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Review Article

A brief history of the discovery of tick-borne encephalitis virus in the late 1930s (based on reminiscences of members of the expeditions, their colleagues, and relatives)☆

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ABSTRACT

Tick-borne encephalitis virus is the etiological agent of a severe human disease transmitted by hard ticks. It occurs in large parts of eastern, central, and western Asia and in Europe with thousands of human cases each year. Here, the discovery of the virus by Soviet scientists in the late 1930s in the Far East is described. The pioneering work involved with this discovery, which resulted in great scientific and epidemiological achievement, was undertaken under the most difficult conditions, and some of the scientists and their technical assistants paid for it with their health and even their lives. This paper briefly outlines the steps on the way that elucidated the basic etiology and eco-epidemiology of the disease, and does not omit that, as one result of the expeditions and the political situation in the former Soviet Union at that time, some scientists were sent to prison.

1. History and preparation of expedition

From the early 1930s, an acute central nervous system disease with a high death rate was recorded in the Far East of the former USSR. Etiology, epidemiology, and pathogenesis were not clear. The neurologists Alexander G. Panov, B.O. Rabinovich, Israel Z. Finkel, and Alexey S. Shapoval who worked in the Far East at that time, presumed that the disease was Japanese encephalitis (or so-called summer encephalitis) or poliomyelitis (Vladimirova, 2002).

Because of tension between USSR and Japan in the years 1935–37, large numbers of troops were located in the taiga along the USSR's border just where the disease constituted a threat. A considerable number of soldiers of the Special Far Eastern Army (commander: Vasily K. Blucher) had a disease with frequently fatal outcome. A military neurologist, Israel Z. Finkel, described it as epidemic encephalitis in 1936. Alexander G. Panov, also a military neurologist, considered it a disease similar to polio in adults and noted some similarities with Japanese encephalitis, but assumed airborne transmission. The etiology of the disease was unknown. Anna M. Tkacheva, a microbiologist from Khabarovsk, tried to identify the pathogen of the new disease in 1936. White mice were infected with a suspension from the brain of a dead patient. In several passages, single mice became ill. However, isolation and maintenance of the infectious agent failed.

Because of an increase in the number of cases among the troops the commander of the Medical Department of the Far Eastern Army appealed for help to Moscow. In that situation, the USSR Ministry of Health decided to send out an expedition. Public Health Commissar Kaminsky offered to send a group of professors to the Far East, including Professor Lev A. Zilber. Zilber refused unless he could take full responsibility, organize the expedition, select the participants and train them. Ultimately, Zilber (Fig. 1), the head of the first medical virological laboratory in the country, was put in charge of the expedition by order of the Army (Kisselev et al., 1992). The expedition was organized with the assistance of the USSR People's Commissariat of Public Health – Narkomzdrav (the name of the Ministry of Public Health in 1930s and 1940s), Marshal K.E. Voroshilov, Military-Sanitary Control, and Marshal V.K. Blucher. Zilber was given the opportunity to choose any specialists he considered necessary to include in the expedition team. He purposely recruited only young people. Later on, he wrote in his reminiscences (see Abelev, 1971): 'Of course, I gathered them and warned about the dangers and difficulties and all the other things. In my opinion, young people offered a huge advantage: They

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Fig. 1. Lev A. Zilber, 1937.

were not tied by old delusions about this disease. Our official documents said that we are going to study summer encephalitis (Japanese encephalitis). I was not sure about that, so we developed three different research plans: plan 1 in case it was indeed summer encephalitis, plan 2 in case it was some other encephalitis, and finally plan 3 in case it was something other than encephalitis. These plans were drawn up thoroughly. From the very beginning, I enforced parallelism in this work. My team was divided into two squads doing the same things in order to be sure about the final results and to decrease the duration of the study, an approach that has convincingly proved its great value.'

