THE FAMILY OF INFLUENZA VIRUSES AND OF PNEUMOTROPIC ANIMAL VIRUSES

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Opredelitel' virusov cheloveka i zhivotnykh
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V. M. Zhadanov

As already recalled we include in this family viruses characterized by a more or less pronounced pneumotropicity. A typical representative of this family is the causal agent of influenza, which has been studied in very great detail. Its size has been determined by electron-microphotography, and has been found to be about 80 mμ for viruses A and A_1 and about 100 mμ for virus B. The elementary bodies have a coccal or beanlike shape. This virus is characterized by a rather complex antigenic structure, and in particular, soluble antigen has been discovered. The existance of a hemagglutinin and toxic factor has also been established.

As already recalled in Chapter Two, when the elementary bodies of a virus enter the cells of the host tissues, they break down into smaller particles. By treating the elementary bodies with lipoid solvents two fractions have been separated, an enzyme, which induces hemagglutination, and the above mentioned soluble antigens, which corresponds to the small viable particles of viurs formed when the elementary bodies break up within the cells of the host tissues. These particles evidently constitute the forms of existence of the virus inside the cells, where they take part in the metabolism. After the death of the affected cell, elementary bodies are apparently formed out of these particles. However, these data do require serious verification.

The influenza viruses A, A_1, and B are independent, but of related species, and very closely resemble each other, although immunologically they differ sharply (in the neutralization reactions and in cross-resistivity experiments), but they have group antigens which can be discovered by the aid of serological reactions.

The causal agent of influenza is characterized by a pronounced pneumotropicity, easily adapts itself to the organism of mice and polecats, and is cultivated on chick embryos. It may be adapted in the animal organism to other tissues as well, for instance, to nerve and neoplastic tissue.

The causal agent of swine influenza closely resembles influenza virus A; and there is reason for believing that swine influenza is in fact influenza virus A adapted to the swine organism during one of the recent influenza pandemics. These four viruses, the causal agents of human influenza A, A_1, and B, and the causal agents of swine influenza, form a sharply circumscribed group, immunologically distinct from the other viruses. (Recently a new influenza virus has been described, which differs from those hitherto known in its antigenic structure and other biological properties; it has been termed the causal agent of influenza C.

There are, however, certain properties of these viruses which resemble those of other causal agents of human and animal diseases, and, above all, those of two pneumotropic human viruses: the causal agents of the common cold and that of a typical pneumonia. The virus agents of the common cold induces a disease that resembles influenza, but with a milder course and a more pronounced catarrh of the upper respiratory passages.

Like influenza, the common cold is accompanied by the production of an immurity that is intense, but disappears even more rapidly than that for influenza. The virus is cultivated on the chick embryo. Its other properties have been little studied. The causal agent of a typical pneumonia was isolated 1944 by Eaton and his associates. It was found to differ from the viruses of the genus rickettsiaformis, which also induce a typical forms of pneumonia in Man and animals; in size tropism, cultivability in the animal organism, and in certain other properties, it is closest to the viruses of influenza. The causal agent of epidemic parotitis, which is the largest in size of the virus group under consideration, is also very close to the influenza viruses. Pneumotropicity is less pronounced in it than in the above enumerated viruses. Finally the causal agent of the Asiatic false fowl-pest (Newcastle disease) is also close to the influenza viruses.

Pneumotropic viruses have also been isolated in animals. Among them we may name the viruses inducing pneumonia in mice (differing from the large viruses of the psittacosis type), the causal agents of fowl laryngotracheitis, and the pneumoenteritis of cattle and cats. The latter viruses affect not only the respiratory passages but also the digestive tracts.

One of the above mentioned characteristics of the influenza viruses, is their property of agglutinating the erythrocytes is extinguished with strict specificity by the homologous serum that neutralizes the virus. This property is so pronounced that the hemagglutination reaction has found widespread application as a diagnostic test for influenza. Study of the above enumerated viruses has shown them to possess similar properties. Thus, for instance, the virus of a typical pneumonia agglutinates human erythrocytes, the virus of mouse pneumonia agglutinates the erythrocytes of the mouse, and the virus of the Asiatic false fowl-pest agglutinates the erythrocytes of the chicken and other animals.

