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**LABORATORY OUTBREAK
OF HEMORRHAGIC FEVER
WITH A RENAL SYNDROME**

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Laboratory Outbreak of Hemorrhagic Fever With a Renal Syndrome

(Clinico-Epidemiological Characteristics)

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At the present time, hemorrhagic fever with a renal syndrome is strictly differentiated from simple hemorrhagic fevers by its clinico-epidemiological peculiarities and is an independent nosological unit.

Allied diseases are grouped under the designation of hemorrhagic fever with a renal syndrome. They are described in various localities and have received local names, such as Far Eastern (Dal'nevostochnaya), Middle Volga (Srednevolzhskaya), Yaroslavl (Yaroslavskaya), Tula (Tul'skaya), and others (Chumakov and co-authors, 1961; Smorodintsev and co-authors, 1944).

The majority of researchers consider the etiological agent of the disease as an unknown virus, which still hasn't been isolated by anyone because of the absence of suitable forms (Smorodintsev and co-authors, 1953; Chumakov and co-authors, 1956).

Also, the epidemiology has been studied comparatively little, mainly based on materials of individual epidemic outbreaks and disseminated sporadic morbidity in loci of this infection. At the present time it has been established that hemorrhagic fever with a renal syndrome is a zoonosis and is characterized by its natural localization. Apparently, the reservoir for the infection in nature is the various species of Muridae rodents. The maximum morbidity is of a clearly pronounced fall or winter seasonal character, connected with the increase in the number of Muridae rodents and their migration from their natural habitat to the home of man. The hemorrhagic fever virus is probably discharged by rodents with their urine and feces. In natural foci, the source of infection for man may be the various species of rodents. Thus, in Tulskaia Oblast the morbidity of people in 1958 was connected with the chestnut vole (Gubergrits, 1960; Povalishina and co-authors, 1961), in the Urals with the chestnut and red voles (Solomin and others, 1953), in the Far East - with the forest mouse, field mouse, and the Mikhno vole (Vasyuta, 1961; Ugryumov, 1961), in the Upper Volga Basin - with the field mouse (Povalishina, 1960), in Sweden and Norway - with lemmings, in Manchuria and Korea - with field mice, and in Bulgaria - with the chestnut vole and the field mouse (Bratovanov and co-authors, 1962).

Even though the problem concerning the possible source of the infection does not give rise to doubts, the problem concerning the mechanism of transmitting the infection from rodents to man remains unclear. On the basis of epidemiological observation, the possibility is suggested of the existence of 4 mechanisms of transmission: Vector, contact, alimentary and inhalation.

Several researchers connect the vector route of transmission with Gamasidae (Smorodintsev and others, 1953; Margulis, 1960). The presence of the etiological agent of disease in pools of the Gamasidae ticks, Hirstionyssus isabellinus, Haemogamasus glasgowi, and Eulaelaps stabularis, is shown in the experiments of Chumakov and his co-authors (1955) on pyrotherapy, and by Japanese authors for Laelaps jettmari (1941-1942). But these forms do not usually attack man and the possibility of infection through ticks is repudiated by the majority of authors (Ugryumov, 1960, 1961; Chumakov, 1960; Lebedev, 1960; Avakyan, 1960; Vasyuta, 1961; Povalishina and co-authors, 1961).

Some propose that the basic path of transmitting the infection is the dropping of the virus on the injured skin or mucous membranes of man during contact with objects or produce contaminated by the fresh excretions of rodents (Chumakov, 1960; Povalishina, 1960, 1961; Lebedev, 1960).

The alimentary route of transmitting the infection is recognized by the majority of researchers and is supported by several epidemiological observations (Yankovskii, 1960; Piven, 1961; Bratovanov and co-authors, 1962; Vasyuta, 1961).

