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In recent years Soviet scientists have discovered and investigated a few new infectious diseases in man. Among these newly diagnosed diseases, Crimean hemorrhagic fever and Far Eastern hemorrhagic nephropathia encephalitis deserve special attention. These infectious diseases are endemic and viral in origin. They are characterized by an acute febrile course and by a progressive hemorrhagic syndrome, typical changes in the blood, changes in the internal organs of the body and in the nervous system.

The infections are closely related to already known fevers of virus etiology which are transmitted by arthropods as are yellow fever, dengue, pappataci fever, Colorado tick fever, and some of the other dengue type endemic virus diseases; this is verified by the similarity of their pathogenic bacteria and the natural habitat, by the clinical blood picture, and also by the symptomatology and course of the infectious process.

Moreover, the regularity in development of various manifestations of the hemorrhagic diathesis, in connection with acute fever, present a characteristic picture of the clinical and pathological process of the new diseases mentioned, so that it is important that they be known. This allows us to place them into the group of virus hemorrhagic fevers.

At the present time there are grounds to include, in this group of infectious diseases, the disease recently investigated by us which is

*Omsk Oblast (55°00'N 73°E) is one of the administrative units in Siberia. It is roughly a rectangular area drained by the Irtysh River which flows through the oblast from southeast to northwest. In the north the oblast extends as far south as 57°N which is the transition belt between taiga and wooded steppe. The City of Omsk (55°00'N 73°24'E) is the capital of the oblast.*
called Qoxk hemorrhagic fever, and possibly other hemorrhagic diseases of unknown etiology which were observed in Central Asia and described by Professor Sipovskii in 1944, Ioff (1945), Mikhailov (1946), and others.

It is necessary to stress that not all modifications of the diseases of the group to which hemorrhagic fever and similar diseases belong, have yet been established; this group remains to be studied. Preliminary data on hand show that not only similarity of certain features exist among the hemorrhagic fevers, but also that there are definite variations among some of them.

Far Eastern nephro-nephritis, described by Smorodintsev, Churilov, Ratner, and others, differs from Crimean hemorrhagic fever by a more severe hepatic pathology, in connection with disturbance of blood circulation in the kidneys, frequent hemorrhages in the peritoneum, "myeloid changes" in the blood resulting from severe toxicosis of the bone marrow, as well as significant peculiarity of the epidemiology of the pathogen itself - the virus.

Neither of these diseases is contagious and they are not transmitted by an affected individual to a healthy person as was the case in a minor outbreak of a closely related disease in Turkmenia, described in 1946 by Mikhailov. This disease was marked by extreme infectiousness (through contact with the blood of the patient who had epistaxis) and a high mortality resulting from profuse hemorrhages from the mucous membranes.

Apparently, the diseases comprising the hemorrhagic fever group have some similar pathological manifestations but are not identical with each other, and are distinct diseases.

We began our study of hemorrhagic fevers in 1944. Jointly with a number of scientists from the Academy of Medical Sciences of the USSR and with the military medical officers of the former independent maritime army in Crimea, we produced the first detailed description of Crimean hemorrhagic fever as a specific disease which was not previously known to science. We succeeded in proving the distinct virus etiology of this disease and its transmission by ticks, the endemic source of which are found in nature in the steppe regions of the Crimea. We also learned the immunogenic and serologic properties of this infection - the cause of active immunity, antigen and antibody reaction in the blood of individuals. We successfully carried out experiments in its treatment with a specific immune serum developed methods of laboratory diagnosis, and organized zoological and parasitological investigations in the areas where the disease existed. These data were published in 1945 in a scientific symposium called (Krymskai Gomorragicheska Likhoradka) "Crimean Hemorrhagic Fever" and in 1947 in a symposium named (Novosti Meditsiny) "News of Medicine" under the title of (Virusne Bolesti) "Virai Virus Diseases".
The discovery and successful research on hemorrhagic fever in the Crimea caused the study of diseases of similar etiology in other oblasts of the Soviet Union to be undertaken.

We became especially interested in an epidemic disease of unknown etiology which was observed in Omsk oblast; a few of the symptoms of this disease indicated that it was similar to Crimean hemorrhagic fever, being accompanied by frequent hemorrhages from the mucous membranes, acute fever (in more than half of the cases), leukopenia, thrombopenia, and symptoms involving internal organs and the nervous system.