The comparative study of the phenomenon of hemagglutination has proved very useful for attaining insight into the nature of the viruses in the influenza family. A common property of all these viruses is the occurrence of hemagglutination at low temperatures, and its connection with the presence of virus corpuscles, but not with the presence of a soluble antigen. Hemagglutination may be induced both by the living particles of virus and by those killed by heat or chemicals. Hemagglutination takes place after adsorption of the virus particles onto the erythrocytes lose the power of agglutination not only when homologous virus is added, but even on addition of a few other viruses of the same group. The viruses of influenza, epidemic parotitus, and Newcastle disease have proved to be closest to each other in this respect.

The close resemblance of the latter viruses to each other is expressed not only in the presence of common hemagglutinines, but one in a number of other biological properties. All of them have a similar antigenic structure, the very same inhibitory agents act on all of them, while recently the existence of common group antigens for all three viruses has been demonstrated. A detailed study of the viruses of influenza, made in recent years, allows the conclusion that a number of its antigenic variants, which are presently designated as types, do in fact have such profound differences, that they should be recognized as independent species, (of chapter 11). Within the limits of these species, there are a few variants, which differ in a number of biological properties, including immunological properties as well.

In accordance with the data above presented, the following systematic classification of this family is proposed.

PNEUMOPHILACEAE FAMILY

A. Genus Pneumophilus, includes the following species: Causal agents of influenza, which should be subdivided into the following species, ordinarily designated types.

1. Pneumophilus gripposus A, causal agent of human influenza type A.

2. Pneumophilus gripposus A_1, causal agent of human influenza type A_1.

3. Pneumophilus gripposus B, causal agent of human influenza type B.

4. Pneumophilus gripposus C, causal agent of human influenza type C.

5. Pneumophilus suis, causal of swine influenza.

These five influenza viruses are more closely related to each other than the remaining species of the genus.

6. Pneumophilus parotitedis, causal agent of epidemic paraotitis.

7. Pneumophilus pullorum, causal agent of Asiatic false fowl-pest.

8. Pneumophilus paragripposus, causal agent of influenza like diseases.

9. Pneumophilus pneumoniae, causal agent of human primary a typhical pneumonia.

10. Pneumophilus rhiritidis, causal agent of the human common cold.

11. Pneumophilus muris, causal agent of mouse pneumonia.

12. Pneumophilus rattum, causal agent of pneumonia of white rats.

13. Pneumophilus equil, causal agent of infectious bronchitis of horses.

14. Pneumophilus troglodytidis, causal agent of chimpanzee "whooping cough".

B. Genus Enterophilus includes the following species:

1. Enterophilus vitulorum, causal agent of cattle pneumoenteritis.

2. Enterophilus felis, causal agent of cat gastroenteritis.

3. Enterophilus pullorum, causal agent of chicken laryngotracheitis.

4. Enterophilus murinus, causal agent of the diarrhea of suckling mice.

The above systematic classification of the viruses of the pneumophilaceae family still provides no grounds for judgement as to the paths of evolution of the systematic

group as a whole. In this respect, however, it is possible to be entirely definite about the influenza viruses. The common origin of the influenza viruses is indubitable, and this is confirmed not only by their far-reaching biological similarity, but also by their serological similarity. In their antigenic structure, the viruses of influenza A, A_1, and swine influenza are closest together, but the viruses of influenza A, B, and C also resemble each other in that they have a paralyzing action on the human organism and induce diseases hardly distinguishable in their chemical characteristics. There is no doubt that the viruses of human influenza have a common origin and an immediate genetic affinity. The question of the viruses of influenza A and swine influenza is more complicated. If the data of Šhope are to be believed, the virus of swine influenza is distinguished by the peculiarity of its ecology: living as a parasite in the swine organism, it is transmitted not only by contact but also through worms; it can survive a long time in the organism of the worms, and then enters the swine organism again when these worms are eaten. These data, however, have not been verified since their publication, and induce disbelief.

