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The Public Health Importance of Tick-borne Encephalitis in Europe

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After an historical survey establishing the distinction between Russian spring-summer encephalitis, a serious disease with a high mortality rate caused by a virus spread by the tick Ixodes persulcatus, *and the milder Central European encephalitis, which is spread by* I. ricinus, *the public health aspects of the latter disease are discussed. The factors affecting the incidence of the disease—tick population, role of rodents and insectivores, etc.—are considered. Only a small proportion of those infected develop clinical symptoms. Measures for the control of the disease include* (a) *vaccination of humans,* (b) *reduction of the tick population by cultivation of the land, by spreading the enemies of ticks and by dusting with insecticides, and* (c) *reduction of the infectivity of ticks by vaccination of domestic animals. It is concluded that, under the conditions prevailing in Central Europe, mass vaccination is not to be recommended, although those working regularly within a natural focus of infection should be vaccinated.*

HISTORY

In 1937-39, three successive research expeditions were organized by the Ministry of Health of the USSR to try to elucidate the origin of an infection of the central nervous system occurring in different areas of the Far East of the USSR. The infectious character of the disease had been established in 1933-35. Investigations carried out by, e.g., clinicians, microbiologists, virologists and zoologists, quickly established the viral origin of the disease and the tick *Ixodes persulcatus* was shown to be the vector of the virus. The disease was called Russian spring-summer encephalitis (or Far East or taiga encephalitis) and the virus later became known as the tick-borne encephalitis virus. The clinical course of the disease, its pathology and epidemiology, as well as the properties of the new virus, its ecology and the ecology of vectors, have been carefully and thoroughly studied. The most recent studies have been concerned with the possibility of effective short- and long-term prophylaxis and with the effective control of ticks in order to eradicate the virus in the natural focus of infection (e.g., Graščenkov, 1964).

When the results of the early studies became more widely known (Čumakov, 1959; Zil'ber, 1939; and others), it was realized that many other areas of the USSR were experiencing an exactly similar disease. A milder form of the disease was also observed in the European part of the USSR, where the tick *Ixodes ricinus* was found to be the vector of the virus.

Tick-borne encephalitis was recognized in the Leningrad region in 1945, in the Byelorussian SSR in 1944, in Krasnoyarsk in 1945, in Kaliningrad in 1952, and elsewhere (Karpov & Fedorov, 1963).

After the Second World War, the disease and its agent—tick-borne encephalitis virus—were shown to be present in other countries. In Czechoslovakia, Gallia et al. (1949) and Rampas & Gallia (1949) identified tick-borne encephalitis in West Bohemia, and later other workers observed the disease in different regions of the country.

In Hungary, the first positive proof of tick-borne encephalitis was reported by Fornosi & Molnár (1952). Shortly afterwards studies were carried out in Poland (Przesmycki et al., 1954; Szajna, 1954), Bulgaria (Vaptsarov & Tarpomanov, 1954), Yugoslavia (Bedjanić et al., 1955; Kmet et al., 1955; Vesenjak-Zmijanac et al., 1955) and Austria (Pattyn & Wyler, 1955; Richling, 1955; Moritsch & Krausler, 1957). A review (von Zeipel et al., 1958) summarized the evidence for tick-borne encephalitis in Sweden, and the disease was reported in Finland (Oker Blom, 1956), Romania (Draganescu, 1959) and eastern Germany (Sinnecker, 1960). Recent reports from

