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Tick-borne Encephalitis in Europe

Some aspects of epidemiology and control

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Tick-borne encephalitis is a virus infection of man and animals usually affecting their central nervous system. The disease develops following a tick bite or after drinking infected goat's and probably also cow's or sheep's milk. The domestic animals become infected by ticks harboring the encephalitis virus.

Various infections such as Russian spring-summer (tayga) encephalitis (Zilber, 1939), bi-phasic meningoencephalitis (Smorodintsev et al., 1954), Central European encephalitis (Gallia et al., 1949) and louping-ill are classed under the term of tick-borne encephalitis.

Louping-ill is predominantly a disease of sheep. No special attention has been paid to naturally occurring human infections, the clinical course of which has been studied mostly on laboratory infections. Other encephalitides have a different clinical course, varying from mild benign forms (the majority of Central European encephalitides and bi-phasic meningoencephalitides of Bielorussia and Ukraine) to the very severe ones ending in paralyses of different muscle groups, destruction of nerve centres and sometimes in death, as is the case with Russian spring-summer encephalitis. This occurs in the eastern parts of European Russia (Ural) and prevails in Siberia and the Far East.

Ticks of the Ixodidae family act as both vectors and reservoirs of the virus.

Russian spring-summer encephalitis is transmitted by Ixodes persulcatus ticks. Haemaphysalis concinna and Dermacentor silvarum ticks (Ryzhov and Skrynnik 1941 ; Skrynnik and Ryzhov 1940) can also participate in the maintenance and circulation of the virus, but are of minor importance. Ixodes ricinus acts as vector and reservoir of the bi-phasic [illegible] encephalitis as well as of louping-ill viruses.

The antigenic properties of the viruses recovered from diseased or apparently healthy host animals and human cases are very similar. The viruses under consideration belong to the B group of arbor viruses (Casals and Brown, 1954). The louping-ill, bi-phasic meningoencephalitis and Russian spring-summer encephalitis viruses can be distinguished from one another either by the antibody absorption and agar gel precipitin technic (Clarke, 1960) or by the pathogenicity for Macaca rhesus monkeys (Ilyenko and Pokrovskaya 1960). The viruses of Central European Encephalitis and bi-phasic meningoenecephalitis have been shown to be antigenically identical (Clarke, 1960). The geographical distribution of the infections of man and animals occurring in natural foci of infection is as follows: northern parts of Great Britain (louping-ill); the European part of the Soviet Union (Both Russian spring-summer encephalitis and bi-phasic meningoencephalitis); and Austria, Bulgaria, Czechoslovakia, Finnland, German Democratic Republic, Hungary, Poland, Rumania, Sweden and Yugoslavia (Central European encephalitis) (Blaškovič 1958 a, b).

Fig. 1.

Viruses with a similar antigenic structure were discovered in the Eastern Hemisphere outside Europe in Siberia (Omsk hemorrhagic fever), India (Kyasanur forest disease) and Malaya (TP 21, Langat virus). Quite recently, a new virus antigenically closely related to the viruses of the tick-borne encephalitis group was discovered in Canada and USA (Powassan virus) (Mc.Lean and Donohue 1959, Casals 1960, Thomas et al. 1960). The infections caused by all these viruses are of world wide importance.

1. Ecology of the tick-borne encephalitis viruses

Tick-borne encephalitis belongs to diseases occurring in natural foci of infection. Pavlovsky (1939, 1956) defines a natural focus of an infectious disease "as a tract of country of a definite geographical type containing habitats*) in which certain

*) Geographically well-defined area characterized by the presence of a particular flora and fauna.

given interspecific relationships have evolved between the pathogen (the microorganism) and the vector or vectors. The latter transmit the infective agent from animal donor to animal recipient under conditions of the external environment conducive to, or preventing circulation of the microorganism among the participants of such biocenoses".

This definition is very useful for understanding the natural history not only of tick-borne encephalitis but also of other infections such as tularemia, leptospirosis, babesiosis, yellow fever etc., which are called transmissible diseases in the Russian and arthropod-borne infections in the American-English literature.

Man actually does not play a role in the circulation of tick-borne encephalitis virus in nature, he being the dead link in the chain of infection.