The question concerning the importance of the inhalation mechanism of transmitting the infection calls for a discussion. In the opinion of some researchers, the prevalence of sporadic morbidity and the absence of outbreaks in epidemic breeding places during the threshing of stacks strongly populated by rodents, is evidence against a possible air-borne path of transmission (Povalishina, 1960; Margulis, 1960). However, a number of authors suggest the possibility of an air-borne contamination (Solomin, 1953; Bratovanov and co-authors, 1962; Kushchenko and co-authors, 1960; Yankovskii, 1960; Ugryumov, 1961).

Another very important problem, which still hasn't been solved, arises in connection with this - the stability of the etiological agent in an external environment.

Other problems are still unclear - the susceptibility of people and the duration and intensity of post-infection immunity. There isn't a common opinion about the length of the incubation period, forms of manifestation of the illness, and other things.

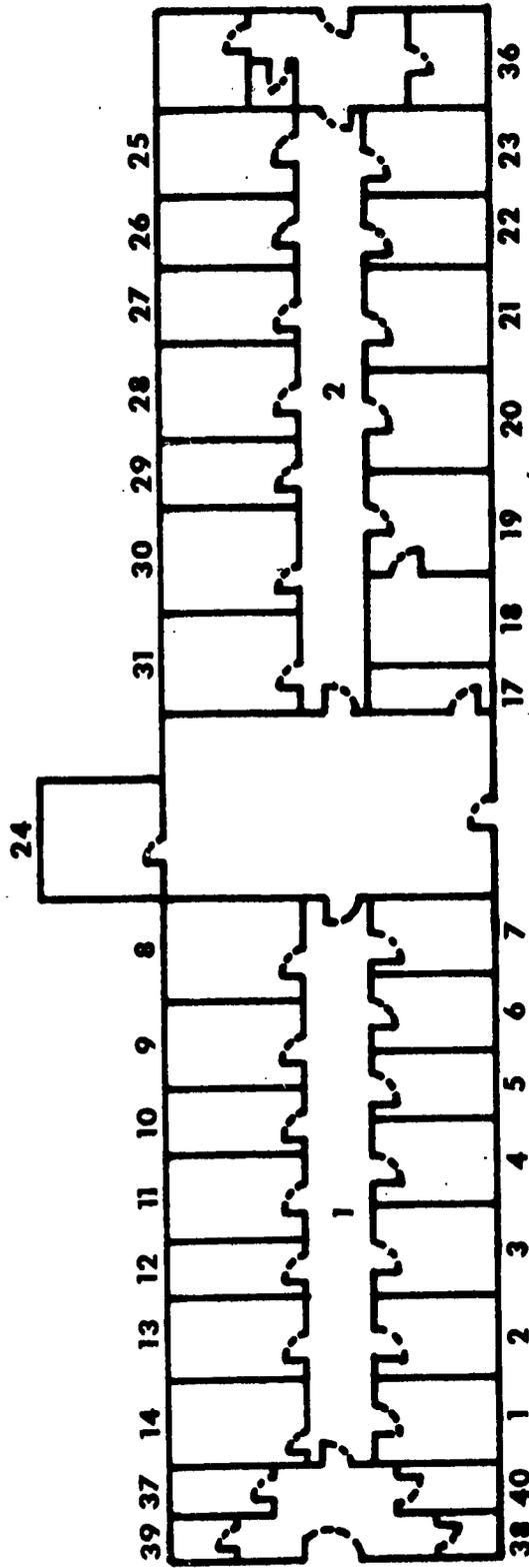


Figure #1. (page 122) Laboratory Layout of the Department. 1st section on the left, 2nd section on the right. Rooms 2 and 12 - quarters for wild animals.