Swine influenza in general is an enigmatic disease. Epizootics of it have coincided with epidemics of influenza among human beings. Is it not, perhaps, a peculiar artifact, a result of the adaptation of human influenza A to the swine organism? Is it not, perhaps, for that reason that these two viruses so closely resemble each other that swine influenza has still not become an independent disease (and perhaps will never become one), while the viruses of human influenza, split off from their ancestor, have now reached an independent existence in human society? This thought arises when we compare the influenza viruses, especially if we take in consideration the extraordinary viability of the influenza virus, as a result of which, during the period of an epidemic, new variants of this causal agent are always being formed, over and over again.

This circumstance deserves special consideration. In studying the strains of influenza virus isolated in various countries during epidemics, and in non-epidemic periods, a considerable variability of the influenza virus was discovered under natural conditions. We have already mentioned above the existence of four causal agents of human influenza (A, A_1, B and C), differing in a number of biological properties (varying degree of pathogenicity for laboratory animals, quantitative differences in hemagglutination activity with respect that the erythrocytes of different animals, certain differences in the courses of the diseases induced, etc), but mainly in the structure of the antigenic apparatus, as a result of which, all four viruses do not mutually induce the formation of a cross-immunity, nor do they confer a partial (group) cross-immunity.

On the further analysis of the antigenic structure of the influenza viruses, it was found that variants with finer immunological differences exist within the limits of each species. These variants are found both on comparison of different strains of influenza virus isolated in different places or at different times, or on comparing the lines of one and the same strain adapted to the organism of different laboratory animals.

In connection with the abundance of contradictory data in the literature on the question of the variability of the influenza virus, A. S. Gorbunova and L. L. Fadeyeva undertook investigations at our laboratory with the object of classifying the influenza viruses and elucidating the regularity of their variability. The summary results of these investigations were published by us in collaboration with V. D. Solov'yev, as well as by the above mentioned associates.

At one time Burnett, studying the process of adaptation of influenza virus to the organism of laboratory animals and chick embryos, reached the erroneous conclusions on the mutational variability of influenza virus known in the literature as the theory of O-D variations. In comparing the original strains of influenza A virus with t e strains repeatedly passaged through chick embryos, Burnett took the index K/C as a criterion for evaluationg the variations that had taken place. This index was the ratio between the chick-erythrocyte agglutination titer to the guinea-pig-erythrocyte agglutination titer. He found that the K/C index was less than unity in the original strains and more than unity in the passaged strains. Evaluationg these observations, Burnett concluded that the original (O) strain had been converted by spontaneous mutations into t e derivative (D) strain. On the basis of these data, he attempted to explain the origin and cessation of influenza epidemics by the mutation of the influenza virus considering the O-variant to be the epidemic strain while the D-variant assures the survival of the influenza virus in sporadic cases.

All this "theory" is constructed on a fallacious methodological foundation, and illustrates only the blind-alley condition into which scientists taking the positions of Weismanism-Morganism must inevitably fall. Everything in this "theory" is entirely wrong: the selection of such a fortuitous criterion for the evaluation of variability as the K/C index, the attempts to interpret the variability of the influenza virus as the result of spontaneous "mutations" instead of environmental influences, the coarse biologization of the epidemic process, without attempting to understand its actuationg forces, and the speculative arguments on the existence of "epidemic" and "sporadic" strains of influenza virus.

V. D. Solov'yev and A. S. Gorbunova made experimental checks and established the fluctuation of the K/C index in the various virus strains isolated even during the same outbreak. In studying the process of variability of the influenza virus on adaptation to animal organisms, they showed that this variability bears an adaptive character and is caused by the action of the amimal organism on the virus.