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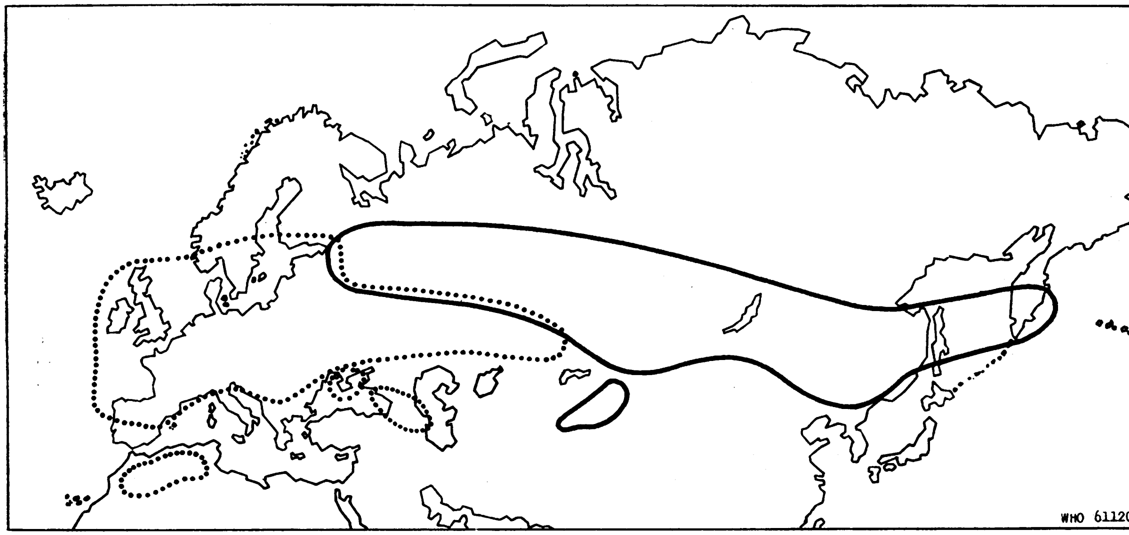
FIG. 1

DISTRIBUTION OF THE TICKS *I. RICINUS* AND *I. PERSULCATUS* [a]



[a] Dotted line: *I. ricinus;* full line: *I. persulcatus.* After Smorodincev (1958).

south-west Germany (Scheid et al., 1964), based on serological investigations, suggested the existence of natural foci of tick-borne encephalitis in the Federal Republic of Germany.

The louping-ill virus, which causes a serious meningo-encephalitis in sheep, is antigenically very closely related to the tick-borne encephalitis virus. In Scotland, north-west England and Ireland, natural foci of louping-ill were detected and the tick *Ixodes ricinus* was also proved to be the vector of the virus.

The geographical distribution of louping-ill and tick-borne encephalitis viruses in Europe, based on the geographical distribution of *I. ricinus*, is shown in Fig. 1, which also indicates the distribution of *I. persulcatus*.

TERMINOLOGY

Discussion is at present taking place on the nomenclature of the diseases and the respective viruses of the tick-borne encephalitis group. The louping-ill virus is excluded from this discussion, because louping-ill was a disease well known to farmers before the discovery of the tick-borne encephalitis virus.

The clinical picture and epidemiology of Russian meningo-encephalitis in the Far East of the USSR were well described in 1933-35 (Panov, Finkel & Shapoval, cited in Karpov & Fedorov, 1963). This disease *sui generis* was variously called spring-summer encephalitis, tick-borne encephalitis, taiga encephalitis, spring epidemic encephalitis, spring-summer meningo-encephalitis, and Far East tick-borne encephalitis. These designations all relate to the disease whose vector, the tick *I. persulcatus*, had been established. The disease has often been very serious, with a mortality rate of 30%-38% (Panov, 1956).

A milder form of the disease was observed in some European areas of the USSR, where the tick *I. ricinus* (Čumakov & Naidenova, 1944) was proved to be the vector and where later it was established that infection resulted from drinking raw goat's milk. Zil'ber & Šubladze (1946) suggested that these milder cases of tick-borne meningo-encephalitis might be caused by louping-ill virus. Smorodincev et al. (1953) and Davidenkov et al. (1953) classified the more benign form of tick-borne encephalitis as a new clinical entity and named it biphasic virus meningo-encephalitis. The disease acquired by people who drank infected milk was called biphasic milk fever by Čumakov et al. (1954). In 1951, an outbreak of milk-borne meningo-encephalitis was described in Rožňava, a town in south-east Slovakia (Blaškovič, 1954). Because more than 600 persons who were found to be infected had drunk raw cow's milk to which goat's milk had been added, this previously unknown way of infection with tick-borne encephalitis virus was suspected. A clinically distinct disease is Omsk haemorrhagic fever (Čumakov et al., 1951), caused by a virus with an identical antigenic structure to the tick-borne encephalitis virus.

This situation was complicated by the fact that viruses with identical antigenic structures were reported from Czechoslovakia (1948) and other European countries, and the viruses isolated were named according to the country in which they were discovered (see under " History ").