Virus circulation in nature is effectuated by different instars of Ixodes persulcatus, Dermacentor silvarum and Haemaphysalis concinna ticks in the tayga and forests of the Asian part of the U.S.S.R. and in woods of the Ural, and by Ixodes ricinus ticks in Western Russia and the rest of Europe. We will deal with the ecology of the virus in respect to Ixodes ricinus. The geographical distribution of the main vectors and reservoirs of virus is evident from Figure 2.

Fig. 2.

The circulation of the virus in nature is illustrated schematically in Figure 3.

Fig. 3.

Ixodes ricinus ticks are sucking the blood as larval instars mainly on small rodents and insectivorous animals, birds and reptiles. Occasionally they feed on bigger and big beasts of chase (deer, roebuck, fox, hare), domestic animals (cow, sheep, goat) and man. The nymphal instars are feeding on all the animal species mentioned and man, but especially on domestic animals grazing in areas infested by ticks. Adult ticks are found almost exclusively on big wild and grazing domestic animals and man.

Both wild and domestic animals do not succumb after ~~infection by~~ a bite by a virus carrying tick. There are neither deaths nor signs of disease, except of a slight temperature increase, in domestic animals inoculated subcutaneously with large amounts of virus (0.04 ml. per kg. body-weight of a 10% suspension containing 10^8 mouse LD_{50} per 0.03 ml.) (Grešíková, 1957 a,b,c). Nonimmune domestic animals (goats, sheep) grazing for one season in a natural focus of tick-borne encephalitis produce only specific antibodies without a clinical manifestation of disease (Škoda and Blaškovič 1958). Specific complement-fixing, haemagglutination inhibiting as well as virus neutralizing antibodies develop quite regularly in animals infected naturally with the virus. The demonstration of antibodies serves as a basis for conclusions about the presence of virus in nature.

The infectious process caused by virus transmitted to a host animal depends on the state of susceptibility or immunity of the animal (Benda 1958).

In animals which acquired immunity following a previous infection, feeding of infectious ticks will not cause viremia, whereas viremia of varying duration will develop in nonimmune animals. The viremic phase lasts 4-6 days in roes and hares, on the average 5 days in laboratory mice (Libíková and Albrecht 1958), and 6, 5 and 4 days respectively in goats, sheep and cows (Grešíková, 1957 a,b,c). The affected animals in the viremic stage serve as source of infection for noninfectious ticks. Because virus remains infective in engorged ticks for several consecutive instars and may even be transmitted transovarially, the persistence of the virus in a natural focus of infection is secured provided that there is a sufficient supply of hosts. Virus spread is secured into the next surroundings by the ticks themselves and into distant areas by means of host animals including migrating birds. The duration of viremia and the level of virus content in the blood are of decisive importance for the preservation of virus in nature (Gordon-Smith, 1954).

Following the viremic stage, during which the virus can be isolated from wild animals in nature (Przesmycki et al., 1960), the virus becomes fixed in tissues, predominantly in the brain, where it can be easily demonstrated. Following experimental subcutaneous infection with 100-1,000 mouse LD_{50} of virus of Micromys minutus mice caught in the field it was possible to demonstrate the virus in them after 31 days (Mornsteinová and Albrecht, 1957). It is not known whether animals preserving the virus in brain tissue can serve as source of infection for ticks by developing secondary viremia. The presence of circulating antibodies seems to offer evidence against such a possibility. Alimentary infection of predators after consumption of such animals cannot be excluded, however. So far, no satisfactory evidence of this has been offered.

The state of immunity of host animals, both wild and domestic, can be one of the regulators of the amount of virus present in ticks and of the total amount of virus present in a natural focus of infection. We mentioned already that immune animals do not develop viremia even if infested with infectious ticks. On the contrary, the virus doses from the ticks act as revaccination doses leading to increased titres of antibodies.

On the other hand, antibodies affect the virus present in ticks. Extensive experiments (Benda 1958) showed that blood from an immune animal can [redacted] show no effect on the virus titer in infectious ticks following engorgement, or can cause a decrease in the titer. There is a decrease in the titer of virus transmitted to the next instar of such ticks as compared with the controls. When nymphs are sucking blood from an immune animal, further transstadial transmission of virus is irregular or does not take place. Sucking of immune blood does not free the tick from virus, it causes a decrease in the titer of virus or an irregular transmission of virus to the subsequent instars.

