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)⁎

Vladimir I. Zlobina, Vanda V. Pogodina, Olaf Kahl

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)

ARTICLE INFO

Keywords:
Tick-borne encephalitis virus
TBE
Ixodes persulcatus
Lev A. Zilber

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. 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 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...
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 finally worked.

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 designed 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.I. Olshhevskaya 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.
There were no fatalities among the participants of the 1937 expedition.

**August 15th**

Completion of the expedition.

**August 20th**

L.A. Zilber reports the results of their work to the USSR People’s Commissariat of Public Health calling the new disease ‘spring epidemic encephalitis’ or ‘tick-borne encephalitis’.

Zilber’s report was endorsed by the USSR People’s Commissariat of Public Health. Thus, in a very short time, under the unbelievably hard conditions of the Far-Eastern taiga, a group of young enthusiastic scientists under the professional guidance of Zilber, elucidated the etiology of a new, severe and emergent disease in a systematic study. They discovered the previously unknown virus and were able to isolate several virus strains, they determined the vector, an ixodid tick, they detected the main eco-epidemiological features of the disease, and they studied its clinical picture and its pathology. They were the first to test and show the effectiveness of immunotherapy in tick-borne encephalitis patients. They proposed and successfully introduced methods of prevention based on the avoidance of tick bites.
On September 15th, 1937, the Pravda newspaper published an article entitled ‘A major Contribution to Medicine. Study of Spring Encephalitis’, which related the success of Professor Zilber’s expedition. Zilber (1939) wrote: ‘Unfortunately, the great scientific success of the expedition was achieved at the price of infections acquired by some team members. It is difficult to say how some of them became infected. All the measures of ordinary prophylaxis while working with infectious materials were thoroughly observed by all team members. We were pioneers, the first people on Earth holding this formerly unknown virus in their hands. It is possible that the comparatively primitive conditions of work and also fatigue resulting from 12-h workdays played some role. But I could not withhold my team from this hard work. They were working with exceptional passion and true enthusiasm. In the following years, there were cases of lethal contagion while working with this virus in specialized virological laboratories in Moscow. These facts make us think about the extraordinarily high infectivity of the virus. It is no surprise that the first encounter with this virus resulted in human victims. They could have been much more numerous.’

3. Further expeditions

Further expeditions followed soon to enlarge the knowledge of the newly discovered tick-borne encephalitis virus and to test prophylactic measures.

In 1938, a second expedition was sent out by the USSR Narkomzdrav to the Far East under the leadership of the Academician E.N. Pavlovskij (Fig. 9). The head of the virological group was A.A. Smorodintsev. A major aim of the expedition was the study of tick-borne encephalitis virus circulation and the involved reservoir hosts in natural foci. Moreover, they developed an inactivated vaccine. The

---

Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Function, profession</th>
<th>Institution, city</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zilber, Lev Alexandrovich</td>
<td>Head, virologist</td>
<td>Central Viral Laboratory, Moscow</td>
</tr>
<tr>
<td>Levkovich, Elizabeth Nikolaevna</td>
<td>Team guide, virologist</td>
<td>Central Viral Laboratory (Head: Zilber, L.A.), Moscow</td>
</tr>
<tr>
<td>Chumakov, Mikhail Petrovich</td>
<td>Virologist</td>
<td>Microbiological Institute, Dept. of Viruses (Head: Zilber, L.A.), Moscow</td>
</tr>
<tr>
<td>Ozsewskaya, Vitalia Lovova</td>
<td>Epidemiologist</td>
<td>Military Medical Institute, Dept. of Epidemiology, Moscow</td>
</tr>
<tr>
<td>Finkel, Israel Zinoveyevich</td>
<td>Neurologist</td>
<td>Military Hospital, Khabarovsk</td>
</tr>
<tr>
<td>Shapoval, Alexey Nikitovich</td>
<td>Entomologist</td>
<td>Military Hospital, Khabarovsk</td>
</tr>
<tr>
<td>Gutevich, Alexander Vasilyevich</td>
<td>Entomologist, acarologist</td>
<td>Military Medical Academy, Dept. of E.N. Pavlovsky, Leningrad</td>
</tr>
<tr>
<td>Skrynnik, Alexandra Nikitovna</td>
<td>Zoologist</td>
<td>Military Medical Academy, Dept. of E.N. Pavlovsky, Leningrad</td>
</tr>
<tr>
<td>Grachev, P.E.</td>
<td>Microbiologist</td>
<td>Military Medical Academy, Dept. of E.N. Pavlovsky, Leningrad</td>
</tr>
<tr>
<td>Ryzhov, N.K.</td>
<td>Virologist, laboratory assistant</td>
<td>Anatomic Bureau, Moscow</td>
</tr>
<tr>
<td>Kestner, Alexander Grigoryevich</td>
<td>Pathologist, morphologist</td>
<td>Central Viral Laboratory, Moscow</td>
</tr>
<tr>
<td>Zorina-Nikolaev, Galina Nikolayevna</td>
<td>Virologist, laboratory assistant</td>
<td>Central Viral Laboratory, Moscow</td>
</tr>
</tbody>
</table>