The most essential differences between the Omsk fever and Crimean hemorrhagic fever consist of:

1. Presence of a second wave of high temperature (5 to 20 days after the first wave) in cases of Omsk fever which does not occur in cases of Crimean hemorrhagic fever;

2. Presence in almost 100% of the cases of Omsk fever of symptoms of a unique atypical bronchopneumonia, which was practically absent in Crimean hemorrhagic fever;

3. In Omsk fever, intracutaneous hemorrhages rarely accompany hemorrhagic rash and intestinal hemorrhages, while the contrary is the case in Crimean hemorrhagic fever. Clinically there are a number of other differences in the etiological and epidemiological characteristics of both diseases; it is especially notable that the tick Hyalomma marginatum, which is the carrier of Crimean hemorrhagic fever, is completely absent in the fauna of the affected rayons of Omsk oblast.

The study of the Omsk disease of unknown etiology was inaugurated in 1946 under the leadership of Professor P.M. Akhremovich who carried on his work with the aid of the following members of the Omsk Medical Institute: G.A. Sizemova, Iu. V. Veselov, V.P. Konstantinov, I.S. Novitskii, A.A. Gavriiivskaia, the zoologist A. V. Fedlushin, Professor of the Agricultural Institute, the entomologist G. I. Netskii, and others. But no progress was made in solving experimentally the problem of etiology and the method of transmission of the Omsk disease, because local facilities were insufficient. For that reason, at the request of the Omsk oblast health department, the Ministry of Health of the USSR and the Academy of Medical Sciences of the USSR in 1947 sent an expedition under the leadership of the author of this article. The following specialists in infectious disease were members of the expedition: Professor A.F. Pilibin and Doctor Iu.S. Klein; neuropathologist Doctor N.V. Sorokin; virologist - scientific assistants A.F. Beliawa, N.S. Slavina, and A.V. Gagarina; and laboratory assis-
I.I. Aranova and K.K. Vinogradova. We succeeded in organizing harmonious and fruitful efforts of a large body of various specialists from the Personnel of the expedition, from several clinics of the Medical Institute, from the Malaria Institute of microbiology, the Malaria Control Station and Agricultural Institute. About 50 people participated in the work.

The author of this article was at the head of the group of virologists; two clinical groups respectively headed by Professor A.F. Bilibin and Professor R.V. Akhremovich; the zoological and parasitological group was headed by Professor A.V. Fedushkin and the entomologist G.I. Netlik; the epidemiological group was headed by the instructor N.V. Log; the pathological anatomist was professor I.S. Novitskii.

Together with Doctor A.P. Beliseva, the author of this article carried on studies independently from the work done by the members of the expedition even after the expedition broke up. This work, dealing with Omsh and Crimean hemorrhagic fevers, was carried on in the Omsh laboratory of the Institute of Neurology of the Academy of Medical Sciences. Experiments were also conducted as to the relationship between Omsh fever, ricketsiales, and cross immunity; these experiments were made with monkeys in the Glimmed affiliate of the Academy of Medical Sciences of the USSR with the following doctors participating: Doctor S.S. Kershunov (institute of Virology), Dr. N.A. Voroshilova, and L.I. Kart'ianova. In this article we will deal mainly with the accomplishments of the expedition as regards the etiology and epidemiology of Omsh fever. The occurrence of the disease in which we are here interested, in Omsh oblast was observed during autumn and summer months annually, from 1944 on, in the lake and steppe localities, and in some ravens north of the city of Omsh which form the western extremity of the Baraba steppes. Similar diseases were, apparently, also observed in the adjacent ravens of the Novosibirsk oblast, but they were not adequately investigated.

It is important to note that in 1936 and in 1938 the muskrat, Ondatra, was brought in from Karelia, and multiplied rapidly.

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* Coordinates: 43°00'N 41°02'E. Capital of the Abkhaz Autonomous Soviet Socialist Republic, part of the Georgian SSR.