L. L. Fadeyeva, a staff member of our laboratory, has studied the process of adaptation variability of the influenza virus in greater detail. She made parallel passages of strains of A and A_1 influenza viruses on chick embryos in the explantates of mouse tissues and by means of the nasal infection of mice. In the first passages through mice, the influenza virus multiplied well in the lungs, without causing the death of the animals; but after 8 to 10 passages the virulence of the strains began to increase, and after 10-15 passages the virus regularly caused the death of the mice in dilutions of 10^{-5}, accompanied by symptoms of a pronounced hepatization of the lungs; this property persisted firmly during subsequent passages through mice. When the virus was passed through mouse tissues, it first became sharply attenuated (fall in titer), but after 5-6 passages the titer again reached its original value (10^{-7} and 10^{-8} by titration on chick embryos) and remained at this level throughout subsequent tissue passages. The tissue strains multiplied well in the mouse organism and were non-pathogenic for them; after 3-4 successive passages through mice, the virus acquired virulence and regularly caused death of the mice with hepatization of the lungs. As for the third line (passages through chick embryos) there was no substantial change in the properties of the virus during such passages.

Study of the original strains and their variants showed that in all strains there was no substantial change in their antigenic structure, which remained within

the limits, not only of the species, but even of the variant (the WS variant of virus A and the 1949 variant of virus A_1 were studied). However, even though the antigenic structure was indentical, the immunogenic properties of the strains obtained were found to be different, for three variants were discovered in experiments in mouse-immunization experiments, followed by infection with the virulent mouse variant. The tissue avirulent mouse strains, while the immunity after vaccination with chick-embryo strain was 1000 times weaker.

These experiments showed that during the process of adaptation to the organism or tissues of different animals, the influenza virus still maintains its unchanged antigenic structure, but sharply changes its immunlogical properties; immunogenicity is connected with adaptation to the metabolism in the tissues of a definite biological species; while virulence arises as a result of the virus overcoming the protective forces of the organism. On the basis of these data, a highly immunogenic, avirulent, vaccine strains of influenza virus were obtained.

A. S. Gorbunova studied more than 80 strains of influenza viruses isolated in the USSR and abroad form 1933 to 1952, and also, having standard strains at her disposal, she compared the results of her own investigations with the data on more than 800 strains described in the literature. On the basis of this work, she established the existence of the above mentioned four species of influenza viruses affecting human beings: A, A_1, and B and C, differing in antigenic structure. Of these, A and A_1 are the nearest to each other(existence of group antigens) while the remaining viruses have very faintly expressed group antigens. Further study established the existence of antigenic variants within the limits of each of these three species. These variants are designated below, by the designation of the type strains:

In the limits of virus A: WS and PR_8;

In the limits of virus A_1: 1949 and 1952;

In the limits of virus B: Lee and Kri.

Comparison of the species and variants isolated from the time of their isolation showed a definite chronological sequence in their appearance and disappearance.

Thus, for instance, in the USSR up to 1949, the WS variant of virus A predominated, and the PR_8 variant of the same virus was less often met. In the winter of 1949 virus A_1 (variant 1949) was first isolated, after which virus A began to be encountered very seldom. In 1952, at the time of the rise in the incidence of influenza, the "1952" variant of virus A_1 was predominant, and almost all strains of influenza virus isolated at various localities during this period belonged principally to this variant, while virus A disappeared almost completely. As for virus B, the Lee variant had been isolated up to 1950, while since 1950 only the Kri variant has been isolated.

The same changes in species and variants is observed in foreign countries. In the United States, up to 1945, the PR_8 variant was predominant in epidemics of influenza A. Between 1945 and 1947 influenza A_1 appeared everywhere in that country, and at the same time outbreaks of influenza A stopped almost completely. Comparison of the strains of virus A_1 isolated from 1945 to 1951 showed that each year there was a slow but steady variation in the antigenic structure of isolated virus strains. The viruses isolated during the 1945-1947 period were closer to the

"1949" variants, while the viruses subsequently isolated belonged to the "1952" variant. In England, up to 1952, the WS variant of virus A predominated, from 1942 to 1947 it was the PR8 variant of the same virus, while since 1947 it has been virus A_1, and at the same time virus A has disappeared.

Analogous phenomena occurred during these years in other countries as well.

Comparison of these somewhat schematically stated data reveals a most distinct tendency. Up to 1945/1949, the cases of influenza were induced, throughout the whole world, by the A and B viruses; in 1945 first major outbreaks of influenza A_1 were noted; in 1947-1949, A_1 became predominant; and at the same time virus A disappeared everywhere. The later cases were connected with viruses A_1 and B. More detailed analysis shows a change of variants in a definite chronological sequence within each of these species. The variant "1949" gave way to the variant "1952" for virus A_1 and correspondingly the Lee variant was replaced by the Kri variant for virus B.