**Northern Squad** (Khabarovsk region, Obor village)

**Southern Squad** (Primorye region, Vladivostok)

Shchobolaeva, Alexandra Danilovna | Team guide, virologist                  | Microbiological Institute, Dept. of Viruses (Head: Zilber, L.A.), Moscow |
Shubladze, Antonina Konstantinovna | Virologist                              | Central Viral Laboratory (Head: Zilber, L.A.), Moscow |
Soleviev, Valentin Dmitrievich | Epidemiologist                          | Microbiological Institute, Dept. of Epidemiology, Moscow |
Safonova, Tamara Mikhailovna | Neurologist                             | Military Hospital, Vladivostok, Leningrad |
Panov, Alexander Gavrilovich | Entomologist (mosquitoes)              | Zoological Institute, Dept. of Parasitology, Leningrad |
Monchadsky, Alexander Samoylovich | Virologist, laboratory assistant        | Microbiological Institute, Dept. of Viruses, Moscow |
Gnevyshova, Elena Mikhailovna | Microbiologist                         | Institute of Tropical Diseases, Moscow |
Mironov, V.S.                  | Microbiologist                         | Military Hospital, Khabarovsk |
research officer N.V. Kagan and the laboratory assistant N.Y. Utkina died after becoming infected when preparing the vaccine. The parasitologist Boris I. Pomerantsev became infected as a result of multiple tick bites in the Ussuri district during that expedition and died from tick-borne encephalitis.

In 1939, a third expedition was sent out by the USSR Narkomzdrav to the Far East under the direction of I.I. Rogozin. E.N. Levkovich and N.L. Dankovsky administered a newly developed tick-borne encephalitis vaccine to people.

Later M.P. Chumakov and N.A. Zeitlenok found new tick-borne encephalitis virus foci outside the Far East, in the Ural and Transural regions.

In 1940, an expedition of the Union Institute of Experimental Medicine was sent out to the Far East. The head of the squad was E.N. Levkovich. They organized a mass immunization against tick-borne encephalitis leading to elimination of the disease in some districts.

This may read like the end of the story of the discovery of tick-borne encephalitis virus, but it is not.

4. After the discovery of the tick-borne encephalitis virus

It was 1937, a period of massive oppression in the Soviet Union. This occurred in the party ranks, in the army, among scientists, artists, workmen, and peasants. The leader of the first expedition, Professor Zilber, and two of his team members, A.D. Sheboldaeva and T.M.
Safonova, were arrested after slanderous denunciation. Zilber and his colleagues were accused of spreading Japanese encephalitis virus under the guise of performing scientific research and of spreading the newly discovered and isolated dangerous virus among military contingents in the Far East and among the inhabitants of Moscow (Kisselev and Levina, 2005). However, the charges were so absurd and Zilber’s innocence was so evident that he was released in 1939. Perhaps, this release occurred because of the arrival of the new leader of repressive measures, Lawrenti Beria, who tried to disguise mass terror by releasing a small number of prisoners (see also Kisselev et al., 1992). It also needs mentioning that Zilber’s followers and his colleagues, as well as the famous writer V. Kaverin and the microbiologist and epidemiologist Zinaida Ermolyeva, who gave the USSR penicillin during World War II, campaigned vigorously for Zilber’s release.

After his release, Zilber published classic, basic articles on tick-borne encephalitis (e.g. Zilber, 1939). He wrote a monograph on

![Fig. 7. E.N. Levkovich, G.N. Zorina-Nikolaeva, and M.P. Chumakov, Obor (Khabarovsk territory), 1937. In search of the unknown infectious agent.](image1)

Fig. 7. E.N. Levkovich, G.N. Zorina-Nikolaeva, and M.P. Chumakov, Obor (Khabarovsk territory), 1937. In search of the unknown infectious agent.