For solving these and related problems, great significance is placed in epidemiological observations of laboratory acquired infection where it is possible to establish the precise period, and the extent and type of contact with the sources of infection. There are available, in writing, descriptions of epidemic outbreaks and individual cases of the disease among laboratory workers and expedition members during the course of studying hemorrhagic fever with a renal syndrome. Ugryumov (1961) reported about 10 cases of disease among 14 members of an expedition engaged in the capture and examination of rodents. During the investigation of an epidemic outbreak in Tuskaya Oblast, 14 expedition members who had direct contact with live rodents became ill. The method of infection here, based on data by Chumakov and co-authors (1959), was by contact. It was noted that there was no disease among the workers who had anything to do with rodents killed with *davilkami Gero* (TN: Snap trap or guillotine trap for catching and killing rodents. *Gero* or *Hero* no doubt designates the pattern of the trap). This set up a basis to surmise that dead rodents cease to be infectious (Chumakov and co-authors, 1959; Gubergrits, 1960), and consequently the virus has little stability in an external environment.

The materials on the epidemiological examination of a laboratory outbreak of hemorrhagic fever with a renal syndrome, which we will cite in the present work, will shed light on several important epidemiological problems which haven't been solved before, due to the absence of sufficient facts.

The outbreak of hemorrhagic fever with a renal syndrome was observed among the workers from a department of the Scientific Research Institute from 18 Oct through 1 Dec 1961. As the epidemiological investigation showed, the sources of infection were mouse-like rodents, brought in on 24 Sep by expedition workers who were studying tick-borne encephalitis in the Malmyzhsk Rayon of the Kirovskaya Oblast. The morbidity of hemorrhagic fever on the local population of several rayons of this oblast was established in 1960 (Vasyuta, 1961), however, there was no information about the presence of the disease in the Malmyzhsk Rayon.

Among the rodents brought in were 180 European chestnut voles, 75 red voles, 70 forest mice, 16 yellow-necked mice, and 16 voles (*Microtus oeconomus* (*Tungusla*)). After the completion of a 10 day local quarantine and subsequent 2 week quarantine in the Institute, the rodents, on 7 Oct, were transferred over to permanent accommodations for animals (rooms #2 and 12), located in a building belonging to the department.

This is a single story building with a corridor running its entire length and exits at both ends. One of them served as a direct entrance and exit for all the workers, and other for carrying out garbage and for other housekeeping necessities.

Doors from all the laboratories of the department led out into the corridor; the building was divided into two sections with a small hall in the center (fig. 1). 63 of the department's personnel work constantly in this building, the remaining 34 work in other isolated accommodations but visit the department on official business. Frequently, personnel from other departments and institutions come to the department for consultations and to attend conferences.

Initially the first cases of the disease among the personnel were not severe and didn't receive the proper attention. This contributed to the erroneous diagnosis of flu, which was given by the doctors of the rayon polyclinic. Beginning with 25 Oct, the morbidity began to increase rapidly and by 1 Nov, 30 men were already ill. This compelled the suspicion of the possibility of a laboratory acquired infection.

The morbidity of the permanent workers in the building was never uniform. It depended on the degree and duration of contact by the workers with the rodents and on the distance of the working places from the rooms where the rodents were kept. The first ones to become ill were those who had direct contact with the rodents that were brought in or who worked in laboratories located next to rooms #2 and 12 where the rodents were kept. Thus, in scrutinizing the first 30 cases, which appeared by 1 Oct, it turned out that, by this time, out of 23 persons working in the 1st section (rooms #3, 9, 10, 12, and 13)*, 20 had become ill, and at the same time only 10 of the 33 workers in the 2nd section became ill. Subsequently the disease continued to spread among the workers of the 2nd section who were a greater distance away from the rooms where the rodents were kept.

*Translator's note: In figure #1, room #12 is indicated as one of the two rooms where the wild animals were kept.

During October when the rodents in question were located in the department's main building, out of 63 permanent personnel, 5 had had hemorrhagic fever previously and apparently were immune, consequently 58 men were at risk, of these 52 became ill (89.6%). The morbidity of workers from other laboratories of the department depended on the frequency of their visits to the main building. Thus, out of 34 workers from other buildings, 14 visited the department's premises frequently, and 11 of them (78.5%) became ill with hemorrhagic fever. The remaining 20 workers visited the department from 1-3 times during this period and 6 of them (30%) became ill.

