
The following were present at the meeting:

Dr. AUJALEU, Directeur de l'Hygiène Sociale, Ministère de la Santé Publique, Paris.

Dr. Georges BLANCH, Director of the Pasteur Institute of Morocco, Casablanca.

Dr. P.C.C. GARNHAM, Lecturer, London School of Hygiene and Tropical Medicine, London.

Professor RODHAIN, Institut de Médecine Tropicale Prince Léopold, Antwerp.


OIHP

Dr. M. GAUD, Director of the Office International d'Hygiène Publique, occupied the chair.

WHO

Dr. Mohammed M. SIDKY, Medical Officer, World Health Organization.

The object of this preliminary meeting was to determine the state of our present knowledge of human rickettsioses in Africa and to prepare for a more extensive meeting which will take place at the beginning of February 1950 in Leopoldville.

1. HISTORY AND GEOGRAPHICAL DISTRIBUTION OF THE RICKETTSIOSES

The Expert Group decided on the immediate preparation of a short but accurate historical account of the human rickettsioses, as well as of their geographical distribution in the three sectors of Africa, namely, in North Africa, South Africa and Central Africa.
1.1 **North Africa**

Dr. Blanc has been entrusted with the preparation of a study on North Africa, which is of special interest having regard to the importance of the initial work carried out in African territories.

Dr. Sidky will request the Regional Office of WHO for the Eastern Mediterranean to cover this question for African territories which are members of the Organization.

1.2 **South Africa**

Dr. Gear will be asked to give an account of work carried out in South Africa.

1.3 **Central Africa**

The following have been given the task of preparing these studies:
- Belgian Congo, Professor Rodhain,
- British territories in Central and East Africa, Dr. Garnham,
- French West Africa and French Equatorial Africa, Médecin Général Vaucel.

1.4 The Portuguese and Spanish health authorities will also be asked for information on the subject as regards the territories under their jurisdiction.

Furthermore, Dr. Vaucel and Dr. Garnham will collect information concerning Liberia from American, English and French doctors conversant with this subject.

2. **PRESENT STATE OF OUR KNOWLEDGE**

2.1 **Rickettsioses already known and studied**

In the opinion of the experts these are:
- epidemic (or classical) typhus;
- murine typhus;
- boutonneuse fever;
- tick-typhus (or tick-borne typhus);
- Q fever.

2.2 **Characteristics of the above rickettsioses**

2.2.1 Epidemic typhus, whose causal agent is *Rickettsia prowazeki*, is endemic in the countries affected, and under favourable circumstances, assumes the proportions of a widespread epidemic.

The outstanding clinical characteristics are: the severe nature of the disease, the rapid appearance of marked prostration (typhos),
macular erythema, without any particular localization, and gangrenous complications, which usually develop at a late stage.

From the **pathological** point of view, the microscopical lesions are characterized by thrombosis of the capillaries and the small arterial and venous vessels, resulting from lesions of the vascular endothelium. This thrombosis is associated with the development of peri-vascular nodules.

**Inoculation** - On intraperitoneal inoculation with 4-5 cc of blood taken from a patient in the first days of the febrile stage, the guinea-pig, which is the animal of choice, develops a febrile reaction lasting 5 - 6 days at the end of an average period of 10 days. This reaction always ends in recovery, without pronounced inflammation of the tunica vaginalis. When inoculated under the same conditions, the rat shows only a mild inapparent infection.

**SeroLOGY** - When carried out with strain O X 19 the Weil-Felix reaction is generally positive at an early stage (from the 6th or 7th day of the disease), giving a high titre. An agglutination titre below 1/200 should not be considered as a positive sign. The reaction is negative with strain O X K.

Serum from patients suffering from epidemic typhus agglutinates suspensions of *R. prowazeki*. This specific reaction, which occurs at an early stage as the Weil-Felix reaction, should, like the extremely valuable complement-fixation test, be carried out only by highly specialized laboratories.

