War Medicine Series

The paper printed below is based on a lecture which was one of a series recently given at the British Postgraduate Medical School, Hammersmith

LOUSE-BORNE TYPHUS FEVER

BY

Sir J. W. D. MEGAW, M.B., D.Sc., I.M.S.(ret.)

(Concluded from p. 403)

Diagnosis

The diagnosis of severe cases in established epidemics is easy and mistakes are rarely made. On the other hand sporadic cases, especially when they are mild, are often missed. An attitude of watchful suspicion and resort to laboratory tests are essential if these mistakes are to be avoided. M. D. Mackenzie states that 87 groups of cases have occurred in Glasgow between 1901 and 1926: in 36 of these the first case was wrongly diagnosed. There is reason to suspect that a good many sporadic cases may have occurred in this country without being detected. In every case in which there is the slightest possibility that the disease may be typhus early and repeated Weil-Felix tests should be carried out. This test, though not infallible, is by far the most reliable method of diagnosis that is generally available. All large laboratories have facilities for carrying out the reaction, which in most cases becomes positive before the end of the first week, though it may, exceptionally, be delayed till the ninth or tenth day, and in rare cases it remains negative. The special feature of the reaction is that the titre of agglutination rises rapidly, usually reaching heights of 1/500 or over towards the end of the fever or in early convalescence; then it falls to a low level, but titres of 1/50 or 1/100 may persist for weeks or even months. A reliable strain of *Proteus* OX 19 is essential; this is best obtained from the Oxford Standards Laboratory. In Great Britain complete naked-eye agglutination in a dilution of 1/100 is strong evidence of typhus fever, but if repeated tests are made the maximum titre is seldom less than 1/500. If the titre remains constant throughout the illness and convalescence a false positive should be suspected even if the reaction is positive in dilutions of 1/200 or more. The reaction is also positive in rising and falling titre in flea-borne typhus, often also in tick-borne typhus, but so rarely in other diseases that mistakes are very unlikely to occur. Recent work in America suggests that agglutination tests in which suspensions of *R. prowazeki* made from yolk-sac cultures are used may prove to be more strictly specific than the Weil-Felix reaction. The same remark applies to complement-fixation tests in which similar cultures are employed as the antigen; but neither of these tests has yet come into general use.

When laboratory facilities are available an attempt should be made to isolate the virus by intraperitoneal inoculation into guinea-pigs of 2 to 5 c.cm. of blood taken from the patient at the height of the fever. Isolation of the virus is the one method by which an absolute diagnosis can be made.

When persons who have been inoculated against fevers of the typhoid group are attacked by typhus the Widal reaction is often positive in rising and falling titre, so that a mistaken diagnosis of typhoid has often been made by medical men who were not aware of this fallacy in the reaction. When inoculated persons are suspected of having typhoid and the blood cultures are negative the serum should be tested for typhus by the Weil-Felix reaction. The Wassermann reaction also may be positive during attacks of typhus.

For rapid bedside diagnosis a modification of the Weil-Felix reaction is sometimes used. A drop of the patient's serum is placed on a glass slide; to this is added a drop of suspension of *Proteus* OX 19 which has been tinted with methylene blue; the mixture is then tilted up and down for two or three minutes.

In positive cases clumping is visible to the naked eye, but the standard test should be carried out in all reactors to find the titre of agglutination. Another modification has quite recently been described by German workers; this, called the "dry-blood agglutination test," has already proved its value as a means of making large-scale surveys of suspected populations. One or more droplets of each person's blood are allowed to dry on a labelled glass slide; suspensions of *Proteus* OX 19 are afterwards stirred in over the dried droplets; the slides are tilted up and down, and the results observed at intervals up to 10 minutes. In positive cases the clumping can easily be seen with a pocket lens. The standard test should be carried out in all positive cases.

Differential Diagnosis.—Typhus fever may simulate typhoid, meningitis, influenza, bronchitis, pneumonia, febrile catarrh, appendicitis, measles, small-pox, dengue and other fevers, especially during the first few days before appearance of the rash and development of agglutinins. Differentiation is seldom difficult if typhus is suspected and the usual laboratory tests are made. The simultaneous occurrence of other diseases, even in the same patient, is not infrequent during epidemics; in such cases serious mistakes may be made if a complete examination is not carried out. Flea-borne typhus can be distinguished from louse-borne typhus only by animal inoculation, though a knowledge of the conditions in which the infection has occurred will usually prevent difficulties from arising.