Some clarification of the terminology used by virologists resulted after Clarke (1962) reported that, by the agar gel precipitin method, the following viruses—members of the tick-borne encephalitis group—could be distinguished: louping-ill, Russian spring-summer encephalitis, Omsk haemorrhagic fever, Kyasanur Forest disease and Langat, and the virus isolated in Czechoslovakia and designated Central European tick-borne encephalitis virus. More recent work (Clarke, 1964) has shown that louping-ill virus, Central European tick-borne encephalitis virus, Russian spring-summer encephalitis virus, and Powassan and Negishi viruses form a group whose members are antigenically closely related and which can therefore be considered as subtypes of one virus.

It is certainly useful to distinguish these viruses and the diseases caused by them. The designation of one of these viruses as Central European is unfortunate, because viruses with the same characteristics occur in the north, centre, south, west and east of Europe. A geographical approach to the designation of this virus is not adequate. Virologists from different countries are considering the desirability of distinguishing Russian spring-summer (Far-East, taiga) encephalitis virus from the European subtype; perhaps the first could be called the Eastern subtype and the second the Western subtype of tick-borne encephalitis virus.

PUBLIC HEALTH ASPECTS

In considering the public health aspects of tick-borne encephalitis in Europe, we shall omit louping-ill and discuss the infection caused by the virus whose vector was proved to be the tick *I. ricinus*.

Epidemiology

There is no need to describe in detail the epidemiology of the disease (see Blaškovič, 1961); the general features and certain peculiarities will, however, be mentioned. In the other papers in this Supplement, new findings or the confirmation of some previous ones are described more fully.

People become infected (*a*) by being bitten by a tick, (*b*) by drinking infected raw milk or (*c*) by inhaling infected material. The last is most likely to occur under laboratory conditions, but the possibility of infection taking place in this way in a natural environment cannot be excluded; for example, a man might be infected as a result of inhaling dust containing the infected faeces of a tick while working in a stable.

In Europe the disease shows a seasonal incidence, corresponding to the two peaks in the tick population; the first peak occurs in May-June and the second in September-October. Comparison of the tick population curves and the morbidity rate in humans shows that there is approximately 14 days' difference in the two peaks; this gap is roughly the same as the incubation period of the disease, which varies between four and 14 days (Libíkowá, 1961).

Age-distribution curves show that the disease primarily affects those over 20 years old. This is brought out in the results of serological surveys on people living near a natural focus of infection. Forestry workers and persons collecting fruit in woods, campers and shepherds are usually infected by a tick bite. Small family outbreaks caused by drinking raw goat's milk mostly affect women and children.

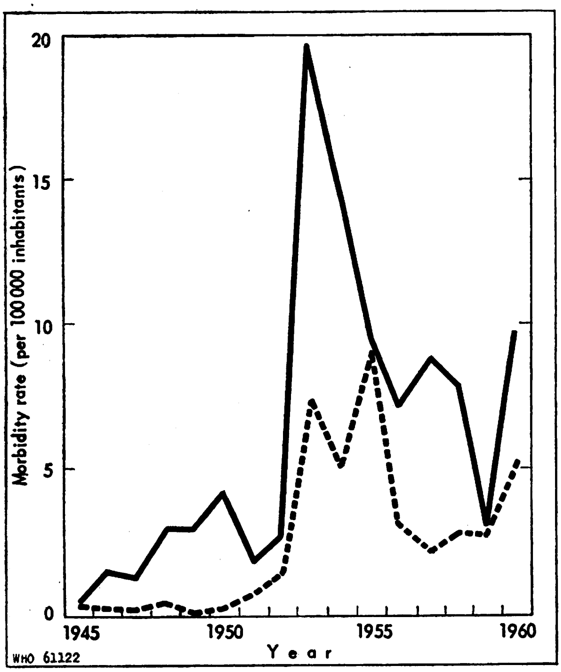
Most of those infected do not develop clinical symptoms, latent infections being common, particularly among people living within the natural focus of infection, presumably because of immunization with small doses of virus. People requiring hospitalization suffer from severe headaches and various symptoms of meningitis and encephalomyelitis, which are often alarming. These symptoms are characteristic of the second (localized) phase of the disease, the first (viraemic) having the usual symptoms of an acute viral infection. The upper respiratory tract is most commonly affected. Hospitalization lasts on the average 3-6 weeks and there is a prolonged convalescence during which general pains and weakness may predominate.

