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THE PROBLEM OF RICKETTSIOSES IN THE USSR AND CURRENT TASKS CONCERNING IT

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The study of rickettsiae and rickettsioses is at present being set apart as a new and independent subdivision of the branch of medical sciences which deals with infectious diseases. Accordingly, the new discipline of rickettsiology is being differentiated as a subdivision of medical microbiology and has been added to the older subdivisions of protozoology, bacteriology, and virology. [The editor of the periodical says here in a footnote comment that it is hardly expedient at present to separate the theory of rickettsioses into an independent discipline.] It is therefore natural that in plans made for research, the study of rickettsioses has also been separated in the form of an independent problem.

The separation of the study of rickettsiae and rickettsioses into a special subdivision of the medical science on infectious diseases is expedient and timely. Specifically, this separation is based on the characteristics which typify the biology of rickettsiae as that of an individual group of intracellular microorganisms, the work on which required the application of special laboratory methods. This separation is also justified by the specific characteristics of the clinical and pathomorphological aspects of rickettsial diseases, by the considerable spread of these diseases, and by the presence among them of forms which are of great significance from the standpoint of public health, such as typhus, Q fever, tsutsugamushi fever, and Rocky Mountain spotted fever. Furthermore, the separation of rickettsioses into a special group is based on the peculiar traits of their epidemiology, which, as a rule, is associated with the presence of blood-sucking transmitters such as lice, fleas, ticks, or mites. Often, the identical infection is present among animals in the focus of the disease in question. In accordance with this, the study of rickettsioses is connected with the appropriate subdivisions of parasitology and medical pathology, including the study of natural foci of transmissive infection, as this subject is understood by Ye. N. Pavlovskiy.

As a result, the attempt to generalize and summarize the data on rickettsioses which had been accumulated required the publication of an extensive monograph and manual, which, in turn, illustrates the extent and specific characteristics of the subject under discussion (P. F. Zdrodovskiy, Ye. M. Golinevich, Ucheniye o Rikketsiyakh i Rikketsiozakh [The Science of Rickettsiae and Rickettsioses], Medgiz, Moscow, 1953, 440 pp).

At the same time, one must take into consideration that the study of rickettsioses is still in a period of initial development which has not been completed and that it is being continuously supplemented by new facts and discoveries, while the increased importance of rickettsioses in the infectious pathology of humans is becoming clearer. As far as the actual significance of rickettsioses for the regional pathology of the USSR is concerned, it is determined by the following data. During the past 17 years (1936-1953), Soviet investigators have detected or discovered on the territory of the USSR the following endemic rickettsioses: murine typhus, vesicular rickettsioses or rickettsial pox, boutonneuse fever, the tick rickettsioses of Central Asia, paroxysmal tick rickettsioses, and Q-fever or pulmonary rickettsioses. In addition to that, residual forms of epidemic typhus are still found, and locally there is occurrence of trench fever.

Thus, the existence of eight different forms of rickettsioses has been established in the USSR, among them six endemic rickettsioses connected with corresponding enzootics among wild or domestic animals. One must particularly emphasize that in recent times, foci of Q fever have been discovered in some

localities of the USSR. Q fever is a disease which affects both human beings and farm animals. It has been suddenly discovered everywhere in Europe and in a number of regions of Asia adjacent to the USSR.

Let us now discuss the research problems and particular organizational problems which arise in connection with rickettsioses. Within the framework of the present review, we will limit ourselves to a discussion of the most important problems of a general type and will not touch on special laboratory research. One of the most important tasks is further investigation of the geographic distribution of endemic rickettsioses which are already known and the existence of which has been established. This investigation should be accompanied by a more thorough study of the regional epidemiology of these rickettsioses. This refers particularly to murine typhus and to the whole group of tick rickettsioses (North Asiatic rickettsiosis, vesicular rickettsiosis, and boutonneuse fever) and must be particularly stressed in relation to Q fever. In addition to this, the search for new types and varieties of rickettsioses is indicated.