Out of 94 persons who visited the department by chance, 44 became ill. Here the frequency of visiting the department proved to be the deciding factor. Out of 13 persons who visited the department often, 10 became ill, and out of 81 persons who visited the department from 1-3 times, 34 became ill.

The length of stay and the places visited by outside personnel were various, and this reflected on their morbidity. However, cases have been established of single momentary (not more than 5 minutes) visits to the department after which the disease followed. Among the outside visitors, attention is directed to a group of persons who remained in the department for 3-4 hours only on the 24th of October. Out of 24 persons in this group, 18 became ill.

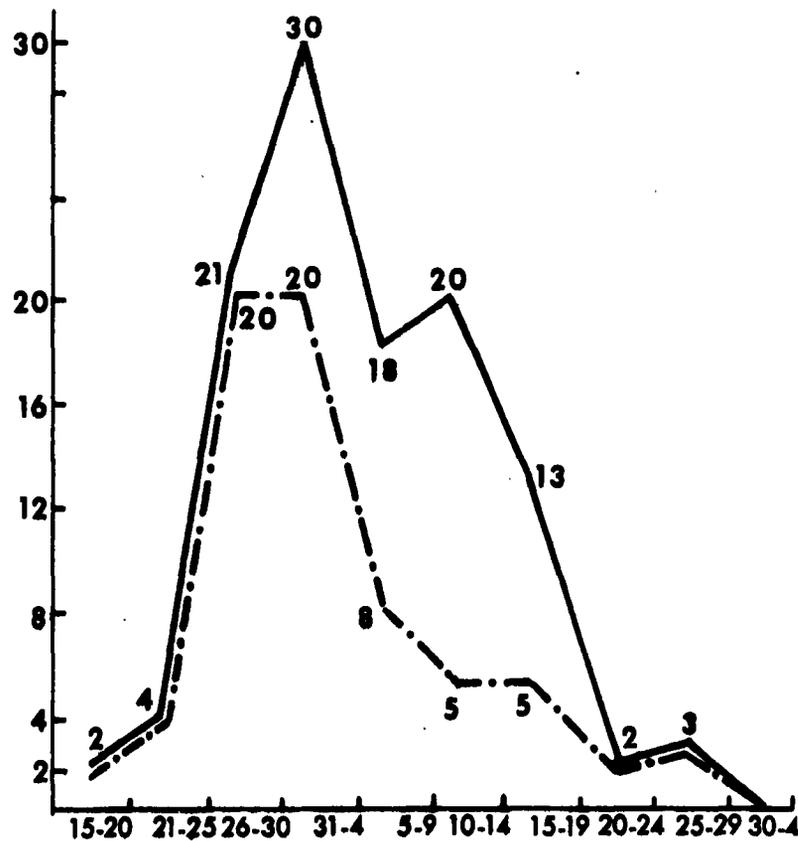


Figure #2. (page 123, erroneously marked 132) Dynamics of Morbidity. (Oct. - Nov.)

_____ equals general morbidity.
 -.-.- equals morbidity of department workers.

These facts show the extremely high susceptibility of people to the virus of hemorrhagic fever with a renal syndrome. It is possible that such a high susceptibility and morbidity are characteristic only for laboratory outbreaks and is caused by a distinctive mechanism of transmitting the infection and the great concentration of virus in a closed accommodation. From 18 Oct through 29 Nov, 113 persons had the disease. The outbreak had an explosive character (fig.2). The original increase in morbidity before 30 Oct was caused by the disease solely affecting those who worked constantly in the main building of the department. In the beginning of November, personnel who had visited the department by chance began to become ill. By 10 Nov the overwhelming majority of the department's personnel were sick, and new cases of illness among them were small. All the same, the morbidity of outside personnel was high, which is related to the belated infection depending on the date they visited the department.