The mortality rate generally does not reach 1%, although in some regions of Austria during 1954 it was reported to be 2%-4.5% (Grinschgl, 1955).

A characteristic of the epidemiology of tick-borne encephalitis is its increased incidence in some years (Fig. 2; Kolman, 1965).[1] The incidence depends on the many factors that affect the number of viruses circulating in a given focus of infection; this in turn

[1] See also the paper by Blaškovič et al., this Supplement, page 89.

FIG. 2
MORBIDITY RATE OF VIRAL ENCEPHALITIS IN CZECHOSLOVAKIA, 1945-60



Czechoslovakia.
Slovakia.

After Kolman (1965).

depends on the population of vertebrate hosts and vectors (Blaškovič, 1960). The factors involved in the transmission of arbovirus infection from animals to man have been well described by Smith (1964) and can be summarized as follows: (1) duration of infectivity, (2) duration of incubation period, (3) stability of virus, (4) population factors, (5) climate and microclimate, (6) animal and human behaviour and (7) susceptibility of the host.

There are many unanswered questions concerning the epidemiology, diagnosis and prophylaxis of tick-borne encephalitis. These problems are very closely related to the principal one, namely, the ecology of the virus. In order to supplement existing knowledge, the team of the WHO Regional Reference Laboratory for Arboviruses at the Institute of Virology, Czechoslovak Academy of Sciences, Bratislava, has investigated the natural focus of tick-borne encephalitis in the Tribeč region in Central Slovakia. The region under investigation is shown in Fig. 3; the other papers in this Supplement are devoted to the work carried out in this area.

ECOLOGY OF THE TICK-BORNE ENCEPHALITIS VIRUS

The vector of the virus is the tick *Ixodes ricinus* in all stages of development. The tick is also a reservoir of the virus, because the latter is transmitted from one instar to the next. Transovarial transmission also occurs; it was found to account for 6% of experimental transmissions under conditions holding in Czechoslovakia (Benda, 1958c). Despite the fact that the percentage of transovarial transmissions under European conditions is much lower than in Siberian taiga encephalitis, it is sufficient under certain conditions to ensure the continuity of virus. Insectivores and rodents are able to harbour the virus during the winter; either long-lasting viraemia is produced, which supplies the parasitizing larvae with the virus, or viraemia is evoked shortly after the winter sleep (posthibernation viraemia).[1]