The tick-borne encephalitis virus is transmitted transstadially in ticks. This fact has been known since the first investigations on tick-borne encephalitis and has been demonstrated successfully by most investigators in different species of ticks: Ixodes persulcatus (Chumakov, 1944), Dermacentor silvarum (Ryzhov and Skrynnik, 1939), Ixodes ricinus (Benda, 1958b) and Ixodes hexagonus (Streissle, 1960). On the other hand, van Tongeren (quoted after Verlinde, 1956) did not demostrate the virus in ticks 6 days after engorgement. He concluded that the tick remains infective only so long it contains rests of the blood.

Transovarial transmission of the virus has not been demonstrated by all investigators with an equal regularity, or it was not confirmed.

In Ixodes persulcatus the transovarial transmission of virus was regularly demonstrated by repeated experiments (~~Serdyukova and Shubladze, 1941; Shubladze~~ Chumakov, 1944). More recent investigations (Dumina, 1958; Benda, 1958b) seem to indicate that the transmission is irregular, its rate amounting to about 6% in both Ixodes persulcatus and I. ricinus ticks.

The problem of transstadial and transovarial transmission of virus in ticks has been the subject of often discussions. It has been concluded that the results can be compared only if ticks, viruses and hosts from the same locality are used. The fact that differences exist in the amount of virus circulating in different foci of infection, in the vectors (Ixodes ricinus, I. persulcatus, Haemaphysalis concinna or Dermacentor silvarum) as well as in the host animals, can itself lead to a different behavior of the virus used to the tick examined. The positive isolation rate of virus from tick pools varies from 2-25% in different localities in the U.S.S.R. (Smorodintsev, 1958). In Czechoslovakia, the virus isolation rate from ticks occurring in natural foci was higher in western than eastern parts of the country, but it never reached values commonly obtained in natural foci occurring in the Siberian tayga or habitats not changed by human action.

Feces from infectious ticks contain fully virulent virus, whose infectivity persists for considerable periods even at room temperature. The feces represent basically undigested blood from the host and the virus contained in them comes either directly from the animal host or from the tick's intestinal tract, where maximum amounts of virus are present. The virus namely multiplies in the intestinal tract of ticks and later it spreads from there to different organs, especially to the salivary glands (Pavlovsky and Solovyov, 1940, 1941).

The role of gamasoid mites in the circulation of tick-borne encephalitis virus is limited to virus maintenance in a microfocus, i.e. in nests of rodents and birds. Tagiltsev (1958) studied 27 species of these small ectoparasites living from their hosts' blood. Virus could be transmitted by these mites from one species of birds or small rodents to another species only within the limits of ecological relationships of the animals mentioned. In a natural focus of tick-borne encephalitis it was possible to isolate the virus from Dermanyssus hindinis. The role of mites in the ecology of tick-borne encephalitis virus has not yet been fully elucidated.

Similarly, not much is known about the role of fleas and mosquitoes as natural vectors of the virus. Experimental results

(Slonim and Kramár, 1955) offered suggestive evidence against a role of mosquitoes in virus transmission, because in Culex pipiens, C. molestus, Aedes vexans and Anopheles messae mosquitoes which sucked on a 10% mouse brain suspension containing $10^5 - 10^6$ mouse LD_{50} of virus per 0.03 ml. the virus did not multiply and after 2 days it could no longer be recovered from their bodies. In contrast to this are the findings of Polish authors (Przesmycki et al., 1960) who repeatedly obtained positive isolations of tick--borne encephalitis virus from Anopheles and Aedes mosquitoes as well as from fleas caught on animals in a natural focus of tick--borne encephalitis in the Bialowies forest national park. This seems to offer suggestive evidence of virus transmission between small rodents and birds (Rosický, 1959).

The data mentioned above on the transovarial and transstadial transmission of tick-borne encephalitis virus in ticks indicate that the maintenance of virus in a natural focus is sufficiently guaranteed. Nevertheless investigations have been carried out on the possibility of virus hibernation in vertebrate hosts, in whose blood or organs the virus would persist during their winter sleep, at a time when the ticks are inactive.

It was found that the virus persisted in the blood from hedgehogs in an experiment in which the animals were kept in a refrigerator at $+4^{\circ}$ C (von Tongeren, 1957).

Bats were inoculated subcutaneously with 200,000 mouse LD_{50} of virus in 0.1 ml. and placed in a cave, where these insectivorous animals are normally hibernating. The virus persisted in the blood from the 7th to the 23rd day of hibernation, and viremia could be demonstrated for a further 7 days after hibernation was interrupted. In the liver and spleen the virus was found 11 days and in the brains 14 days after the hibernation was interrupted (Nosek et al., 1960).