The reservoir of the virus of epidemic typhus consists of man, the louse and its excreta. Infection takes place by penetration of the virus either through the excoriated skin or through the mucous membrane, especially the conjunctiva.

2.2.2 **Murine typhus**, whose causal agent is *Rickettsia mooseri*, which cannot be distinguished morphologically from *R. prowazeki*, is a disease without any epidemic potential which occurs in Africa only in sporadic cases, generally isolated but sometimes in groups.

Clinically it shows features similar to epidemic typhus, particularly an eruption of the same type, but the general symptoms, especially prostration, are much less marked and prognosis is usually favourable.
However, as with the rickettsioses as a whole, the general state of the patient is affected and convalescence is long and tedious.

Pathologically, the same endothelial lesions are observed as in epidemic typhus.

Intraparitoneal inoculation of the guinea pig with blood from an infected person under the conditions given above for epidemic typhus results, after 5 - 7 days incubation, in a pronounced febrile reaction, which lasts about 5 days but does not bring about the death of the animal. The characteristic reaction is the early appearance of orchitis with inflammation of the tunica vaginalis. The liquid exudate and the cells of the tunica vaginalis contain numerous endothelial cells filled with rickettsiae. These cardinal signs may not be very apparent on the initial inoculation, but their importance is emphasized after one or more passages.

In the rat, inoculation causes a severe febrile state without inflammation of the tunica vaginalis which may result in death in certain cases.

Serology - The Weil-Felix reaction is positive with 0 X 19. It develops between the 6th and 8th day but is generally less constant and less marked than in epidemic typhus. The reaction cannot be considered conclusive below a titre of 1/150.

Agglutination of the rickettsiae, deviation of complement, detection of the rickettsiae by cultural methods, are all proofs which confirm the diagnosis, but should be reserved for specialized institutions.

The reservoir of virus, is the rat and its ectoparasites, especially fleas particularly when the animal has an acute attack. The disease is transmitted either by the excreta of infected fleas penetrating the excoriated skin, or mucous membrane, particularly the conjunctivae, or by ingestion of foodstuffs soiled by the urine of infected rats.

2.2.3 Fièvre boutonneuse, whose causal agent is Rickettsia conori, is prevalent in North Africa and throughout the Mediterranean Basin in endemic form. It has no epidemic potential.

From the clinical point of view, it may take several forms but prognosis is usually favourable. The characteristic maculo-papular eruption, which affects the whole surface of the skin including the palms of the hands
and soles of the feet, appears at the beginning of the disease and often continues during and after convalescence. The patient is not prostrated, but on the other hand often shows a degree of mental excitation which may be very marked. Patients frequently show an inoculation sore (tache noire) which initial lesion is accompanied by swellings of the lymph glands.

In cases of infection via the eyes a marked conjunctival reaction is seen. Complications are rare and non-specific.

The pathological lesions are those common to the rickettsioses.

**Inoculation** – After 4 - 5 days the guinea pig inoculated with blood from a patient develops a febrile reaction, with inflammation of the tunica vaginalis. This reaction is more constant and more marked on inoculation by means of infected ticks. In the inoculated rat the infection is inapparent.

In the infected cells the parasites are both intra- and extranuclear.

**Sero...**

The W.-F. reaction is variable. It appears more frequently with OX2 than with OX19. It makes a late appearance, often even at the end of the disease or during convalescence and the agglutination titres are generally low, varying from 1/50 to 1/500. 1/50 is the lowest reliable figure.

Agglutination of the rickettsiae, deviation of the complement, detection of the rickettsiae by cultural methods are all confirmatory of the diagnosis. The reservoir of virus is the tick, in which the disease is hereditary. The dog-tick, *Rhipicephalus sanguineus*, plays the essential part in the transmission of fièvre boutonneuse in North Africa.