Out of 113 persons taken ill, only 5 had first hand and direct contact with these particular rodents, and out of them 3 became ill. Of the 2 who didn't become ill, one was a zoologist who, for many years, worked with wild rodents in localities with natural foci of infection, and the other had hemorrhagic fever in 1960. The majority of those who were taken ill didn't have anything to do with the rodents and didn't even enter the rooms where they were kept. Consequently, in these cases you can completely rule out the possibility of contact infection from the rodents. The disease in these workers as well as the disease in outside personnel after a single short visit to the department allow us to suggest the theory that, during this outbreak, an air-borne transmission of infection was involved. Only an air-borne route of infection can cause such a mass morbidity which develops in a comparatively short time among persons who are epidemiologically connected with each other only by their presence in a common accommodation.

It brings attention to how rapidly the virus spreads and the fact that it provokes a mass morbidity. This is probably explained by the fact that among the rodents that were brought in, there were isolated individuals infected with the hemorrhagic fever virus. During the joint quartering of 20 individuals per cage, the virus spread rapidly among the rodents, which led to an increase in the number of sources of infection. Keeping in mind that the animals may discharge the stimulus with their urine and feces, it can be surmised that the concentration of the virus increased rapidly in the manure and litter which was carried from the cages, out the door, and along the corridor through the entire building without a preliminary disinfection. It becomes evident that the virus possesses a definite stability in an external environment, can be preserved in the dried up urine and feces of animals, and is found in the air together with dust which is raised when the animal cages are straightened up.

The alimentary route of infection is not characteristic for the given outbreak and the vector route may be ruled out completely.

A thorough epidemiological investigation of every case helped to explain even such an important question as the length of the incubation period. In a number of cases we could accurately determine the duration of the incubation period as many of the affected persons visited the department only one time. In cases of repeated visits to the department, the incubation period could be limited by definite dates. As regards to those working permanently in the infected premises, their incubation period can be limited only by the maximum dates from the moment the wild animals arrived (7 Oct) to the day they became ill.

In accordance with the material related by us, it shows that with accurately established dates for the incubation period of 24 men, the shortest duration was 14 days and the longest 32 days (an average of 20.4 days). Of special interest is the duration of the incubation period of the group of 18 affected persons who were at the department's premises only one time and who came under equal conditions of contact with the source of the infection. The duration of the incubation period in their group was as follows: 3 of 17 days, 1 of 19 days, 2 of 21 days, 8 of 22 days, 1 of 23 days, 2 of 25 days, and 1 of 27 days (an average of 21.5 days). In calculating the possibility of infection of permanent workers from the first day the rodents were housed in the department, the duration of the incubation period was an average of 27.5 days. The shortest possible duration in the other group equaled an average of 12.3 days and the longest - 26.3 days.

According to preliminary data, the clinical course of the disease was as follows. The onset of the disease was acute, with a chill which subsequently was observed in some of the patients throughout the entire fever period. The temperature curve was of the remittent type, often with a drop of temperature to normal or subnormal. The fever sometimes continued for up to 15-18 days, and sometimes it was diphasic or with a prolonged subfebrile condition. The patients complained mainly of an intense headache, insomnia and general weakness, nausea and vomiting, thirst, especially in the beginning of the illness, muscular pain and painfulness in the area of the kidneys, and abdominal pain. Pasternatskii's symptom was observed in all the patients. Abnormality of the vasomotors was noticed, the face varied from red to pale, there was conjunctivitis, scleral injection and sometimes hemorrhages in the sclera and conjunctiva. The appearance of group petechia was noted. There was a depressed feeling and relief didn't come about with a lowering of temperature.

In this period the basic symptoms in the urinary system were noticed. During the fever period, diuresis was reduced and subsequently polyuria was observed. There was little albumin in the urine, though in individual cases its content reached up to 1.5-9%. In all the patients the specific gravity of the urine was reduced to 1003-1005. Residual nitrogen in the blood reached up to 75-85. Higher figures were rarely observed.