War Typhus

Typhus fever is far more common and far more deadly in the conditions resulting from war than in times of peace. Great movements of population often involve the transfer of susceptible persons to infected areas or of infected persons to places previously free from the disease. In either case the virus finds a virgin soil in which it flourishes. Overcrowding and lack of facilities for washing cause a great increase in the louse population and in the opportunities for migration of the insects from one host to another. Malnutrition causes lowering of resistance to infection. These factors lead to an acceleration in the rate of transmission from man to man and so to an increase in the virulence of the infection. Correspondingly, the incubation stage is shortened to an almost uniform period of about 8 days; mild attacks are less common and the death rate is higher. Even in areas in which the disease is smouldering in mild endemic form the risk to troops is great, because the soldiers are usually new-comers from non-infected places and so are highly susceptible.

Prevention

The best method of prevention is to eliminate louse infestation. This is a simple matter in normal conditions, but in war it may be very difficult or even impossible. The military medical authorities are fully alive to the importance of the problem; they have worked out an organization to deal with any conditions that can be foreseen. But no regulations, however perfect, can relieve the medical officers of the responsibility for constant vigilance; they must suspect typhus in every doubtful case of fever in areas of possible endemicity, and they must keep a careful watch on the health of the local inhabitants as well as of their own personnel. If the troops are stationed for any length of time in a suspected locality useful information can often be obtained from the local medical men; but undue reliance must not be placed on negative reports, because infection often smoulders in areas which appear to be free from the disease. The "dry-blood agglutination test" already mentioned deserves consideration as a rapid method of carrying out a survey in suspected localities: it has been used with success in German-occupied countries. The test can be carried out more rapidly and easily than the search for malaria parasites in blood films. Details of the method are given in the *Bulletin of War Medicine*, May, 1942, p. 397, and the *Tropical Diseases Bulletin*, June, 1942, p. 372.

The personnel engaged in typhus work of every kind should be young because of the great risk to life in the case of elderly persons. Preliminary inoculation should also be carried out if possible. In dealing with infected persons disinfection of the patient's skin by chemical antiseptics is desirable because of the risk of infection from louse faeces. Buxton suggests lathering the skin with a mixture of 1½ oz. of Jeyes' fluid,

1½ lb. of soft soap, and 10 gallons of water as a preliminary to bathing. For the same reason clothing and bedding should be disinfected by heat rather than disinfested with cyanide gas, which is of special value in the disinfestation of rooms and furniture. Special louse-proof clothing should be worn by persons exposed to risk: if this is not available a fair degree of protection is afforded by wearing rubber gloves and gumboots into which the sleeves and trousers are tucked; the arms and legs should be smeared with camphorated oil made of 1 part of camphor to 9 parts of olive oil or liquid paraffin. The clothing must be changed frequently, and on each occasion a hot bath should be taken after preliminary lathering of the skin with a medicated soap of the type suggested by Buxton.

Medical men in Great Britain will find useful information about preventive measures in the Ministry of Health Memo. No. 252/Med. The general practitioner must always play a leading part in the detection of the first cases: he and the staff of our hospitals ought to keep a close look-out for suspicious cases. There is no need for an alarmist view of the risk of infection in this country; conditions here are very different from those prevailing in great epidemics, in which the danger to the medical and nursing personnel is very considerable. On the other hand the attitude of the medical profession should be one of uncompromising hostility to louse infestation, which is still far too widespread here. Educational propaganda directed towards arousing feelings of disgust and fear against lice must be combined with measures for the control of the insects.