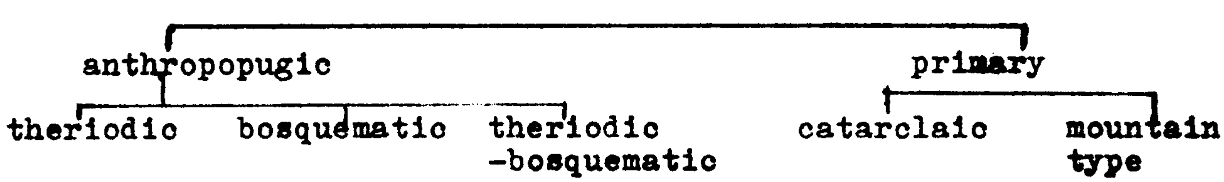
Similarly arranged experiments have to be based on the experirole in the circulation of the virus and that it represents a link open on both sides, i.e. that it can not only accept the virus and maintain it in the blood, but also pass it on to ectoparasites sucking the blood on different vertebrate species and thus to transmit the virus to the latter.

Mention has been made of birds, which can affect the maintenance, circulation and spread of virus in nature. Evidence of this are specific antibodies against tick-borne encephalitis virus in birds and the fact that many bird species are infested by ticks. Tick-borne encephalitis virus could be isolated in western Siberia from Ixodes plumbeus Leach. ticks parasitizing on birds (sand-martin) (Fedorov and Tyushnakova, 1958). Virus isolations from birds' brains are also not infrequent. If such isolations are made from migrating birds, it can be speculated about the role of these birds in spreading foci of tick-borne encephalitis (Ernek, 1958; Blaškovič, 1958a).

We have summarized the knowledge concerning the ecology of tick-borne encephalitis virus. There are some peculiarities in respect to the characteristics of the natural foci of infection themselves. Many steps occur from natural foci hitherto untouched by man to those which underwent the biggest changes following the activity of man. Rosický (1959) applies Pavlovsky and Lasukhin's (1958) scheme to the conditions prevailing in Europe. The division is based on that of whether the activity of man caused changes in the landscape character and modified it for breeding game or domestic animals.

Fig. 4.

Natural foci of tick-borne encephalitis



(From Rosický, 1959)

Theriodic (game) foci are characterized by tree vegetation suitable for breeding game. Domestic animals do not graze in such areas, maximally they pass through them when moving to pastures. The incidence of ticks per 100 square m. area is considerable, in central Bohemia it being possible to collect on such an area about 150 adults and 3,600 nymphs within a year. Such foci are characterized by deciduous woods (the most characteristic trees being the horn beam, Carpinus betulus, and the lime, Tilia cordata). Transmission of the infection to man is effected exclusively by tick bite when collecting fruit etc. or during camping or recreation. Examples of such foci can be found in Bohemia, south Slovakia, in the Steiermark (Austria), in Hungary and most probably in the Bialowieza forest (Poland), which belongs to the most ancient forests in Europe.

Bosquematic (pasture-type) foci developed by degradation of previously woody habitats. Domestic grazing animals are the main source of food for Ixodes ricinus ticks. Natural foci of the pasture type can cover large areas, in which the animals grazing for the whole vegetation period are very intensively infested by ticks, e.g. in Albania, south Slovakia, south Bulgaria and Slovenia to the north of Ljubljana. Infection of man is possible either by tick-bite or by drinking row milk, eventually by consuming dairy products. In such natural foci familiar microepidemies or even explosive epidemies can occur, if milk is not treated in a prescribed way (Raška et al., 1954).

Mixed theriodic-bosquematic (game-pasture) natural foci combine the properties of both previously mentioned foci and are characterized by alternating woody, bushy and grassy vegetation. In a focus of this type in Slovakia it was found by epidemiologic analysis that 60.2% of human infections resulted after a tick-bite and 23.1% after drinking unboiled goat's milk. In 16.7% of cases the source of infection could not be demonstrated (Bárdoš et al., 1954).

Examples of such mixed natural foci can be also found in the Kamniške Alps (Yugoslavia), in the Steiermark (Austria) and in north-eastern Albania (Rosický, 1959).