During the convalescence period, an objectionable sensation in the area of the heart was noticed along with a systolic murmur and bradycardia. There were no basic changes in the lungs and only in one patient was exudative pleurisy observed. From the 3rd or 4th day of illness, a short lived (3-4 days) enlargement of the spleen was determined.

Leukopenia was characteristic in the blood during the first days, sometimes down to 2000 to 2500 leukocytes, with a marked nuclear shift to the left, often as far as myelocytes, and the presence of plasmatic cells. By the 7th or 8th day the number of leukocytes was restored to normal or was changed to a minor leukocytosis. During the convalescence period, absolute lymphocytosis was sometimes observed. The number of thrombocytes came down in several cases to 70,000, especially during hemorrhagic occurrences, and were restored by the 6th - 10th day of convalescence. The ROE (erythrocyte sedimentation reaction) was somewhat accelerated.

The disease proceeded in a mildly serious manner. Cases of a serious tendency were scarce, and an abortive form was noticed in 4 cases. No effects were observed from using antibiotics during the acute period. The prescription, from the first day of the illness, of biomyacin or terramycin in daily doses up to 2g, didn't influence either the lowering of the temperature or the gravity of the illness. All the cases ended in recovery.

The comparative duration of fever and mildly pronounced renal and hemorrhagic syndromes are peculiarities of the clinical course of hemorrhagic fever with a renal syndrome during this outbreak.

The epidemiological analysis of the outbreak showed a complete ignorance of the clinical aspects of this disease on the part of doctors in the polyclinical net. Not in one case, prior to special notification about the outbreak, was a correct diagnosis made by district doctors from a number of polyclinics, and the disease was treated like the flu. The diagnosis of hemorrhagic fever with a renal syndrome in the patients was made on the basis of studying the clinical picture of 85 patients, hospitalized in the Clinical Infection Hospital of the Ivanovskii Institute of Virusology of the AMN, SSSR. With the patients who remained at home, the diagnosis was clarified jointly by doctors of the rayon polyclinics.

Antiepidemic measures for the liquidation of the outbreak brought on the rapid removal (2 Nov) and destruction of the rodents in question and the carrying out of a conclusive wet disinfection. After these measures were carried out, the infection of personnel ceased.

Epidemiological investigation showed that there was no hemorrhagic fever among those who had contact with patients of the disease. This ruled out the contagiousity of the infection. Epidemiological observations during the study of this laboratory outbreak allowed us to make a number of important conclusions, particularly valuable in that the observations were conducted outside of an endemic focus and under conditions that were similar to an experiment.

It was established that mouse like rodents are active vectors and discharge the hemorrhagic fever virus into the external environment with their excrement. The rodents are asymptomatic carriers of the virus. Among the 350 rodents that were brought in, there were no clinical signs of disease and death observed. During post mortem examinations of 104 animals, no pathologico-anatomical or pathologico-morphological changes were found.

Despite the assertion by Margulis (1960), it has been established that the virus, discharged into the external environment by the rodents, does not perish with desiccation, but at the very same time maintains a high degree of infectiousness. Consequently it also doesn't confirm Gubergrits' opinion that the excrement of rodents rapidly loses its infectiousness.

Conclusions

1. Important facts were obtained about the mechanism of transmitting hemorrhagic fever with a renal syndrome. A complete understanding has been introduced on the question of the possibility of air-borne infection, which is repudiated by a number of researchers (Smorodintsev with co-authors, 1953; Povalishina, 1960; Margulis, 1960; Lebedev, 1960).
2. It has been established that people are highly susceptible to the virus of hemorrhagic fever with a renal syndrome, as evidenced by the illness of 89.6% of the personnel working constantly in the contaminated premises, and 42% of the personnel who visited the premises 1-3 times.
3. In 32 cases it was possible to establish accurately the duration of the incubation period, which consisted on the average of 20.4 days with a variation of 14-32 days.
4. It confirms the idea about immunity to the disease in those who previously have had it: 5 workers of those working constantly in the infected area had this disease previously (1-3 years ago) and didn't become ill during the present outbreak.

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