Thus during short intervals of time, measured by only a few years a successive change in the variants and species of influenza viruses has been observed. The appearance of new variants and species is accompanied by the disappearance of old ones. This shift follows a strict sequence and is almost simultaneous in the different countries. The appearance of a new species of influenza virus, A_1, in 1945-1947, is of particular interest. This species took the place of the confidence that before this time virus A_1 did not exist, since by the end of the 1930's a considerable network of laboratories studying influenza already existed in the USSR and other countries; and by that time reliable methods of isolating influenza virus on chick embryos had already been firmly introduced in virological practice. Considering that the increase in the incidence of influenza, and all the more since an epidemic ordinarily embraces a whole country, or in any case at least many cities, it is doubtful that the appearance of a new virus could have remained unnoticed.

In the above mentioned work, Gorbunova established the fact that the A_1 virus did not all at once appear in the form in which it was discovered in the United States in 1945. A comparative study of the strains that were available in the laboratory, and a comparison of their characteristics with descriptions of the strains isolated by different authors showed that already, form 1941 on, strains of virus A were being isolated with antigenic groupings in common with virus A_1. These include the TW strain isolated in the United States in 1941, as well as a few strains isolated between 1941 and 1945 in Sweden and Australia.

All these data allow us to draw the conclusion that virus A_1 arose from the variation of virus A, the origin of virus A_1 being put in 1941 and its final establishment between 1945 and 1947. The new species arose on the basis of the old, and its establishment took place by the accumulation of quantitative variations finally leading to a new quality. It is important to note that this process took place not in a single place, but simultaneously in different regions of the earth, and that since the appearance of the new species, the old species began gradually to disappear, although it was still persisted down to the present time.

Let us attempt to explain the causes of this phenomenon, which is now possible as a result of the considerable deepening of our knowledge of the epidemiology of influenza.

The high infectiousness of an influenza patient, the air-droplet mode of its transmission, and the short incubation period, are responsible for the exceedingly violent spread of an influenza epidemic and the immensity of the territories and the groups of the population affected. As shown by our researches, after an outbreak of influenza a great immune group is created, since, besides the cases with clinical manifestations, a considerable number of people undergo the infection in the subclinical or asymptomatic form. During the inter-epidemic period, the influenza virus survives through sporadic cases affecting mostly children, as well as persons who gradually lose their acquired immunity (V. D. Solov'yev). The incidence of the disease increases somewhat in the winter time, but still does not assume the character of considerable epidemic outbreaks. Further than that, frequent encounter with the influenza virus encourages the stabilization of immunity in the population at large, which thus sharply limits the organisms opportunities for circulation. Under these conditions there is a mass death of the influenza virus, which is unable to overcome the collective immunity; for when it enters the mucous membranes of immune persons the virus rapidly dies off. Apparently, the disappearance of virus A everywhere noted was one of the results of this process, and this influenza virus is now gradually dying out.

The high degree of adaptive variability of the causal agent of influenza, like that of other viruses, however, makes it possible for new variant to appear. Repeated passages through immune organisms, as shown by Luzyanina in her paper, lead to the appearance of new variant, and first of all, variants having immunological differences; such viruses are capable of overcoming the immunity built up among the population.

It is precisely in this direction that the variation of the influenza virus proceeds under natural conditions, as shown by a study of the virus strains isolated in different countries and at different times. The accumulating quantitative variations make a qualitative jump, the appearance of a new species, sharply distinguished immunologically from its parent species, which difference is expressed in variation of antigenic structure. Under certain conditions this new species may spread everywhere. An example of such a process is the appearance of the virus of influenza A_1 which, originating a few years ago, has spread everywhere during a short period of time and has become the predominant species of influenza virus.