**2.2.4 Tick-Typhus**

(Kenya tick-typhus, S. African tick-borne typhus). The causal agent of these forms of typhus is still not satisfactorily determined, but in the case of Kenya typhus it is perhaps Rickettsia conori. In the infected cells the parasites are both extra- and intra-nuclear as in fièvre boutonneuse. The epidemic potential of those diseases is small and they usually occur as sporadic cases or sometimes in small groups. Kenya typhus appears during the rainy season at the time when the grass is high.
Clinically the disease is generally of a mild nature. An inoculation sore is seen in 80% of cases and is accompanied by swelling of the lymph glands. The maculo papular eruption covers all the body including the palms of the hands and the soles of the feet; it appears at an early stage and persists even after the temperature has fallen.

During the febrile stage the patient often shows mental excitation, giving way to very marked depression after convalescence.

From the pathological point of view, the same microscopical lesions already described as characteristic of the rickettsioses are observed.

Intra-peritoneal inoculation of the guinea-pig with infected blood produces high fever after 4-7 days, accompanied by orchitis. There is little hypertrophy of the spleen on inoculation, the gerbil develops only infection.

Serology

With OX2 and OX19 the W.-F. reaction is very feeble and always late. The reaction is more frequent with the OXK strain and gives a relatively high titre, namely 1/100-1/150. Other laboratory methods of diagnosis have not been investigated in the case of Kenya tick-typhus. Cross immunity with fièvre boutonneuse has not been studied.

As regards South African tick-borne typhus, cross immunity with fièvre boutonneuse has been considered either positive or negative, according to the workers concerned.

Ticks form the reservoir of virus and in Kenya, the transmitting agent appears to be either Rhipicephalus sanguineus or Rhipicephalus sineus or Haemaphysalis leachi. Other species of Rhipicephalus have given negative results. In South Africa the disease is generally transmitted by Ambylomma hebraeum.

2.2.5 Q Fever, the causal agent of which is Rickettsia burneti or Coxiella burneti, has occurred in epidemic form in Australia, North America and the Mediterranean Basin. So far, only two isolated human cases in North Africa have been reported from the African continent. These two cases were of the classical pseudo-influenzal type. However, the presence of Q fever virus in North Africa has been demonstrated in spontaneously infected ticks, particularly in Hyalomma dromaderi.
On intra-peritoneal inoculation with infected ticks the guinea-pig develops a very high fever which appears 2 or 3 days after inoculation and lasts 5 to 7 days. This condition, although seemingly benign during the acute period, often causes death at a late stage after an apparent convalescence lasting 1 to 2 months. Inflammation of the tunica vaginalis is never found during the disease, but when sacrificed, animals consistently show very marked enlargement of the spleen with perisplenitis and numerous rickettsiae in the cells of the peritoneal exudate.

When inoculation is intra-muscular, the guinea-pig presents marked oedema at the point of inoculation, followed by haemorrhage and subsequent necrosis of the tissues, with numerous cells filled with rickettsiae.

Serology

The W.-F. reaction is negative with all strains. Agglutination of the rickettsiae is positive in a titre of from 1/5 to 1/40. These serological indications persist for several years. In North Africa the reservoir of virus, which is still insufficiently studied, appears to be the tick, Hyalomma dromedari and probably other ticks found in the Sahara.

3. Differential Diagnosis of the Rickettsioses

3.1 Clinical characteristics

Gravity. Epidemic typhus is a very serious disease. On the other hand murine typhus, fièvre boutonneuse and tick-typhus, although they may be serious in some cases, are generally benign.

Eruption. In both epidemic and murine typhus the eruption is macular and relatively discreet, with small spots; it affords no basis for a differential diagnosis between these two diseases. In fièvre boutonneuse and the various forms of tick-typhus on the other hand, the eruption is highly characteristic. It consists of large papulo-macular elements which may cover the whole body, including the palmar and plantar areas, and persists until the disease abates. This eruption is frequently accompanied by a sore at the site of infection with associated adenopathy.

Nervous phenomena

While prostration is one of the most evident symptoms of the disease
in epidemic typhus, and, to a lesser extent, in murine typhus, a more or less marked stage of mental excitement occurs during the febrile period of fièvre boutonneuse and the various forms of tick-typhus. On the other hand, the same symptoms of marked depression are found in all the rickettsioses during convalescence.