Mountain-type natural foci are characterized by a very low incidence of ticks, and by a high altitude (above 1,000 m. above the sea level). It is assumed that virus circulation is secured here by mites and fleas and that it is of a microfocal character. The action of man does not affect these areas and cases of human infection are extremely rare, if possible at all. The existence of natural foci of this type can only be revealed by a serological survey, eventually by virus isolation (Bárdoš et al., 1954). This type of natural foci is included among primary foci and it presumably represents a marginal relic of an originally widespread focus, which has been interrupted by the action of man.

Primary natural foci not affected by the activity of man do no more exist in Central and Southern Europe. They are approached by the Bialowies forest national park in Poland.

Categories. Natural foci of tick-borne encephalitis as classified above form a part of larger areas showing in a different degree signs of human activity (Rosický and Hejný, 1959). These regions can be divided into 5 groups: (1) the natural region, (2) the slightly cultivated region, (3) the moderately cultivated region, (4) the highly cultivated region, and (5) the completely cultivated region. This grouping is only of a formal importance, but it explains the existence of natural foci of infection in the individual landscape types, the validity of a focus depending on the landscape character, and the possibility of a spread of a focus from regions with a higher type of cultivation into regions with a lower type of cultivation.

2. Epidemiology of tick-borne encephalitis

Two ways have been mentioned by which man becomes infected: a tick-bite or drinking row milk. They both were confirmed epidemiologically and experimentally on several occasions. Experimental data and epidemiological experience offer, however, suggestive evidence of additional possibilities. Bárdoš et al. (1954) found in examining the patients in a natural focus of tick-borne encephalitis of a theriodic-bosquematic type that 60.2% of the infections resulted after a tick-bite, 23.1% by drinking row goat's milk and in the remaining 16.7% the source of infection could not be determined. There was no evidence of a transmission from man to man.

The tick-borne encephalitis virus is rather resistant to the effect of external factors (pH, temperature), especially if it is protected by proteins or lipids. It remains infective during acidification of milk, preparation of cheese from unboiled milk, or in butter prepared from infectious milk. This applies to artificially infected starting product (milk), which contains large amounts of virus (10^6-10^7 LD_{50} per ml. of milk), whereas the milk from infected cows rarely contains more than 10^3 mouse LD_{50} of virus per ml. of milk. When kept in a refrigerator at 4^o C, infected butter and cheese remain infective for 2 months and 2 weeks, respectively (Grešíková 1958a, b).

Experimental pasteurization (Grešíková et al., 1960) at different temperatures for varying periods of time, these factors being carefully controlled, showed that the virus is safely inactivated in the milk at 72^o C for 10 seconds.

Laboratory infections are for the most part aerogenous and repeatedly occur in workers who are preparing virus suspensions in a warring blendor. Thus this way of human infections has also to be taken into account. However, laboratory conditions are not characfrom laboratory work offer for the epidemiologist a basis for taking the following additional ways of infection into account in the epidemiological analysis: inhalation of a virus containing aerosol during milking or of an aerosol containing infective tick feces which contaminate the skin of domestic animals. This possibilities presume a closed space and a considerable concentration of virus (Blaškovič, 1960). Another possibility is the inhalation of infective tick feces when working up wool and furs from domestic animals from a natural focus of infection (Bárdoš, personal communication).

Infections resulting from a tick-bite or from drinking milk show a characteristic seasonal incidence, which depends on the climatic conditions and on the activity of ticks. Epidemics from milk are either familiar microepidemics or they are of an explosive character (Raška et al., 1954). An example is the large epidemic caused by drinking unpasteurized infectious milk in Rožňava in 1951, when more than 600 peaple became infected, but there were no fatal cases (Blaškovič, 1954). The incubation period of an alimentary infection is 4-14 days and that after a tick-bite 8-20 days.

Fig. 8.

The disease incidence in Czechoslovakia is not the same in every year. A higher incidence of tick-borne encephalitis was registered in 1948 and 1953. The varying incidence depends on many factors which affect quantitative differences in the circulation of virus in a given natural focus of infection. The amount of circulating virus depends on vertebrate hosts and vectors (ticks), as shown schematically in Figs 9 and 10.

Fig. 9

Fig. 10

This scheme has to be supplemented by the properties of the virus itself which circulates in nature: the relations to the vectors, hosts, the resistance of the strains against physical and chemical factors, their genetic properties etc.