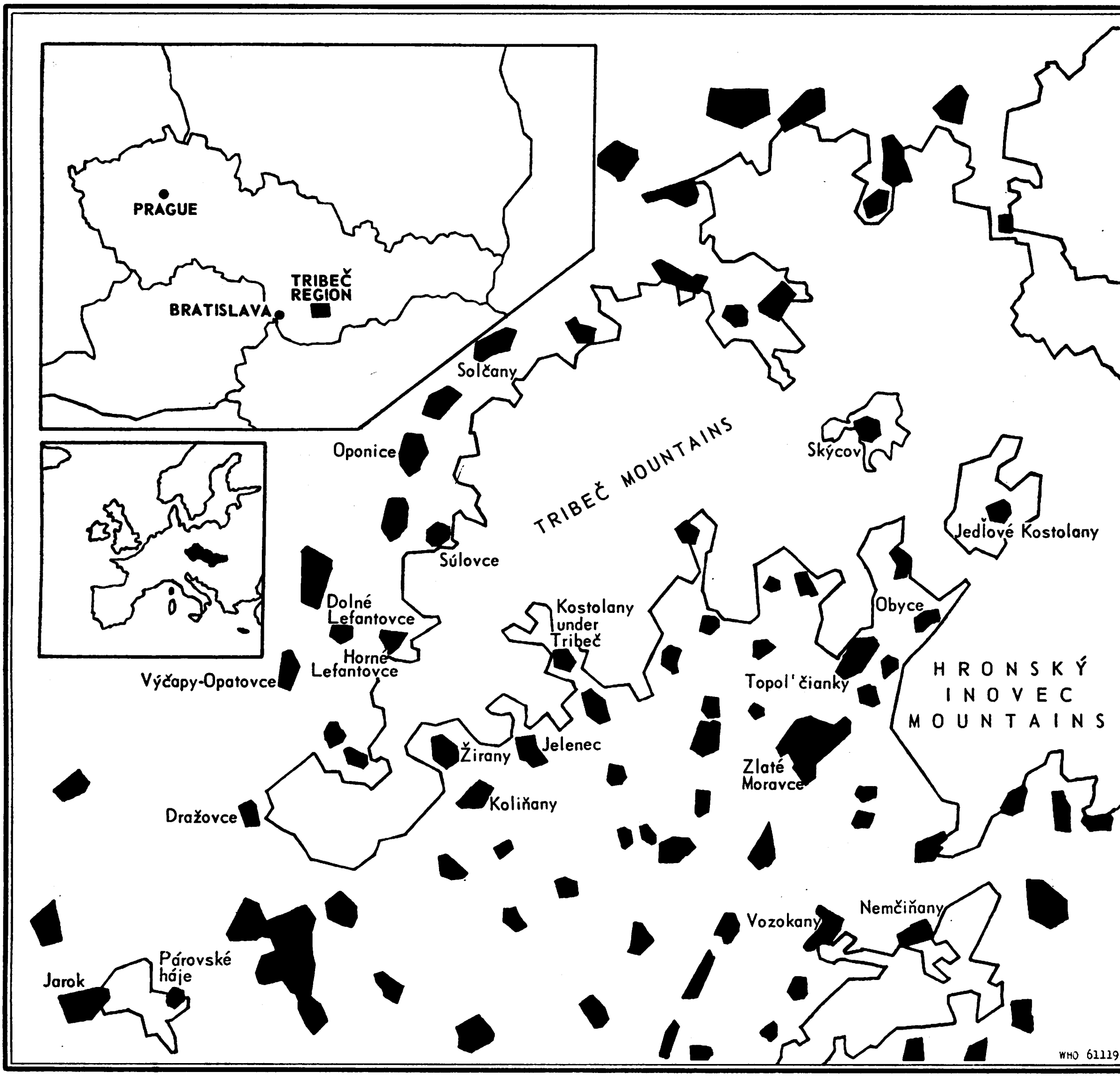
The circulation of tick-borne encephalitis virus under European conditions and its relation to the ticks and their hosts is illustrated in Fig. 4 (see also Blaškovič & Nosek, 1965).

The circulation of the virus in nature is ensured without man's activity. Man acquires the infection when any starving virus-carrying instar of the tick feeds on him. While engorging the blood—the process of full engorgement lasts several days—the tick transmits the virus to man. Man, however, does not represent a further source of infection, because during his viraemic stage he falls ill and, instead of pursuing his occupation in the wood, where he might be bitten by a starving non-infected tick, he rests in bed. Man is therefore a blind link in the circulation of tick-borne encephalitis in nature.

The epidemiological features of the infections depend on the conditions under which the virus circulates in nature. These in turn depend on whether the land is in its natural state or has been modified for raising game or domestic animals. Game-type natural foci are characterized by vegetation suitable for the raising of game; in these foci man becomes infected only by tick bite. Pasture-type natural foci have developed by the conversion of wooded habitats into pastures; man becomes infected either by tick bite or by drinking raw goat's milk. Mixed game-and-pasture natural foci are characterized by alternating wooded, bushy and grassy vegetation; both ways of infection are possible. Primary natural foci unaffected by the activity of man no longer

[1] See the paper by Nosek & Grulich, this Supplement, page 31.