** Presumably between 1944 and 1947 (the translator).

*** Coordinates: 56°00'N 71°00'E (approximate)

**** Coordinates: 55°00'N 63°00'E

***** Coordinates: 65°00'N 33°00'E (approximate)
Along many lakes and in the steppes. Since 1914, during the autumn and winter months, planned hunts for Onatra takes place for its fur; tens of thousands of skins are processed during the year. Besides Onatra, there are large numbers of small mouse-like rodents, Micrurus (Stegocephalos) priscus, which are hosts for the tick, Dermacentor pictus, which often bite man. Onatra lives mainly along the lakes and is usually free from these ticks. Moreover there is no coincidence between the seasonal illness of the individuals (spring and summer) and the hunting season for Onatra, i.e. the period of maximum contact of people with Onatra (December and January). This proves that there exists no direct connection between previous occurrence of this unknown disease among people living in Omsk oblast and the importation of Onatra thereto, or inauguration of the hunting season. Information as to the presence of a corresponding spontaneous infection in Onatra is absent.

Before 1915 this disease, in which we were interested, was observed in a limited degree in Omsk oblast and was treated as a typhoidal, atypical form of typhus. Later, no confirmation of any kind was found to support this diagnosis. It began to be known as a separate disease of unknown etiology: spring-autumn fever (due to the pronounced double wave nature of the disease in May and in August) and also simply as Omsk fever.

A relatively larger number of cases of the disease was noted in 1915 and 1916 and somewhat fewer cases in 1944 and 1947 with 1% to 2% fatality.

The most characteristic epidemiologic features of Omsk fever may be stated as follows:

1. The illness occurs in rural areas among people who work in the steppe or who visit the steppe: people of all ages are susceptible but predominantly affected are people in the younger age group - between 11 and 20 years of age.

2. A seasonal occurrence was observed, spring-summer-autumn, with two periods showing a maximum number of cases (usually at the end of the month of May and in the middle of August). There is no authentic information available about the disease during the winter months.

It is important to note that insofar as the seasonal occurrence of Omsk fever is concerned, it does not coincide with the non-icteric leptospirosis or "Swamp fever", which is characterized by a rise in morbidity in July during the mowing season and when people bathe in the reservoirs. It is during that same period, however, that a sharp drop in incidence of Omsk fever is noted.
3. The endemcity of this disease was observed, i.e., the repeated occurrence of the disease in certain steppe raons, in spite of the presence of a significant immunity in those who once had the disease. The number of cases during the season varied—depending on the density of population—anywhere from 1, 2, or 3 up to 45 or 50 cases of Omsk fever.

4. There is absolutely no contagiousness among people. No cases of transmission were discovered within the same hospital and none was noted among members of the same family. People who took care of the sick or who came in close contact with them did not contract the disease.

On the basis of data produced by the clinical picture, the existence of any kind of special form of alimentary toxicosis of the type of septic anqina, indicating clearly the infectious process, is excluded; it is also rejected by epidemiological observations.

The role of insects such as lice, fleas, bugs, flies, mosquitoes, etc., in spreading the disease is excluded for many reasons.

The theory that the disease is transmitted by way of the bites of ticks, which are found in large numbers in affected raons, fits well with the facts. According to data collected by the zoologist, Professor A.V. Fedishin, the seasonal activity of these ticks parallels the occurrence of Omsk fever; it has two peaks and the former precedes the latter by only one or two weeks; this completely corresponds to the probable incubation period of the disease in man.

It is not very clear, however, why it is that in other raons of Omsk oblast, where these ticks are also found in sufficiently large numbers, such diseases have not been encountered. Apparently, not only the ticks, but also some local animals which are hosts of these ticks, play an important role in forming the natural foci of this disease.

In 1945-1946 the workers of the Omsk Institute of Microbiology and of the Tularemia Control Station (A.A. Gavrilyovaia, E.D. Khishmir and others) carried on a persistent search for a microorganism in the etiologic agent of Omsk fever and also, without any success, attempted to reproduce the disease in guinea pigs, and in white mice by infecting them with the blood of those affected.