For the precise diagnostics in territorially new foci of endemic rickettsioses and for the differentiation of new types of rickettsiosis, the isolation of the causative factors (rickettsiae) from patients is required and also detection of these factors in the corresponding links of the epidemiological chain, i.e., in the blood-sucking parasite vectors, in wild animals on which the blood-sucking transmitters parasitize, and among domestic animals, if the latter as such form a source and reservoir of the infection. It is well known that from the standpoint of the methods applied, this task is carried out by infecting experimental animals with the material in question. This work is conducted, as a rule, with the use of guinea pigs, and the causative factor is later detected in them according to the general rules for the detection of rickettsiae.

The differentiation of the rickettsia strains isolated in this manner is carried out by methods which make possible a comparative characterization. These methods are cytomorphological, involving multiplication in the cytoplasm and in the nuclei of affected cells; cultural, involving propagation in egg cultures; experimental, involving experiments on animals; and seroimmunological, involving testing for direct serological reactions and cross reactions and carrying out experiments on the immunization of animals. In the course of this work, the strains under investigation must be preserved by passing them through animals (this is a method which is only of relative importance), or still better, by culturing these strains. It is best to preserve the Rickettsia strains (egg cultures or rickettsial material from animals) in a dessicated form.

One must note particularly that in the process of a preliminary search for the foci of these rickettsioses, as well as in the subsequent study of these foci, it is of great importance to apply methods of serological investigation on sick humans and animals suspected of having rickettsioses.

Generally speaking, it is important to keep in mind that serological methods of investigation, under application of specific rickettsial antigens, play a most prominent role in contemporary work on the detection and differentiation of rickettsial infections among humans and animals. It is essential to take recourse to these methods in carrying out such work. The methods in question, which comprise the agglutination reaction and quite particularly the reaction of compliment fixation, make it possible to recognize with certainty among humans and animals the occurrence of a rickettsiosis infection either in the past or at present, while at the same time, the group and type specificity of the causative factor of the infection can be established.

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Accordingly, the specific serological diagnosis of rickettsioses is the principal method for identifying these diseases among patients at hospitals. This method of diagnosis is absolutely indispensable in all types of epidemiological and epizoological investigations of rickettsioses, including their retrospective investigation.

Specific serological diagnosis as a preliminary and orienting method of investigating suspicious patients is particularly indicated in the detection of and search for new endemic rickettsioses, in view of the fact that the serological detection of rickettsiosis of some group or type in human beings is a good index of the presence in the region in question of natural foci of the rickettsiosis in question.

Advisable also are serological investigations of wild and domestic animals to find enzootic sources of the rickettsiosis infection in the region where infections occur among humans. On the other hand, the fact that the infection is present in humans may indicate that wild or domestic animals are also affected.

Generally speaking, specific serological diagnosis which is supported by the isolation of the causative factor either in work on the detection of new foci or in connection with special tasks is one of the basic and obligatory methods for the detection of rickettsioses. Any procedures used for the mass investigation of humans and animals with a view to detecting rickettsioses are completely valid only when serological tests are applied. At the same time, the serological characterization of rickettsiae according to their antigenic structure is the basic prerequisite for the differentiation and classification of these organisms.

As has already been stated, the application of the reaction of complement fixation is particularly indicated for purposes of the specific serological diagnosis of rickettsioses. In addition to the clarity of the results obtained and the possibility of their application in retrospective serological diagnosis, the reaction of complement fixation with the use of the so-called full antigens (Golinevich) makes certain the diagnosis of all types of rickettsioses, including those of the tick-transmitted group. The possibility of diagnosing tick-transmitted rickettsioses is particularly important because no corpuscular antigens exist for them, so that the reaction of agglutination can not be carried out. Furthermore, the experience acquired at our laboratory has shown that the reaction of complement fixation can be carried out with serum dried on paper and sent from the foci being investigated to the central laboratories (Yablonskaya).

Finally, one must take into consideration the possibility of supplying full antigens for the reaction of complement fixation at a very low cost, which is not a matter of indifference in the case of mass investigations, because the corpuscular antigens used in the reaction of agglutination have a very high primary cost.