FIG .3
THE TRIBEČ REGION OF CZECHOSLOVAKIA



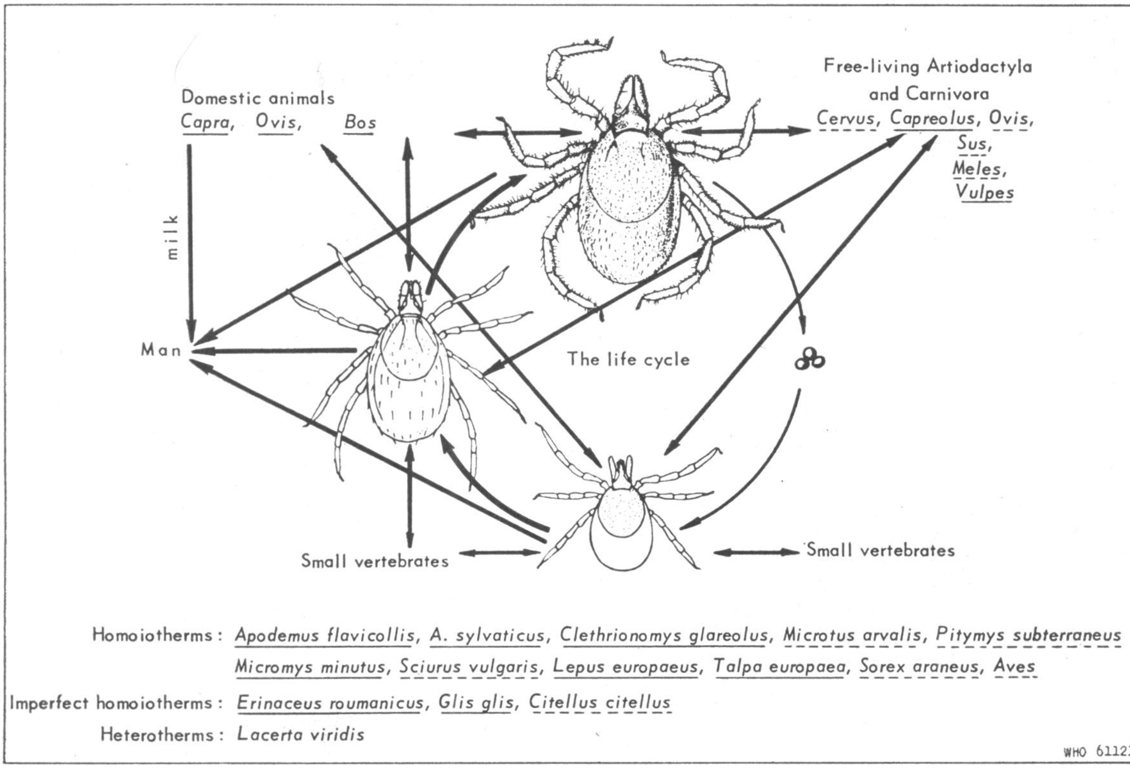
Scale, 1: 320 000.

exist in Europe, except perhaps in some national parks or in very small relict areas.

The cultivation of land greatly influences the viability of a natural focus of tick-borne encephalitis. Complete cultivation, with control of small rodents, leads to almost complete eradication of ticks and to control of infection. This is the case in very fertile regions, converted to the efficient production of cereals or vegetables. There are, however, other habitats—uncultivated and slightly, moderately or highly cultivated regions—where the incidence of ticks is inversely proportional to the degree of cultivation of the land (Rosický & Hejný, 1959). In a given geographical area, however, different degrees of cultivation and different natural foci may exist. There are micro-areas where the virus is absent and very closely related habitats where ticks are abundant and may be harbouring the virus.

FIG. 4

TROPHIC CONNECTIONS OF *I. RICINUS* AND POSSIBILITY OF TRANSMISSION OF TICK-BORNE ENCEPHALITIS VIRUS FROM RESERVOIRS IN TRIBEČ REGION [a]



[a] **Hosts established as reservoirs of TBE virus are underlined with a solid line, and those not established with a broken line.**

Control measures

It is evident that the effective control of tick-borne encephalitis in man must be based on an exact knowledge of the conditions that govern the circulation of the virus in nature. This knowledge is, however, not yet fully available and further studies are needed to elucidate (*a*) how a given natural focus of tick-borne encephalitis persists, (*b*) how it becomes extinct, and (*c*) how a focus develops in an area where previously no human infection has occurred. These problems are closely related to the possibility of forecasting the spread of the virus in nature and making an epidemiological prognosis (the programme of epidemiological surveillance).

Ecological studies on the vector and its host animals have opened up another way of control: the control of ticks and rodents and the individual protection of man.