Our microbiological group of the expedition had carried out the supplementary investigation, in 1947, as to the possible participation in the etiology of the disease of any bacteria, spirochaeta or rickettsias, and obtained negative results. Frequent examinations of blood
serum during convalescence with the oil-relix reaction, using three cultures of proteus, Ox19, Ox2, and OxH, showed either an absence of antibodies, or in some cases, low titers, which proves that there is no possibility of identifying Omsk fever with common rickettsial infections. Our efforts to produce experimental illness with Omsk fever by infecting laboratory animals (guinea pigs, mice, rabbits, rats) met with little success, because no clear clinical reaction was observed in these animals. The local microbiologists, before us, came to the conclusion that it is impossible to transmit Omsk fever from affected people to experimental animals.

In this connection we had to use a variety of methods to prove the infectious nature of Omsk fever and to make a special effort to adapt the virus to the experimental animals. We solved that problem finally. In 3 to 12 days after injecting guinea pigs with whole blood from people who had the fever, a mild fever occurs, characterized by a rectal temperature of 37.5°C to 40.0°C (100°F to 104°F), lasting 1 to 3 days, of intermittent irregular type, followed by complete recovery. Hemorrhages, which are observed in man, were not observed in guinea pigs. Evidently, such mild reaction, did not attract sufficient attention at first and, therefore the opportune time was missed for a second injection of the virus; we consequently began re-injection from one guinea pig to another, using whole blood, taken on the 2nd or 3rd day of the fever (even if it is in a mild form), or using the brain of the affected guinea pig which was previously killed; in that way with great difficulty a more virulent form of the disease was produced after 5 to 7 injections in approximately 15 specimens of blood of those ill less than 6 days. The disease in guinea pigs takes the form of fever of brief duration and as a rule is without fatal results. It is often accompanied by marked leukopenia, 2,000 to 4,000 leukocytes instead of 6,000 to 10,000 and some loss of body weight. In 3 to 6 weeks after the febrile period, the guinea pigs disclosed a specific immunity to re-infection with Omsk fever virus.

In a number of cases the guinea pigs became ill after being injected with the blood serum of those affected. This blood serum was filtered through a Seitz filter or Perkefield filter which prevents the passage of bacteria. Thus, in the experiments on guinea pigs we established that the causative agent of Omsk fever was filterable and the fact of its regular presence, in the blood of those ill, up to the sixth day of the fever.

Parallel with the adaptation of the Omsk fever virus to guinea pigs, similar attempts were undertaken to increase the pathogenicity of the blood of affected individuals through passage in white mice, white rats, and rabbits by combined cerebral and intraperitoneal
injection with subsequent re-injection, in 7 to 8 days, with the brain or blood of the animals which did not become ill ("Dumb culture"). Experience with the adaptation in rats and rabbits was either negative or not convincing, whereas mice, after 1 to 2 "dumb cultures", appeared to have a clinically pronounced disease, rarely at first, and then more often a clinically virulent form with fatal results.

Following subsequent cerebral passage in mice, the virus rapidly increased in virulence and produced the disease in most instances irrespective of the method of inoculation.

We, thus, succeeded in the repeated isolation in mice of the virus from the blood of those who had the fever, as well as from the blood and brain of experimentally inoculated guinea pigs. Using similar methods in our experiments with mice and guinea pigs, we isolated the virus three times from the salivum of ground up field ticks (Dermacentor pictus) and thereby proved experimentally the transmission of the virus of Omsk fever by these ticks. Transmission of Omsk fever by ticks was suspected as far back as 1846 by the zoologist R.V. Fedushin and the entomologist G.I. Natskii. During the process of the examination of individuals and ticks infected with the disease, more than 30 verifications of the virus were produced in mice; this bespeaks the regularity with which this virus is encountered in cases of Omsk fever. Illness among most mice which were infected with adapted strains of the virus lasts about 24 hours and is characterized by general progressive weakness, convulsions, meningeal symptoms, at times by paresis and semi-paralysis of the extremities, followed by prostration and death; no hemorrhages of any kind were observed in mice.

Pneumonia was observed comparatively early in the mice which were infected intra-nasally, and symptoms of general weakness and prostration predominated; simultaneously with that, paralysis of extremities was encountered. Distinct involvement of the nervous system is also discovered in cases of abdominal and subcutaneous inoculation of mice proving the neurotropism of our virus.