Preventive Inoculation

Many kinds of protective vaccines have been tried; these fall into two main groups: (1) killed vaccines made from the rickettsiae of the disease; and (2) living vaccines containing the rickettsiae of flea-borne typhus, which have antigenic properties similar to those of louse-borne typhus. The living virus, attenuated in various ways, has been used on a large scale in French North Africa with apparent success: the vaccine acts by causing an unapparent or mild attack of the disease, but in some cases severe or even fatal attacks have resulted owing to an unexplained increase in virulence of the rickettsiae. There is a natural reluctance to use a virus whose constancy cannot be guaranteed, and, besides, there is some risk of introducing infection into places which are free from the disease.

Killed vaccines are free from risk; the first of these to be used on a large scale was Weigl's vaccine, which undoubtedly gives a considerable degree of protection. The preparation of each course of vaccine for one person involves inoculation per rectum of about a hundred lice, which have to be fed for some days on immunized persons and then dissected to extract their infected guts. This vaccine is clearly impracticable for everyday use. Cox has worked out a method which holds out promise of success; he grows cultures of *Rickettsia prowazeki* in the yolk sacs of developing chick embryos; suspensions of these cultures contain enormous numbers of rickettsiae, and large quantities of killed vaccine can be prepared at a small cost. The vaccine immunizes animals, but the crucial test of its effectiveness on human beings has not yet been completed. German workers have naturally been interested in Cox's vaccine; they are known to have taken up its preparation, and there are suggestions that it has already been found effective in reducing the severity of attacks which have occurred in inoculated persons. Killed rickettsial vaccines have not hitherto been found capable of producing complete immunity against virulent infection, but there is good evidence that they often lessen the risk to life.

The control of typhus fever in war conditions may be extremely difficult, as is shown by a report which appeared recently in a German medical journal. No fewer than 117 men engaged in guarding prisoner-of-war camps in one military district in Poland were attacked in November and December, 1941, in spite of delousing and orders to avoid close contact with the prisoners. The fatality rate was 35% in 82 of these persons who had not been vaccinated, but was *nil* in 35 who had been given one or more doses of a vaccine of unspecified type. In the same report there is a statement that 104 cases of a milder form of the disease were treated in the same hospital in the following two months. The patients were

soldiers who had just returned from the eastern front; they had evidently become infected on the journey, but the virulence of the infection was low and there were no deaths.

Treatment

German physicians have been trying hard to find a curative drug, but although some of them have made great claims for sulphapyridine others are equally emphatic that it is useless except, possibly, in complications caused by organisms for which it has a specific action. The latest claim is for mepacrine hydrochloride (atebrin), preferably combined with pamaquin (plasmoquine); detailed evidence is promised, but in view of past disappointments it may be best to avoid undue optimism. No further reports have appeared about the use of intravenous solutions of chlorine which were claimed by Danielopolu to give almost miraculous results in the severest cases. Convalescent serum or direct transfusions of blood from convalescents may have some value if given early, but few observers are enthusiastic about their efficacy.

Good nursing and a light nutritious diet, rich in all the vitamins, form the basis of treatment. The free use of subcutaneous injections of normal saline or Ringer's solution is advocated by several physicians. Plenty of liquid should be given by the mouth. Chloral hydrate in doses of 15 to 40 gr. often relieves headache, joint pains, insomnia, and restlessness: if it fails lumbar puncture may be needed. Warm or even hot baths have their advocates. Complete rest, attention to the toilet of the mouth, and the prevention of bed-sores are other important points. Even in mild cases the patient must be kept in bed for at least a week after the temperature has fallen: in severe cases complete rest for periods up to three weeks or longer is essential because of the risk of sudden heart failure. For anaemia, iron and liver extract are needed.

In a disease which shows such extreme variations in the severity of different outbreaks, and even at different periods during the same outbreak, great caution is needed in estimating the effect of any special line of treatment. With any scheme of treatment the case mortality may range from *nil* to 30% or more.

The Other Fevers of the Typhus Group

As already stated, these are primarily diseases of lower animals, or "zootic" diseases, and are not capable of being naturally transmitted from man to man as is the case with louse-borne typhus, which is primarily a human, or "demic," disease. This general statement needs qualification in the case of flea-borne typhus: this disease is caused by a virus which is so closely related to *R. prowazeki* that many experts regard it as a variety of that organism rather than a distinct species. Some workers hold that the virus of flea-borne typhus, after being transmitted in the first instance from rat to man by the rat flea, may at times become capable of being transmitted from man to man by human lice. This is a disputed point, but even if the virus should occasionally be transmitted from man to man the resultant disease would automatically become louse-borne typhus and would have to be handled accordingly. Flea-borne typhus may possibly be the ancestor of the human disease, whose virus in that case would have originated as a modification of the rickettsiae of flea-borne typhus.