Apparently, the regularities in the evolution of viruses which we have described may be observed not only in influenza, but also in other widespread (ubiquitous) acute infections. Knowledge of these regularities allows us to explain on the one hand the existence of profound immunological differences in the influenza viruses themselves, which differences perhaps may have required a few years for their development, and on the other hand, the existence of other viruses, (the rickettsia that are the causal agents of tick encephalitis) an exceptionally conservative antigenic structure, persisting throughout many million years. Knowledge of these regularities allows us to approach the development of effective measures of prophylaxis and control of the virus diseases of Man on a sound scientific basis.

(HUMAN AND ANIMAL VIRUSES)

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V. M. Zhdanov

GENUS 3. HAEMORRHAGOGENES ZhK 1949

The morphology of the elementary bodies has not been studied; the viruses pass Berkefeld N and Seitz filters. When dried in vacuo they survive cold for a long time. The viruses for the most time studied are immunologically related among themselves and to the virus of tick encephalitis.

Pantropic viruses, inducing characteristic diseases in Man and animals, fever with the development of a hemorrhagic diathesis. The reservoir of the virus in nature is formed by small mouselike rodents and other wild animals. The vectors and perhaps also the primary hosts are the Ixodes ticks.

This genus includes four species.

1. Haemorrhagogenes tchumakovi nom. nov. (Chumakov et al, 1944).

Synonym: Pantropus Tchumakovi Rychkov 1950. Causal agent of the hemorrhagic fever of the southern regions of the USSR.

The morphology has not been studied. No elementary bodies could be found under the optical microscope. The virus passes Berkefeld N and Seitz SF filters. It survives storage in glycerine; after dessication in vacuo it lives in the cold for about two years.

In the animal organism it induces the formation of neutralizing and complement-fixing bodies. Immunologically it differs from the causal agent of hemorrhagic fever of the Eastern Regions of the USSR.

It is pantropic virus which primarily affects the vascular system and causes the development of a hemorrhagic diathesis. Cats and young rabbits are susceptible. The laboratory model is the cat, in which the fever and a fatal hemorrhagic syndrome develops after infection. It is cultivated in the chick embryo.

Its natural reservoir has not been determined. Its vectors are the ticks Hyalomma marginatum marginatum, who transmit the virus transovarially to their progeny. Man is highly susceptible; he is infected under natural conditions by tick bites and develops a grave hemorrhagic fever. Diagnosis is by neutralization and agglutination tests on virus isolated from kittens.

2. HAEMORRHAGOGENES SIBIRICUS ZhK 1949 (Chumakov et al, 1947)

Synonym: Pantropus Tchumakovi subspec. dermacentori Ryzhkov 1950. Causal agent of hemorrhagic fever of the Eastern Region of the USSR.

In the morphology of its elementary bodies, filterability, and resistance, it resembles the preceding species. Its immunological differences from that species, however, are revealed by neutralization and agglutination tests, its reactions resembling those of the virus of tick encephalitis. It is a pantropic virus easily adaptable to nervous tissues. When treated with formalin it still maintains its immunizing properties (formol vaccines).

In contrast to the preceding species it is more easily adaped to white mice and is pathogenic for a wide range of animals: monkeys guinea pigs, cats, field-voles and onagers, by any method of administration. The laboratory model is the white mouse. Passages are made by infecting into the brain. It is cultivated on chick embryos.

The probable reservoir of the virus in nature is the narrowskull field-vole, and also many other species of mouse-like rodents which transmits the virus transovarially to its progeny. Na ural foci are found in the wooded-steppe regions.

Man is susceptible, is infected by ticks, and develops disease after a 2-4-day incubation, showing hemorrhagic fever, with a pain syndrome, leucopenia and nephritis.

Diagnosis is effected by isolation of the virus and the neutralization and agglutination tests.

3. HAEMORRHAGOGENES ORIENTALIS ZhK 1949
(Massaji et al. 1949)

The causal agent of the Manchurian hemorrhagic fever. There are unreliable data in the presence of elementary bodies similar to the Teyleria of cattle. It passes Bacterial filters.

Monkeys are susceptible, mice only slightly so.

