or fixed tissue sections (Wolbach, Todd and Palfrey, 1922). Since nonpathogenic rickettsiae may be encountered in the intestinal tract of normal lice, the demonstration of rickettsialike organisms in smears of louse feces or intestines is not sufficient evidence upon which to base a diagnosis of typhus infection. *Rickettsiae prowazeki* are present only in the intestinal lining cells and the feces of infected lice; they have not been demonstrated in other tissues, such as the salivary glands; they are not passed from generation to generation of lice in the egg.

The course of typhus infection in the human head louse is identical to that in the body louse (Goldberger and Anderson, 1912), but the latter is far more important in transmission of epidemic typhus. (References: Wolbach, Todd and Palfrey, 1922; da Rocha-Lima, 1930; Buxton, 1939.)

Monkeys, guinea pigs, rats and other rodents, developing chick embryos, and certain arthropods are susceptible to experimental infection with classic epidemic typhus. Monkeys inoculated with *R. prowazeki* undergo a febrile illness of a few days' duration from which they survive as a rule (Nicolle, 1909; Anderson and Goldberger, 1912). A skin eruption has been described in typhus-infected monkeys, but more often this is absent. The animals suffer loss of appetite and become apathetic, but otherwise exhibit no evidence of illness. In typhus research, the inoculation of monkeys is neither satisfactory nor practicable.

Typhus was transmitted to guinea pigs by Nicolle, Conseil and Conor (1911), who observed that the animals responded to inoculation by developing a fever of several days' duration. Typhus is established in guinea pigs by the intraabdominal inoculation of blood taken from a typhus patient during the febrile period. If the specimen is obtained in the first week of illness, whole blood may be used. After the seventh or eighth day it is advisable to allow the specimen to clot; after centrifugation the serum is separated and stored for use in serologic tests; the clot is then ground with an equal volume of a sterile diluent, such as saline solution, skimmed milk or nutrient broth. After allowing gross particles to settle out, the suspension of ground clot is inoculated into two male guinea pigs, each weighing about 500 grams; each animal is given four to five cubic centimeters. Female pigs may be employed successfully, but, for reasons to be mentioned in the section on murine typhus, male guinea pigs are preferred. Removal of the serum from the clot serves to increase the chance of successful detection of rickettsiae by eliminating antibodies which are present in the patient's blood serum after the seventh day of illness. In some instances, the pigs may be sick during the first 18 to 24 hours after the inoculation, probably as a consequence of the large volume of blood which is required for successful isolation of rickettsiae. A small percentage of animals may succumb at this stage. Usually, however, the animals remain entirely well after