These squads were the Northern Squad working in the Khabarovsk Territory and the Southern Squad working in the Primorsky Territory (Fig. 2). The Northern Squad was led by Elizabeth N. Levkovich (Fig. 3; see also Fig. 4 with some members of the Northern Squad and Table 1 with the names of all those on the expedition). The squad's place of work was in the Oborsky timber enterprise, which was most unfavorably situated for study of the disease. The Southern Squad was led by Alexandra D. Sheboldaeva, and its place of work was Vladivostok, Primorye region. Unfortunately, the archive of the Southern Squad has not survived. The majority of the team members were young people in their twenties. Zilber, working in both squads was in his early forties.

Levkovich wrote in her reminiscences in 1958 (see Pogodina, 2001): 'The Northern Squad's work was difficult because they had to work in a remote taiga village of a timber enterprise. Because of the lack of roads, the team members had to go through virgin taiga with all their equipment including the experimental animals. Very quickly, they created a scientific campus (they did not build much, but they defined and organized a scientific campus where virtually no sort of campus had existed previously), and they used trailers made for forest workers to establish provisional virological and parasitological laboratories, an animal house, and a clinic for infected patients. All the forest workers in this village were examined by the medical staff. There was an endless flow of critically ill patients and others with residual paralysis after old infections. The fatality rate among people with encephalitis in Obor, a small village in the Khabarovsk territory, was extremely high: 32% in 1932, 24% in 1937, 13% in 1938, and 27.5% in 1939.'

After the expedition's arrival in Khabarovsk, comprehensive studies at the two bases commenced quickly, and the first significant results were obtained within only two weeks. Figs. 5–8 illustrate the conditions under which the participants of the expedition had to carry out their pioneering work.

2. The course of events in 1937 (after Pogodina, 2001)

May 15th

Expedition's arrival in Khabarovsk

May 17th

Formation of the Northern and Southern Squads

May 19th

Zilber studies medical reports which do not support the theory of a droplet or contact infection, because most infections occurred in the taiga in the spring. Zilber examines a recovering encephalitis patient, Mrs. Vasilieva, a housewife living in a small taiga village. She recalls a tick bite 12−14 days before the onset of her disease (outside the mosquito season), which leads Zilber to hypothesize that the pathogen is transmitted by ixodid ticks.

Zilber, after reading a veterinary paper, realizes that the number of human infections increased two weeks after a peak of tick bites in cattle, further supporting his vector tick theory.

Late May

Alexander V. Gutsevich, the entomologist of the Northern Squad, collects blood-sucking arthropods in the forest by exposing his forearm. From the collected ticks (*Ixodes persulcatus*, the taiga tick), Mikhail P. Chumakov prepares a suspension and injects it into some white mice. Subsequently, he succeeds in isolating the virus from diseased mice. In addition, the virus is isolated from ticks feeding on the infected mice. Thereby Chumakov strengthened the hypothesis that ticks are the vectors of the causative agent.

June 10th

Zilber proposes tick bite prophylaxis as a new measure against the disease. He sends out team members to warn people working in the taiga to try to avoid tick bites, which proved successful because only one of those highly exposed people subsequently in that tick season fell ill.

June–August

The epidemiologist V.L. Olshevskaya organizes medical examination of the whole village population and frequently finds people with neurological symptoms.

Both Levkovich and Chumakov in the Northern Squad and A.K. Shubladze and V.D. Soloviev in the Southern Squad isolate the virus from blood and spinal fluid of febrile patients (altogether 29 strains).

In the clinic of the Northern Squad, the neuropathologist A.N. Shapoval studies the clinical peculiarities of the disease and makes attempts to treat patients. Altogether, 64 patients were hospitalized, and 12 of them died.

The pathologist A.G. Kestner determines changes in all the body organs and systems of deceased patients, the most significant ones occurring in the CNS.

Chumakov cuts his finger during the autopsy of a dead patient and falls ill with a severe bulbopoliomyelitic (focal) form of tick-borne encephalitis (after the description by A.N. Shapoval) with various symptoms. He receives immune serum from a convalescent's blood, a successful immunotherapy described by A.N. Shapoval, and survives, but residual effects are right arm paralysis and hearing loss.

In the Southern Squad, V.D. Soloviev (optic nerve damage) and E.F. Gnevysheva (psychosis) fall ill with encephalitis. Mironov and Monchadsky have a mild disease without sequelae.