Thus, the detection and investigation of rickettsioses is impossible locally without the application of contemporary methods of specific serological investigation, among which diagnosis with the aid of the reaction of complement fixation is the most important from every standpoint. This leads to two important requirements. First, the Ministry of Health USSR must secure the mass production of all types of rickettsiosis antigens, including full antigens for the reaction of complement fixation. Secondly, the laboratories located in the regions affected must familiarize themselves with the methods of the specific serological diagnosis of rickettsioses, particularly the reaction of complement fixation. Without practical organizational solution of the problems involved, both from the standpoint of methods and that of technology, one cannot solve the problems of the geographic distribution of rickettsiosis and of their group and type differentiation, combined with a precise clarification of the elements of their regional epidemiology and epizootology.

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As has been mentioned above, foci of Q-fever have been discovered lately in some regions of the USSR. In the localities in question, there was infection with Q-fever of cattle and other farm animals (Shifrin, Chumakov, et al; Khodukin and Lysunkina; Kulagin and Kekcheyeva). The findings relative to Q-fever imposed on medical and veterinary workers the task of carrying out investigations with a view to clarifying the actual distribution of the Q-fever rickettsiosis and establishing precisely the nature of its epidemiology (the presence of the infection among domestic animals and in natural foci, i.e., among ticks and wild animals).

Initially the investigations in question, primarily serological investigations with the aid of the reactions of agglutination or of complement fixation, should be carried out at major meat combines in various regions, so that if Q-fever is discovered among the workers at the meat combines and among the cattle that are being slaughtered, one may transfer the investigation to the regions where the sick animals have been bred. One should also carry out serological investigations aiming at the discovery of the Q-fever rickettsiosis among patients having atypical pneumonias or lingering influenza. This applies particularly to persons who are associated with some activity in the field of animal breeding or an activity involving the processing of raw material of animal origin, particularly wool.

It is quite clear that in addition to epidemiological and enzoological investigations, work should be done at rickettsiosis laboratories with a view to a comprehensive investigation of any new rickettsiosis which may occur.

One should pay particular attention to the study of the distribution of murine typhus and of the characteristics of the epidemiology of this disease, having in mind the basins of the Black Sea, the Caspian Sea, and the low-lying lands in the valleys of the rivers within these basins, as well as the coastal regions of the Far East. In addition to this, thorough research on the tick rickettsiosis of the Northern Asiatic type must be carried out in the regions of Central Asia. It is also necessary to carry out comprehensive investigations of the paroxysmal tick rickettsiosis described by Ukrainian authors (Sirotinin, Ruchkovskiy, Padalka, et.al.), since the position occupied by this particular rickettsiosis with relation to other rickettsioses is not clear, because the characteristics of the causative factor are not known. In addition, it is advisable to conduct work reviewing the nature of the so-called hemorrhagic fever from the standpoint of the possibility that this disease may have rickettsial etiology, at least in some areas of western Siberia. This problem can perhaps be successfully solved with the aid of a serological investigation of patients, involving application of a complete selection of rickettsiosis antigens.

While limiting ourselves to tasks which are primarily of a regional character, as far as the endemic rickettsioses discussed above are concerned, we will now consider the tasks connected with the problem of the residual forms of typhus, which, to a major degree, coincide with those raised by the problem of recurrent typhus.

As a discussion conducted in 1952 has shown, the majority of Soviet specialists qualified to interpret the nature of residual or recurrent forms of typhus adheres to the concepts of the classical epidemiology of typhus, which recognizes the significance of the louse factor and of the loss of immunity in those who have been repeatedly infected (see the articles on the subject published in Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii during 1952).

In contradistinction to the prevalent view, K. N. Tokarevich and G. S. Mosing expressed agreement with the views of Zinsser and Parrot, which have received wide recognition abroad, and advanced the hypothesis of recrudescence in recurrent typhus. They consider that at least in a certain number of cases,

typhus assumes a latent form of indefinite duration, and recrudescence takes place under certain conditions, so that the clinical characteristics of recurrent typhus appear again.

Finally, our laboratory (Zdrodovskiy, Golinevich, and Kulagin), on the basis of characteristics of the epidemiology of sporadic forms of typhus and the detection in these forms of a new intermediate variant of Prowazek rickettsia (R. prowazeki var. intermedia, Golinevich 1950), expressed the opinion that these forms are produced by a special variety of rickettsia which perhaps does not arise within the chain man-louse-man but in some other epizootological connection. The assumption was made that the modified causative factor of typhus circulates within a chain formed by Gamasidae mites and domestic rodents (Zdrodovskiy, Kulagin). In other words, the question was advanced as to whether there isn't a reservoir of the causative factor of typhus outside of human beings similar to that present in all other rickettsioses, with the exception of trench fever.