According to Iurovetskaja and Korokina, changes typical of encephalomyelitis are observed upon histological examination of the cerebrum of mice affected with Omsk fever. Omsk fever virus is regularly present not only in the cerebrum of the ill mice, but also in the blood, in the spleen and in other organs; this shows that viral septicemia is present. According to L.N. Belieeva, the virus of Omsk fever reproduces well on living (7-day) chick embryos, appearing in the cerebrum and within the membrane of the embryos in large concentrations: from 10 thousand to 100 thousand minimum lethal doses. After infection of the yolk sac with the filtrable virus, the embryos
die in 2, 3 or 7 days. In our laboratory, A. A. Avakian systematically
examined smears, stained according to Lovevskii and Dorosov, and
prepared from cultures of the virus in the embryos (8 cultures), and
also from all organs of affected mice and guinea pigs; he found neither
rickettsiae nor organisms of any kind. The virus of Omsk fever, found
in mice, as well as from the blood of affected individuals and ticks,
filters very readily through Seitz, Berkefeld V, and N, and Chamberland
L filters and therefore, belong to the ultravirus category. Moreover,
like many other ultraviruses, it appeared to be capable of survival for
at least 2 months either in picroxine or in dry powder in vacuo.

We immunized mice with vaccine made from a formalized cerebral
emulsion, and were convinced of its effectiveness: A high degree of
immunity was rapidly developed which was established by a comparison
of titers of the virus in vaccinated and control mice. This opens up
tangible perspectives for prophylactic use of vaccination with killed
virus.

The species Microtus (S. sibiricus) praevalis, which were trapped
in the steppe of Omsk oblast, were found to be highly susceptible to
the filtrable virus of Omsk fever. This fact deserves particular
attention because, these mouse-like animals in Omsk oblast are the
principal hosts of the tick Dermacentor pictus from which we isolated
the Omsk fever virus.

Cats also appeared to be susceptible to cerebral infection with
Omsk fever virus; in the cat the cerebral infection was pronounced,
while in white and grey rats and in rabbits the infection was usually
subclinical, with the virus preserved in the brain for a period of
three weeks.

An enormous and unexpected increase in virulence of the virus
developed from transplanting it from mice. A number of cases of
illness occurred among the laboratory workers of the expedition who
were conducting nasal inoculation of the virus in mice and Microtus.
These inoculations were undertaken by workers wearing gauze masks,
glasses, and rubber gloves, (i.e. they observed strict laboratory
techniques). Nevertheless, illness did occur among workers although
in a relatively mild form, all ending in recovery. Apparently those
workers became infected by way of the respiratory tract because of
the insufficient protection that a 2-layer gauze mask offers.

A similar increase in virulence of the virus occurred when we
were infecting the muskrats, Ondatra, which were captured in Omsk
oblast, to determine their susceptibility to human Omsk fever virus.
Ondatra after subcutaneous or abdominal inoculation, became ill without
fever; post mortem examination showed evidence of hemorrhagic pneumonia,
however. Those who had anything to do whatsoever with the Ondatra, including the zoologist and the pathologists, subsequently contracted the disease. The clinical picture of the illness was typical and left no doubt that the diagnosis was Omsk fever. Fortunately, these cases of laboratory infections were not malignant and all cases ended in recovery. The virus that was isolated from the blood of the infected laboratory workers was in almost all cases the same as that found in mice and guinea pigs which had the disease.

Moreover, by means of neutralization tests and complement fixation reactions, we succeeded in discovering specific antibodies against our virus in the serum of those who became ill with Omsk fever spontaneously and to an equal degree in the serum of those laboratory workers who recuperated from the illness. All these data serve as unquestionable proof that the virus isolated by us, and which was found in mice and guinea pigs, is the causative agent of Omsk hemorrhagic fever.