**Pulmonary phenomena**

Pulmonary manifestations, which occur in epidemic, murine or tick-typhus only as relatively rare and late complications, form one of the essential elements in the diagnosis of Q fever from the outset of the disease.

**Complications**

Among the manifold complications which may arise during rickettsial complaints only gangrene is characteristic, since it is found solely in epidemic typhus.

### 3.2 Pathological anatomy

There is no special lesion enabling the various rickettsioses to be distinguished from one another. On the contrary, they all show the same endothelial lesions characteristic of these diseases.

### 3.3 Epidemiological Forms

Epidemic typhus is both endemic and epidemic. It is clearly distinguished from other rickettsioses by its high endemic potential, due to biological conditions which favour the spread of the disease.

Murine typhus is endemic and, in Africa, occurs only in isolated sporadic cases or small groups of cases.

Fièvre boutonneuse and the various forms of tick-typhus are endemic and their appearance as isolated or multiple cases depends on conditions favouring the multiplication of the reservoir of virus, which is also the vector, and its accidental contact with man.

So far Q Fever has not been observed in Africa in epidemic form.

### 3.4 Transmission of infection

Man, the louse and louse excreta act as reservoir of virus for epidemic typhus. The animal vector is the louse. The infecting agent penetrates into the organism via the mucous membrane or the excoriated skin.
The rat, rat-fleas and their excreta serve as reservoir of virus for murine typhus. The animal vectors are the rat and the flea. Infection occurs in the same way as with epidemic typhus, although the digestive tract appears to play a more important part.

Fièvre boutonneuse and the various forms of tick-typhus have, as reservoir of virus, ticks which act at the same time as vectors, either by their bite or by the penetration of their excreta into the mucous membrane or excoriated skin.

Q Fever has probably various types of Acarina as reservoir of virus and infection may arise from the bites of infected ticks or through the digestive and respiratory tracts.

3.5 Laboratory tests

Although non-specific, the W.-F. reaction gives valuable pointers in differential diagnosis.

It is positive in high titre at an early stage in epidemic typhus; it is also positive in murine typhus, but in a less constant manner and the titre is not so high. With the OXK strain the reaction is negative for both epidemic and murine typhus.

In fièvre boutonneuse agglutination with OX19 occurs only at a late stage and is inconstant; the agglutination titre is always low. With OX2, agglutination is more frequent and better marked.

In the various forms of tick-typhus the reaction is late and not very pronounced with OX19 and OX2; it occurs more frequently and gives a higher titre with OXK.

The W.-F. reaction is negative with all strains in the case of Q Fever.

The agglutination of specific rickettsiae, complement fixation and, of course, the detection of the causal agent by cultural methods, all represent confirmatory evidence for any of the rickettsioses.

3.6 Inoculations

A marked febrile reaction, without inflammation of the tunica vaginalis is observed in the guinea-pig after intra-peritoneal inoculation with epidemic typhus. Only a mild, inapparent infection develops in the inoculated rat.
In murine typhus, inoculation of the guinea-pig results in a febrile reaction accompanied by orchitis and inflammation of the tunica vaginalis. On inoculation the rat develops a severe febrile condition.

In fièvre boutonneuse, and probably the other forms of tick-typhus, the inoculated guinea-pig gives a febrile reaction, with inflammation of the tunica vaginalis but this reaction is often variable and difficult to detect.

In the case of Q Fever, the inoculated guinea-pig rapidly develops a strong febrile reaction accompanied by enlargement of the spleen.

3.7 Detection of the causal agent

The search for the causal agent of the rickettsioses cannot at present be undertaken with the patient's blood as starting point. However, this is possible with inoculated animals.

The rickettsiae of epidemic typhus occur in abundance in the peritoneum of the inoculated guinea-pig. Those of murine typhus can be very easily detected in the exudate from the tunica vaginalis.

In the case of fièvre boutonneuse, numerous peritoneal, vaginalis and spleen cells are found to be full of rickettsiae in the inoculated guinea-pig.