All the assumptions expressed remain hypothetical and require further research and precise proof. This refers particularly to the interpretation of data on residual or recurrent forms of typhus from the standpoint of classical epidemiology, because, in a number of cases, the origin of sporadic typhus cannot be explained satisfactorily from this standpoint.

This applies to a still greater degree to the hypothesis assuming recrudescence of recurrent typhus, because precise proofs are often not given and purely speculative discussions and reasoning by analogy are substituted for these proofs. Without factual data, this very important hypothesis, which inactivates practical measures, can not be accepted. From the standpoint of this hypothesis, the search for the causative factor of typhus in persons who recovered from typhus a long time ago must be conducted. With this aim in view, one may utilize to some extent material obtained in surgical operations. In other cases, one may perhaps apply for the same purpose the method of puncturing bones and investigating samples of bone marrow obtained in this manner. This is a method used in hematology and in investigations dealing with leishmaniasis. Finally, one may use material obtained in autopsies carried out on persons who had had typhus. It is obvious that the investigations in question must be carried out with the application of the most sensitive method, namely, that of the infection of clothes lice.

The same requirements must be put to the adherents of classical epidemiology, who must supply objective proof of the applicability of the factor louse-man-louse to the cases of sporadic typhus which are observed and who must also refute conclusively the epidemiological basis on which the hypothesis of recrudescence rests.

To summarize, the problem of residual or recurrent sporadic forms of typhus must be subjected to many-sided investigations and a number of postulates of classical epidemiology must be revised in that connection. These concepts were formulated in the relatively distant past, when the sensitive methods of investigation which are available to contemporary rickettsiology had not yet been developed.

In conclusion, one should state that the detection of residual forms of typhus should be carried out with the aid of specific serological diagnosis, if only by applying one of the simplified methods of microagglutination. The use of a simplified method is permissible unless differentiation between epidemic typhus and murine typhus is to be carried out. For this particular purpose, the ordinary reaction of agglutination or the reaction of complement fixation should be used.

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With regard to the prophylaxis of rickettsioses, one may recommend the following line of research.

First, it is advisable to clarify the question as to whether it would be profitable to pursue work on the prophylaxis by vaccination of the most important endemic rickettsioses, particularly murine typhus, the Northern Asiatic tick rickettsiosis, and Q-fever, with consideration of the possibilities that human beings and farm animals be inoculated. Obviously, the work on the subject will require preliminary experimentation on animals.

Through investigation under practical conditions of the effectiveness of sanitary-antiepidemic measures for the control of endemic rickettsioses, accompanied by experiments on the elimination of individual foci after their comprehensive study from the epidemiological standpoint, are absolutely necessary. In this subdivision of research, one must specifically take into consideration measures for the control of blood-sucking transmitters and of animals, particularly rodents, which form a reservoir of the infection at the foci (for instance, rats and mice in cases of murine typhus and vesicular rickettsiosis). In the same subdivision, one must develop the most effective methods of personal hygiene for purposes of prophylaxis, as far as transmission of the infection by insect parasites (ticks and fleas) is concerned.

Finally, one must carry out a number of clinical investigations on endemic rickettsioses, primarily on the clinical forms of Q-fever, an infection which is new to clinicists and which apparently needs very thorough study. In addition to acquiring a thorough knowledge of the clinical aspects of the diseases involved, one must subject to earnest study the chemotherapy of rickettsioses by means of Soviet antibiotics (syntomycin, levomycetin, and biomycin). In this respect, one should pay particular attention to the investigation of the possibility of combined therapy, using antibiotics together with specific vaccines.

In our opinion, these are the most important tasks in research work to be done on rickettsioses. In conclusion, one may remark that work on rickettsioses must be carried out by microbiologists specializing in rickettsiology and working in cooperation with immunologists, infectionists, epidemiologists, and parasitologists. One must particularly emphasize that collaboration between epidemiologists and parasitologists will lead to good results in this field.

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