The original method of protection was by the well-proved immunological procedure, a specific vaccination programme with a formol-inactivated mouse-brain vaccine being established (Smorodincev et al., 1940). Simultaneously, the use of serum from convalescent patients in the treatment of the acute phase of the disease was recommended (Shapoval et al., 1939). In addition to the use of human convalescent serum, the administration of hyperimmune horse and goat sera was suggested (Čumakov, 1940).

The individual protection of man against infection in a natural focus of infection is achieved by wearing suitable clothes, using repellents and, chiefly, carefully removing unfed ticks from the body. Such individual protection is suitable for scientists and their helpers who are investigating a natural focus of infection or for other specialists (e.g., engineers, geologists and foresters) during their exploratory work in woods. It is not practical for woodcutters, other people who work regularly in woods or campers.

Other measures, which lower or even eradicate the tick population in woods, are more important. Two ways are recommended: agricultural improvement of fields and meadows, with a ban on pasturing cattle in the woods, and dusting the ground with insecticides (Blaškovič, 1961).

Ticks infest neglected pastures, fields and the edges of woods. Small rodents and grazing cattle provide them with food. The removal of shrubs from pastures and the improvement of meadows, fields and footpaths reduce the number of ticks and therefore weaken the source of infection. These methods have probably contributed largely to the eradication of tick-borne encephalitis in countries such as Denmark and the Netherlands, where agriculture has reached a high level of efficiency.

Two biological means of reducing the infectivity of ticks in nature can also be recommended. The first consists in spreading the natural enemies of ticks, e.g., *Hunterellus hookeri* and *Ixodiphagus texanus* (Karpov & Fedorov, 1963). The second is more specific and uses the well-known fact that the stage of immunity of an organism is a limiting factor in the circulation of any infectious agent in nature. Blaškovič (1962) suggested vaccinating with tick-borne encephalitis vaccine all domestic animals (goats, sheep, cattle) grazing on meadows and the edges of woods in a natural focus of infection. After vaccination, the animals develop specific antibodies that protect them from further infection and consequently prevent the excretion of virus in their milk.

Immune domestic animals may reduce the amount of circulating virus in nature in two ways. First, they do not develop significant, if any, viraemia and cannot become the source of the virus for non-infected ticks and, second, they regulate the amount of virus in ticks that have engorged the immune blood (Benda, 1958a, 1958b).

Dusting of woods and shrubs locally or from the air can be an important measure in the control of ticks. Dichlorodiphenyltrichloroethane (DDT) as a 10% dust has proved more satisfactory than hexachlorocyclohexane (HCH) because of its higher stability. Gorsčakovskaja et al. (1953) and Gorsčakovskaja (1957) carried out many experiments and found that 10% DDT powder used at a concentration of 30-50 kg/ha kills all instars of *I. persulcatus* ticks. DDT should be applied in early spring while snow is still on the ground. This massive application is suitable for taiga environments or large woods but less so for the cultivated land and pastures of European countries. There is the danger of exterminating useful insects (e.g., bees) or, if pastures are treated, of impairing the health of grazing domestic animals or the quality of their milk.

The individual protection of domestic animals against ticks by applying 10% DDT powder locally on their skin is also being recommended.

Specific measures in the protection of people

Very soon after the discovery of the virus, immunization with 1%, and later with 5%, mouse-brain formol (1:2000)-inactivated vaccine was introduced, mainly for forestry workers in the taiga region of the USSR (Smorodincev et al., 1940). Two or three applications of the vaccine were recommended. Three different strains of tick-borne encephalitis virus were used at first, but later a monovalent vaccine was introduced. Local reactions were often observed and, exceptionally, lethal ones (one death among 168 000 vaccinated persons: Karpov & Fedorov, 1963, p. 184). Not all of those vaccinated remained uninfected, but the course of the disease in vaccinated persons was mild.

Use of a 5% formolized suspension from chick-embryo tissues infected with tick-borne encephalitis did not give a vaccine of higher immunogenic potency than the mouse-brain vaccine, but it represented an attempt to avoid the undesirable allergenic effect of brain substances (Šubladze & Anjaparidze, 1954).