![Fig. 8. E.N. Levkovich and G.N. Zorina-Nikolaeva. Filtration of the first samples of the TBE vaccine.](image2)

Fig. 8. E.N. Levkovich and G.N. Zorina-Nikolaeva. Filtration of the first samples of the TBE vaccine.
encephalitis and submitted it to a publisher in December 1939 (Zilber, 1945).

The first scientific report on the etiology of tick-borne encephalitis was published in 1938 in the absence of Zilber and Sheboldaeva, and they were not listed as co-authors. However, by sending a letter to Voprosy Virusologii as late as in 1957, the coauthors finally achieved inclusion of the names Zilber and Sheboldaeva in the paper (Vopr. Virus. 3, p. 191) (Kisselev et al., 1992).

Pavlovskij, Smorodintsev, and Petrishcheva, participants of the second and third Far-East expeditions, but not Zilber, Sheboldaeva, or Safonova, received the Stalin prize of the first degree in 1941 (Kisselev et al., 1992).

Zilber was arrested again in 1940. Although he was in the GULAG and accused of betrayal of the Motherland, Zilber did not sign any confession of his ‘guilt’, despite the severe conditions of the northern labor camp and despite numerous questionings. He was not crushed, and he courageously endured privations. In prison, he delivered the possible medical care to other prisoners using any available means. After he delivered the baby of the wife of the GULAG commander, he was given the privilege of running a primitive “microbiology lab” in prison. He developed a method of treatment and prevention of scurvy based on the cultivation of yeast on reindeer moss extracts (lichens Cladonia spp. and Cetraria spp., abundant in the nearby tundra), which saved the lives of hundreds of people.

Friends and famous scientists in the country were risking their lives when writing, at the height of terror and mass repression, of Zilber’s innocence. A group of leading Soviet scientists sent a letter of support to Stalin and in 1944, Zilber was finally released and later rehabilitated.

This was not the first time that Zilber was under a cloud. In the early 1930s, when Zilber was the director of the Baku Institute of Microbiology, he battled a pneumonic plague outbreak under very difficult conditions in the Caucasus, but was made responsible for the epidemic, which was far removed from reality, and was arrested. On this occasion the great Russian writer, Maxim Gorky, sent a letter of support for Zilber to Stalin. Gorky was a good friend of the well-known writer V. Kaverin, Zilber’s younger brother, and, after 4 months, Zilber was released (for more information see Kisselev et al., 1992).

Professor Zilber later became a member of the USSR Academy of Medical Sciences, was a recipient of the Stalin’s Prize for his monograph on encephalitis, was the creator of the first scientific virology division, and Scientific Director of the reopened Virology Research Institute of the USSR Academy of Medical Sciences. He developed an outstanding viro-genetic cancer theory, which was many years ahead of contemporary knowledge, concerning the role of viruses in the development of oncological diseases (Zilber, 1946). Zilber died in his laboratory in 1966, engaged in experimental research and scientific writing until his very last day (Kisselev et al., 1992).

The Far-Eastern expeditions of 1937–1939 had a tremendous influence on the development of scientific medicine in Russia. They showed the priceless experience of research in a new field of science and contributed much to the fast and successful development of virological research. The expeditions promoted a group of talented young scientists, who later became renowned virologists and clinicians and who created their own scientific directions and schools: E.N. Levkovich, M.P. Chumakov, A.A. Smorodintsev, V.D. Soloviev, A.K. Shubladze, A.N. Shapoval, and A.G. Panov. The collected samples and the scientific observations of those expeditions formed the basis for the doctrine of the natural focality of infectious zoonotic diseases by E.N. Pavlovskij (Pavlovskij, 1939, 1944, 1946, 1964), a breakthrough in our understanding of the eco-epidemiology and natural history of transmissible diseases.

Finally, the selfless work of all those scientists became an example to follow for several generations of young researchers who devoted themselves to study viruses and viral diseases.

Acknowledgements

Dr. Katharina Brugger (Vienna, Austria) produced the geographic map (Fig. 2). We are grateful to an anonymous reviewer whose suggestions much helped improve the text. Prof. Jeremy Gray (Dublin, Ireland) read a late version of the manuscript and made very helpful comments.

References