The other "animal" typhus fevers which are conveyed to man by ticks and mites, respectively, have never been known to be transmitted in natural conditions from man to man; cases of these diseases do not call for special precautions to prevent the spread of infection to contacts. On the other hand the possibility that flea-borne typhus may be transmissible by lice must be borne in mind; cases in louse-infested persons or communities should be handled on the same lines as louse-borne typhus, even though the risk of infection is doubtful or negligible in most of the affected localities.

Flea-borne Typhus

This is primarily a disease of rats, perhaps also of mice; it is ordinarily conveyed to man by the rat flea. The usual names of the disease are "murine typhus" and "endemic typhus," but neither name is appropriate: mite-borne typhus is also a murine disease, and both tick-borne and mite-borne typhus have an equal right to be called endemic diseases; even louse-borne

typhus often occurs in endemic form. The numerous other names that have been given to the disease are equally unsuitable. Flea-borne typhus was first recognized only a few years ago, but already it is known to be widely distributed in many parts of the world; the only condition essential for its occurrence is contact between human beings and infected rats which harbour fleas. This contact is most frequent in houses in urban areas, so that the disease is chiefly urban or, at any rate, domestic in type, as opposed to tick-borne and mite-borne typhus fevers, which are rural in their distribution.

The virus, called *Rickettsia mooseri*, is similar in its serological and immunological features to that of louse-borne typhus, but it causes a milder disease in man and a more serious disease in rats than *R. prowazeki*. Mention has already been made of the possibility that the virus may in exceptional conditions become modified so as to be transmissible by human lice from man to man. Some French observers believe that the virus can be conveyed by food which has been contaminated with the faeces or urine of infected rats.

The clinical features of flea-borne typhus are very similar to those of mild louse-borne typhus; the case-mortality rate is very low as a rule, but virulent forms of the disease have been reported from Mexico and elsewhere. The disease should be suspected, even in this country, when sporadic cases of typhus-like fever occur in persons who are free from louse infestation and who

The onset and decline of the fever are usually more gradual than in louse-borne typhus; the rash is maculo-papular and usually extends to the palms, soles, and face. In some localities a local sore with lymphangitis often occurs at the site of the tick-bite. The agglutination response to *Proteus* OX 19 and OXK is very variable, ranging in each case from negative to strongly positive. Complement-fixation tests or agglutination tests in which the specific rickettsiae are employed may prove to be reliable methods of differential diagnosis from the other typhus fevers.

Prevention is by frequent examination of the body for ticks or by wearing tick-proof clothing when living or travelling in affected localities. If the ticks are removed within an hour or two after attaching themselves there is little risk of infection. A drop of tincture of iodine or kerosene should be applied to each tick before it is removed. Killed vaccines made from suspensions of laboratory-infected ticks have been used with success, and now yolk-sac cultures of the rickettsiae are being tried.

Mite-borne Typhus

This disease occurs chiefly in the Far East; cases have also been reported from India. The disease is rural in distribution; the causal rickettsiae are conveyed from infected rats by larval mites, which are microscopic in size. Japan is the home of