The use of formolized, inactivated and lyophilized tissue-culture vaccine from infected culture medium (chick-embryo fibroblasts) has been proposed (Benda & Daneš, 1960; Daneš & Benda, 1960; Levkovich & Zasukčina, 1960). Such a vaccine is being produced at present in the USSR. Three doses of the vaccine (1 ml each), followed by a booster dose a year after the first inoculation, are being recommended (Čumakov et al., 1965). The immunogenic capacity of the vaccine is enhanced by the addition of aluminium hydroxide. This vaccine is administered to new inhabitants of a taiga region and to people working in woods known to be natural foci of tick-borne encephalitis. All laboratory personnel working with the virus should be vaccinated.

Under the conditions prevailing in Central Europe, mass vaccination against tick-borne encephalitis is not recommended. The likelihood of becoming infected is high only for people who come directly in contact with the circulating virus, i.e., those who work daily in a natural focus of infection (e.g., foresters, woodcutters). These people form a group for whom vaccination is highly desirable.

A second group for whom vaccination is suitable includes people living within or near a natural focus of infection and whose occupations or habits (picking wood fruits, grazing cattle, and so on) facilitate infection. It is difficult to make vaccination obligatory for other persons who only occasionally enter a natural focus, e.g., during holidays; it is, however, desirable that they should be warned about the hazards of infection and its consequences and informed about means of personal protection against the ticks that carry the virus.

The main task, however, is to prevent circulation of the virus in nature, by breaking the chain of transmission. At the same time, efforts should be continued to develop an attenuated live vaccine whose administration would ensure a high antigenicity and immunogenicity, and which would be safe.

LABORATORY DIAGNOSIS OF TICK-BORNE ENCEPHALITIS

The diagnosis of tick-borne encephalitis does not present any difficulties in so far as the isolation of the virus is concerned. The serology of this group of viruses has been well elaborated (WHO Study Group on Arthropod-borne Viruses, 1961).

Greater difficulties may arise when a new virus is isolated, and its classification and the determination of its health significance should be explored. For this reason, Regional Reference Laboratories for Arboviruses and the World Centre for Arboviruses have been set up by WHO. The World Centre maintains the prototypes of strains and immune sera, enabling isolates to be classified into known groups, identified with a prototype strain, or accepted as new species.

The health importance of any new isolate should be carefully studied, both in the laboratory and in the clinic, and the epidemiology of the relevant disease should be investigated. This is very often a time-consuming procedure, further extending the effort being expended on the isolation of the virus and on its biological and physicochemical characterization.

RÉSUMÉ

L'auteur examine l'importance pour la santé publique des encéphalites transmises par les tiques en Europe centrale, après un rappel historique qui montre la différence existant entre l'encéphalite verno-estivale russe transmise par *Ixodes persulcatus* et l'encéphalite plus bénigne d'Europe centrale transmise par *I. ricinus*. Il souligne la nécessité et la difficulté de clarifier les données actuelles concernant les nombreuses viroses du groupe des encéphalites transmises par les tiques et d'adopter une terminologie plus précise.

Certaines particularités de l'encéphalite à tiques d'Europe centrale sont signalées. La contamination peut résulter d'une morsure de tique, de l'ingestion de lait non stérilisé ou de l'inhalation de poussières infectées. En Europe, l'incidence de la maladie présente des variations saisonnières correspondant aux fluctuations des populations de tiques. L'affection atteint principalement les personnes âgées de plus de vingt ans. Les infections occultes sont très fréquentes et la plupart des sujets infectés ne présentent aucun symptôme clinique. Quant au taux de létalité, il reste généralement inférieur à 1%. Le vecteur, *I. ricinus*, infectieux à tous les stades de son développement, assume également le rôle de réservoir de virus, de même que certains rongeurs et insectivores.

Les facteurs épidémiologiques ne sont pas encore entièrement connus mais cependant les études détaillées déjà effectuées justifient l'emploi de certains moyens de lutte. Ceux-ci comprennent la vaccination des populations, des mesures d'hygiène générale, l'extension des cultures, l'introduction d'ennemis naturels des tiques, ainsi que l'immunisation des animaux domestiques. Enfin l'emploi des pesticides, notamment le DDT, quoique non dépourvu d'inconvénients, complète la gamme des mesures préventives.

L'auteur conclut que, si une vaccination de masse n'est pas à conseiller, tous les travailleurs séjournant régulièrement dans un foyer naturel d'infection et le personnel de laboratoire travaillant sur le virus devraient être vaccinés.

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