From the problems of human epidemiology we are returning in this discussion to the problem of the ecology of the virus in nature, the knowledge of which offers a most solid basis for the search for effective control measures in the prevention of tick-borne encephalitis. For the application of methods current in epidemiological practice we consider it necessary to obtain a picture as true as possible on the relationship of the virus to the vectors, hosts or reservoirs in a given natural focus. The strategy of the prevention of human infections would then be based on these findings (Blaškovič, 1960). This will apply not only to natural foci already existing, but also to those which could arise when natural conditions are changed by human activity (e.g. in the case of dams, when the water reservoirs could serve as a base for migrating aquatic birds which can be carriers of both virus and infected ectoparasites).

In Europe, the infection is usually benign. Mortality is about 1% or less, this being in contrast to the high mortality following tick-borne encephalitis in the Siberian tayga. Among hospitalized cases from the epidemic in Austria in 1954 the mortality was reported to attain 2 - 4.5%. (Grinschgl, 1955).

The differences in the incidence of infection according to age groups, sex and profession depend on the specificity of the natural focus and on the way of infection.

Infections by milk prevail in children and women. Men are not accustomed to drink goat's milk. Infections by a tick-bite are frequent in elder children and in adults (collecting of small fruit in woods, camping in woods or their vicinity) and in adult men (wood-cutters).

3. Control of tick-borne encephalitis

Protection of man against infection with the tick-borne encephalitis virus can be both specific and non specific.

Individual protection of man who enters a natural focus of tick-borne encephalitis consists in wearing suitable clothes, in using repellents and mainly in careful picking up of unengorged ticks from the body.

More important are measures leading to the eradication or very substantial lowering of the tick population in nature.

Ticks infest neglected pastures, fields and boundary strips. Grazing cattle provide them with sufficient food. They do not appear in well tended pastures. Removal of shrubs from pastures, agrotechnical care of meadows, fields and their surroundings, the improvement of footpaths, a ban on pasturing cattle in the woods, are all measures which will help to reduce the number of ticks and consequently also the source of infection. This simple method of controlling ticks is very effective and has probably led to their eradication, or, at least to a considerable decrease in their numbers, with consequent interruption of the circulation of the encephalitis virus - in some West European countries (Denmark, Holland) where tick-borne encephalitis does not occur.

Results obtained from the U.S.S.R. indicate that dusting the ground with insecticides from the air can also be an important control measure against ticks in natural environments. The most satisfactory substance is 10% DDT, which is more stable than HCH /Gorchakovskaya et al., 1958/. When acaricides were applied over two experimental plots measuring 6.6 and 8 ha every four years, and over an area measuring 482 ha every three years, Ixodes persulcatus ticks were practically exterminated. The amount of acaricides used was 30-50 kg/ha. We think that this method cannot be applied on pastures used by domestic animals without endangering their health and the quality of their milk. The acaricides could be applied in large forests before the workers will enter them /large constructions, wood cutting/. They can also be used for individual protection of domestic animals against ticks /Mačička, 1956/.

Human health can be protected by the following specific methods:

a/ by active immunization with a vaccine and

b/ by using hyperimmune serum or gamma-globulin for short-term prevention or for the treatment of infected patients.

a/ Active immunization. In the U.S.S.R., a formolized vaccine prepared from mouse brains is widely used; it has been administered since shortly after the discovery of the virus /Smorodintsev et al., 1940/. It consists basically of a one percent emulsion from infectious mouse brains inactivated by formol /1:2000/ in a fluid or lyophilized state /Drobyshevskaya, 1956/. The prophylactic value of this vaccine has received favorable evaluation /Panov, 1956/.

The vaccine does not protect everybody from infection, but vaccinated persons do not contract the severe, paralytic or fatal form of the disease.

Vaccination is carried out in persons working in forests known to be a natural focus of infection and in new settlers in the district.

Under the conditions of Czechoslovakia we are embarrassed who actually should be vaccinated in addition to the laboratory personnel. Our country is densely populated. In last years the holiday stays and camping extraordinally increased in places adjacent to the woods. Many people are coming to these places every year during the spring and summer from towns, where they do not have any contact with tick-borne encephalitis virus. Considering the present mode of vaccine preparation /mouse brain suspension/ we do not recommend vaccination of people living in the surroundings of a natural focus of tick-borne encephalitis. There are difficulties with the control of people coming to woods for holidays and camping purposes and remaining there temporarily. The health propaganda informing inhabitants on the ways of infection and on the modes how to prevent it, is of a partial help.