Fevers of the Typhus Group

Epidemic Typhus Fever (preferably called "Demic" Typhus Fever). A human disease, transmitted from man to man by human lice. Associated with louse infestation, poverty, famine, and overcrowding.		The Non-epidemic Typhus Fevers (preferably called "Zootic" Typhus Fevers). Primarily diseases of lower animals, transmitted secondarily to man by fleas, ticks, or mites. Associated with life in the open country and forests or with contact with rats, dogs, etc. "Place" diseases and usually sporadic.		
Names	Louse typhus	Flea typhus	Tick typhus	Mite typhus
Synonyms	Typhus fever, typhus exanthematicus, etc.	Murine typhus, endemic typhus, shop or urban tropical typhus	Rocky Mountain spotted fever, boutonneuse fever, tick-bite fever, etc.	Japanese river fever, tsutsugamushi, scrub typhal typhus, etc.
Virus	<i>Rickettsia prowazeki</i>	<i>Rickettsia mooseri</i>	<i>Rickettsia rickettsi</i>	<i>Rickettsia tsutsugamushi</i>
Vectors	Human lice	Rat fleas	Various ticks	Larval mites
Reservoirs of infection	Man only known	Rats and mice	Various rodents; dogs and other animals suspected	Rats
Agglutination against : <i>Proteus</i> OX 19	++ to ++++	++ to +++	- to +++	- to +
" OX 2	++ to +++	++ to +++	- to ++	- to +
" OXK	- to +	- to +	- to ++	++ to ++++
Rash	Small macules, first on sides of chest, spreading over trunk, arms, and legs. Seldom on palms, soles, and face	As in louse typhus, but often inconspicuous or absent	Often conspicuous; may be nodular. Common on palms, soles, and face	Macular; often on face, rare on palms and soles
Local sore and lymphadenitis	Absent	Absent	Usually absent, but common in some localities, especially North and South Africa	Usually present in Japanese cases; absent or uncommon in Malayan and Dutch East Indian cases
Case mortality	5 to 50%	0 to 4% as a rule	1 to 70%	1 to 60%
Cross-immunity in animals	Strong against flea typhus, nil or weak against tick or mite typhus	Strong against louse typhus, nil or weak against tick or mite typhus	Only slight against other forms of typhus	Only slight against other forms of typhus
Distribution	Cosmopolitan, but not common in the Tropics	World-wide, common in the Tropics	Many localities in America, Europe, Africa, and Asia. Not common near the Equator except at high altitudes	Far Eastern tropical and subtropical countries

have not been in contact with cases of louse-borne typhus. In countries where tick-borne or mite-borne typhus occurs there is often a difficulty in differential diagnosis, but knowledge of the epidemiological conditions, and laboratory tests if available, will usually be of great help. The rising and falling titre of agglutination to *Proteus* OX 19 is the same as in louse-borne typhus, and the reaction to *Proteus* OXK is negative or weak. Prevention is by rat destruction on the same lines as in plague.

Tick-borne Typhus

This disease occurs in many areas in North and South America, Asia, North and South Africa, and Southern Europe. Cases occur chiefly in temperate and subtropical climates during the season of activity of the vector ticks. The chief risk of infection is from bites by ticks which have been infected by animals in the open country or forests of affected areas, so that the disease is rare in urban communities. The handling of ticks which infest dogs has been regarded as the source of infection in some cases. Certain areas in the Rocky Mountains are the home of the classical form of the disease. The virulence of the infection is extremely variable; in some localities it is so great that the case-mortality rate is 70%; in others it is only 5%.

the historical form of the disease; in that country a sore with lymphangitis is said to be uniformly present at the site of the infecting bite, but in other affected countries this is often absent.

A strongly positive agglutination reaction to *Proteus* OXK with a negative or weak reaction to *Proteus* OX 19 is highly suggestive of mite typhus: in other respects the disease has a general resemblance to tick typhus. The virulence of the infection shows the same variability according to locality as is seen in tick typhus.

References.—The recent contributions to knowledge of the typhus fevers are so numerous that detailed references to the literature cannot be given in the space available. Abstracts of the important articles appear in the *Tropical Diseases Bulletin* at frequent intervals.

A case of insulin resistance has recently been described by E. Lozinski and L. I. Frohlich (*Canad. med. Ass. J.*, 1942, **46**, 62) in which 3,000 to 4,000 units of insulin daily were required to prevent hyperglycaemia, acidosis, and coma. Experiment failed to demonstrate any anti-insulin substance in the patient's serum. The pituitary gland was thereupon irradiated with x rays. One month after leaving hospital (i.e., 3½ months after the beginning of irradiation) the required insulin dosage was down to 500 units. Approximately 16 months after irradiation fasting blood sugar was 108 mg. per 100 c.cm. on a dosage of 40 units daily of zinc-protamine-insulin.