By means of the neutralization test of the virus in mice we were able to establish the serological diagnosis of the Omsk disease and to differentiate it from other hemorrhagic fevers. The serum of persons who had recuperated from Crimean hemorrhagic fever, from the acutely febrile hemorrhagic illness of Stalinabad oblast, and from far eastern hemorrhagic nephropathia, did not produce neutralization of the Omsk fever virus, while a good neutralization was produced by the serum of those who had recuperated from Omsk fever. Apparently, the Omsk fever virus differs, as far as the antigen is concerned, from the causative agent of Crimean hemorrhagic fever, from the far eastern hemorrhagic nephropathy, and from the Stalinabad illness. This was confirmed by our experiments on several monkeys (Papio anubis) in Sukhumi, in which we succeeded in producing a febrile illness associated with other symptoms by inoculating them through the abdominal cavity with the Omsk fever virus while another group of monkeys were given repeated injections of the filtrable virus of Crimean hemorrhagic fever.

Forty days afterwards, the monkeys that recovered from the Crimean hemorrhagic fever and the group that survived Omsk fever were cross infected with the viruses of Omsk fever and Crimean hemorrhagic fever.

As a result, the monkeys which first recovered from Omsk fever contracted Crimean hemorrhagic fever, and those which had recovered from Crimean hemorrhagic fever contracted a fever again when infected

* Coordinates 38°30'N 68°45", Tadshik SSR.

** Coordinates: 43°00'N 41°02'E, Capital of the Abkhaz Autonomous Soviet Socialist Republic, part of the Georgian SSR.
with the virus of Omsk fever. These experiments produced proof, thereby, as to the specificity of immunity in cases of Omsk fever and Crimean hemorrhagic fever, which confirm the fact that there is no cross immunity.

In order to further show the differentiation of Omsk fever from the rickettsial diseases, we carried out the following experiments: guinea pigs, which had recovered from the Omsk fever infection and appeared to be immune to repeated introduction of that virus, were infected anew with the Rickettsia of epidemic typhus; and became ill again which proved that protection against this rickettsial disease is absent. We give special significance to an investigation, conducted by us together with A.S. Belissaeva, dealing with the relationship between Omsk fever and the filtrable rickettsiae or "atypical virus pneumonia". This infection is somewhat suggestive of the clinical picture of Omsk fever, but is distinguished mainly by the absence of the hemorrhagic syndrome and by a few other variations.

Our experiments on guinea pigs gave clear proof of the inability of the Omsk fever virus to create immunity to infection by the causative organism of "atypical virus pneumonia" and, consequently, clear antigenic differences between these agents.

DEDUCTIONS

The work done by the Omsk expedition and by the Institute of Neurology in 1947 produced the following results:

1. The discovery of the causative agent of Omsk hemorrhagic fever, a specific filtrable virus which is present in the blood of affected individuals and which is pathogenic for a number of experimental animals.

There is no doubt as to the etiological role of this virus, isolated from certain animals, in view of the fact that it is found regularly in those who are ill, the finding of specific antibodies against this virus (in SK* and RN***) in the blood of people who have recovered and, finally, in view of the identical character of the clinical picture of spontaneously contracted Omsk fever and of that accidentally contracted while working with that virus in a laboratory.

* Complement fixation reaction.

** Neutralization test.
2. During the period of time that the disease was studied, valuable material was collected concerning the clinical, laboratory, pathomorphological and epidemiological characteristics of Omsk disease.

3. It was demonstrated that steppe ticks, *Dermacentor pictus*, which were collected in the regions where there were cases of Omsk fever, contain the virus of Omsk fever and therefore may be sources of infection for man, when they attack.

4. Immunity to Omsk fever was developed in those who were vaccinated with the killed virus, which makes it possible to make practical use of vaccinated to combat this disease.

5. Experiments on monkeys, mice, and others testified to the absence of cross immunological reactions between the virus of Omsk fever and that of Crimean hemorhagic fever and, therefore to the etiological individuality of each of these infections, which appeared similar, but are not identical to each other.

   Experiments on cross immunity in guinea pigs and the results obtained from regular pathological investigations established a clear differentiation between the virus of Omsk fever and the filtrable virus of the rickettsial type such as *Q*-fever or the so-called "atypical virus pneumonia".

6. A practical method of sero-diagnosis of separate cases of Omsk fever and diseases suspected to be Omsk fever was established by using complement fixation reactions and neutralization tests of the virus with specific serum.

   Further cooperation between virologists, immunologists, internists, and pathologists is necessary so as to learn, in our country, the multifold phases of the virus hemorhagic fevers and the diseases related to them.