It was shown that the mouse brain vaccine against tick--borne encephalitis, similarly to other brain vaccines, is not an ideal substrate for parenteral administration to man, because of its allergizing properties and because of the possibility that it can induce demyelizing processes. Although it has been recommended to use infectious brain suspensions from suckling animals /mice, rats - Svet Moldavsky and Svet Moldavskaya, 1959/ which do not possess the properties mentioned above, further attempts have been made to obtain a viral material, which would be well immunogenic and free from impurities. An egg vaccine was not yet introduced, although in the U.S.S.R. it was shown to be satisfactory /Shubladze et al., 1958/.

Main attention is called to the possibility of introducing a vaccine from virus propagated in tissue cultures /Daneš and Benda, 1960a, b, c, d; Levkovich and Zasukhina, 1960a, b/. In addition to a formolized vaccine a search for a living apathogenic virus strain is made. Several approaches are recommended: to look for an avirulent strain from nature or to induce a stable mutant by laboratory procedures /Slonim, 1956; Grešíková et al., 1960/.

b/ The use of hyperimmune serum. Hyperimmune serum is administered by the intramuscular and by the intralumbar routes in the early stages of the disease, before the signs due to disturbance of the ganglion cells of the central nervous system have developed. The administration of human convalescent serum in the same way can also be recommended /used since 1939 by Shapoval et al./, the same as of gamma-globulin prepared from such serum, which was tested experimentally by Bárdoš /1956/ and Bárdoš and Šimková /1958/.

We also have experience on the effect of human convalescent serum and immune gamma-globulin in the treatment of laboratory infections. In some cases, large doses of these preparations were given at the onset of the first phase of the disease. This did not prevent the development of the second stage, but paralysis did not occur in any of the five cases observed. On the other hand, it should be borne in mind that whenever a member of the staff of a neuroinfection laboratory develops a pyrexial condition, we insist on his remaining in bed even after the fever has subsided /i.e. for the time of the "asymptomatic interval"/.

Let call our attention once more to the ecological problems of tick-borne encephalitis and to the possibility of controlling the infection by some intervention in the pathogenesis of the infection and in the circulation of the virus in nature.

We suggested to protect man against infection by milk by means of vaccinating domestic animals with different kinds of vaccine with a simultaneous testing of their immunogenicity. Our assumption that immune domestic animals grazing in great numbers will unfavourably affect the virus circulation in nature as hosts of ticks in two ways was also based on the experiences concerning the effect of immune serum on the tick-borne encephalitis virus in ticks /Benda, 1958a, b/. First, no viremia will ensue in the

FOR [illegible] ONLY

animals following a bite by infectious ticks and thus the animals will not become a source of virus for starving not infectious ticks. Second, the amount of virus in infectious ticks sucking blood from immune domestic animals will be effected by antibodies, eventually all virus will be neutralized.

We vaccinated therefore in 1959 several hundred domestic animals /sheep, cows and goats/ which were grazing in a natural focus. This work is still being continued but preliminary results presented at the Symposium on the biology of viruses of the tick--borne encephalitis complex show that some promising effect could be obtained especially when live virus vaccine was used /Blaškovič et al., 1960/.

Such a biological intervention into virus circulation in nature is substantiated, however, only if domestic animals are driven out to graze in a natural focus of infection. However, even in such regions a single form of intervention will be insufficiently effective in disturbing the virus circulation, if not combined with other means.

It is difficult to evaluate the efficacy of such control measures, because a long-term program is involved. The criteria of evaluation will be based not only on the incidence of the given infection, but also on quantitative and qualitative estimations of the presence of virus in the given area.

This review is in want of an exact epidemiological analysis of the incidence of proved tick-borne encephalitis cases in the individual European countries. No reliable statistical data are available. However the analysis of cases from some years, as e.g. 1948 and 1953, when the disease occurred more frequently in Czechoslovakia, shows that it is necessary to pay attention to the clinics, epidemiology and control of the disease. It is not an easy problem because the methods of research and control of an infection of this kind are complicated. The solution of these problems needs a team work of different specialists and the collaboration of different working groups in the world. I believe that a success in a good protection of human health will be achieved by man's activity in various places with a final goal to cut virus circulation in nature. For this reason I tried to present some aspects and observations.

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