Finally, where Q Fever is concerned, the causal agent is easily detected in the exudate which forms at the point of inoculation whenever the latter is intra-cellular.

When rats are inoculated with murine typhus, the rickettsiae develop in the peritoneum.

3.8 Cross Immunity

Epidemic typhus and murine typhus give complete immunity against one another; on the other hand, there is no cross immunity between these two forms of typhus and the rickettsioses transmitted by ticks. As regards the connexion between fièvre boutonneuse and the other forms of tick-typhus, these have not yet been sufficiently investigated to enable any final conclusions to be drawn. There is no cross immunity between Q Fever and the other African rickettsioses.
4. CLINICAL SYNDROMES PROVISIONALLY ASCRIBED TO THE RICKETTSIOSES

4.1 Congolese red fever

The recent work of the French and Belgian schools has shown that the rickettsioses play a very important part in the very extensive syndrome described under the name of "Congolese red fever". Most of the forms described can be related to either epidemic, murine or tick typhus.

To avoid regrettable confusion it is essential for the term "Congolese red fever" to disappear and for each of the diseases covered by this name to take its proper place in the nomenclature of diseases.

4.2 Scrub typhus

A grave epidemic disease, having features in common with epidemic typhus, has been described under the name of scrub typhus. In view of the epidemiological, clinical and bacteriological conditions, it is at present impossible to give any definite opinion as to the nature and identity of this disease.

5. THE CONTROL OF THE RICKETTSIOSES

5.1 Generally speaking, the control of the rickettsioses should be based on the destruction of the reservoirs of virus and the control of vector agents. Each of the diseases of this group necessitates a prophylaxis adapted to the biological conditions which favour its existence and spread.

5.2 As regards the question concerning plans for action by WHO against epidemic typhus, the Expert Group approved the principle of employing trained demonstration teams to use all possible methods for achieving eradication of the disease in limited and well-chosen areas.

The experts feel, however, that the problem is a complex one which, because of the special social and economic conditions of each country and even of each area inside a country, necessitates careful study and the preparation of a definite plan of campaign in agreement with the local administrative and medical authorities.

From the practical point of view, the experts believe that the work of a demonstration group should deal with:
(a) the control of the principle vector, the louse; delousing of the individual, his clothing, bedding and small everyday articles of furniture, such as carpets, bed-spreads, etc.

To prevent the rapid breeding of the parasites the action taken must be total, i.e. must cover all the individuals in the group. It should also be regularly repeated, quarterly intervals could be suggested provisionally;

(b) the sterilization of louse excreta in infected places, both personal effects and domestic equipment being dealt with. It should be noted that it is sufficient to steep the objects in a weakly antisepctic solution and then to expose them to the sun. It would not be necessary to employ vapour disinfection which causes deterioration in objects exposed to it and is consequently not willingly accepted, as a general rule;

(c) the experts also felt that inoculation throughout the demonstration area would be an additional guarantee.

6. CONCLUSIONS

6.1 Although the investigation of the African rickettsioses is of comparatively recent date, the data already acquired enables the problem to be viewed as a whole.

6.2 The general outline of the rickettsiosis problem has been already settled in North Africa, where the incidence of the rickettsioses, particularly of epidemic typhus, is very considerable.

The same applies to South Africa where important work has already led to the solution of the fundamental problems.

In Central Africa on the other hand, where the various exanthematic diseases were only differentiated at a late stage and then incompletely, investigations at present under way must be actively pursued.

6.3 These investigations should bear on the clinical, epidemiological and bacteriological forms of the rickettsioses as well as on their geographical distribution. Uniform methods should be employed, following the techniques common to the various African countries.

6.4 It is proposed to hold a meeting, the programme for which is in
preparation in Central Africa. This would make it possible to bring together experienced representatives from the various African territories. They could then give an account of knowledge recently acquired during their researches and an exchange of views could take place.

6.5 These investigations will probably show that the human rickettsioses take similar forms in all parts of the African continent.