The reservior of the virus is the small mouse-like rodents. Its vectors are small ticks of undetermined species. Natural foci have been found in Northern Manchuria. Man is susceptible. On infection by ticks, he develops grave fever with hemorrhages and albuminuria.

A similar disease has been found in Korea, and acute epidemic hemorrhagic fever (ryukosei shikketsu netsu, in Japanese); the lethality reaches 12-14 percent. The virus (Kitako et al.) is transmitted by the haemacodal ticks Laelaps Jettmari. The fieldmouse Apodemus agrarius is the reservoir of the virus. Epidemics of this disease were observed in the troops of the Anglo-American occupiers in Korea (1951-1952).

4. HAEMORRHAGOGENES NEPHRITIDIS ZhK 1949
(Smorodintsev et al, 1949)

The causal agent of infectious nephroso-nephritis.

The morphology of the elementary bodies has not been studied. The virus passes bacterial filters. It is pathogenic for cats and a few species of mouse-like rodents (Microtus michnoi).

The reservoir of the virus has not been definitely determined how it is assumed to be the Mikhno field-vole, baby mouse, field-mouse, and karako rats. Possible vectors are ticks and fleas infesting these animals. The area of distribution is the Eastern Region of the USSR.

Man is susceptible, the disease develops after an 11-23-day incubation and takes the form of fever, pain syndrome, and hemorrhagic nephritis.

5. HAEMORRHAGOGENES SUIS NOM. NOV.
(Durand et al. 1936)

Synonym: Legio suariorum Holmes 1948. Causal agent of a disease of young swine in Switzerland.

The morphology of the elementary bodies has not been studied. The virus passes Chamberland L_2 filters. Virus-neutralizing bodies appear in the blood of surviving subjects.

Animals susceptible are swine, white rats, cats, pole-cats, mice, monkeys.

In Man the disease takes the course of fever, meningitis, and hemorrhages. Young persons are affected.

Infection apparently takes place from swine through their excrement.

SUPPLEMENT

In various countries hemorrhagic fevers have been described. Their etiology has been insufficiently studied.

1. The hemorrhagic fever of the South Western Regions of the USSR, accompanied by rise in temperature, pain syndrome, leucopenia, and hemorrhagic diathesis. The virus was isolated from cats and mice (Kalina and Ribac, 1941), but afterwards lost. The serum of survivors gives an agglutination reaction and neutralizes the virus of hemorrhagic fever of the Eastern Region of the USSR. Possible vectors are the ticks Ixodes ricinus.

2-4. Hemorrhagic fevers were also found in the Central Belt of the USSR in two different regions (Chumakov, 1950) and in the Western Regions of the USSR (Avakyan and Shimshelevich, 1952). All of them are viral etiology; the causal agents have been insufficiently studied.

5. Hemorrhagic fever was found in certain regions of Central Asia, mostly rural. Attempts to isolate the virus (Kodukin, 1948), from mice, swine, and rabbits proved unsuccessful, although the rabbits developed a brief fever 6-10 days after infection. Possible vectors are the ticks Hyalomma anatolicum and H, marginatum.

6. Grave attacks of hemorrhagic fever were observed in urban regions of Central Asia (Zhdanov, 1953). Their etiology has remained unelucidated.

7. In Tunis serious cases of gastroenterrhagic fever occurred, attended by a pain-syndrome recalling dengue (Laigret and Corcos, 1945). Their etiology remained unelucidated.

8. In South America and Soth Africa diseases locally called onyalai (or akembe) have been observed. They took the form of an acute thrombopenic purpura with hemorrhagic bullae. The mortality of these diseases was high (Morgan and Squires, 1940). Their etiology has not been elucidated.

9. In Rhodesia, Africa, epidemic outbreaks of thrombophlebitis with fever, meningeal symptoms and lymphocytosis were observed (Manson-Bahr and Charter, 1940). Their etiology has not been investigated.

10. In Yugoslavia an acute glomerulonephritis has been observed. A virus has been isolated (Ristic et. al., 1950) which induces nephritis in guinea pigs, cats and dogs.

11. In souther Scandinavia, there were cases of an epidemic benignant nephropathy (Myhrman, 1951). Its etiology has not been elucidated.