The subject of this paper has received so much publicity in the daily press that all health workers will want to know the details of the peculiar epidemics—if only as a matter of self-defense against the questions of the curious. Its unusual features become of interest to all, not solely the epidemiologist.

Epidemic Hemorrhagic Fever*

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EPIDEMIC hemorrhagic fever is one of the problems confronting our military forces in Korea. This disease of northeast Asia was recognized and studied by Japanese [1-3] and Russian [4-6] investigators in Manchuria and Siberia during the last two decades; Takami [7] and Mayer [8] have prepared English summaries of much of this work. Prior to the first experience by Americans in 1951, the disease was not known to exist in Korea.

In the relatively short interval since the summer of 1951, epidemic hemorrhagic fever has had a considerable impact on medicine in the Far East Command. There were approximately 1,000 cases of this disease during 1951 and about 700 cases since then. Such an incidence of a serious disease always constitutes an important military problem. The fact that American physicians had not observed this dramatic illness previously, plus the medical importance of the disease, stimulated great interest in it and resulted in a number of extensive studies,[9-20] many of which are not yet complete; and most of those that have been finished have not yet appeared in print. It has been my privilege to view a number of these manuscripts during their preparation or prior to publication. Accordingly, in the attached bibliography I have tried to acknowledge the source of the data from unpublished reports and articles in press, as well as from publications.

The Korean observations summarized here were made by members of the Medical Service who were assigned to the Eighth Army in Korea and the Far East Command. In addition, I shall mention certain of the findings of the Epidemic Hemorrhagic Fever Field Unit of the Armed Forces Epidemiological Board, which devoted its efforts for a number of months to problems concerned with the etiology and epidemiology of the disease. It should be emphasized that in essentially all of the discussion my function is that of a reviewer rather than that of an investigator reporting the results of his own observations.

Epidemic hemorrhagic fever encountered in Korea is characterized by a clinical picture [10, 16] of varying severity. The onset is sudden with intense headache, fever, and chills, and generally with anorexia and vomiting. The temperature rapidly rises to 102° to 104° F., orally, and stays in this range for four or five days. When the patients are hospitalized 24–48 hours after the onset, a definitive diagnosis of hemorrhagic fever is difficult or impossible to make. However, at this time a tentative diag-

* Presented before the Epidemiology and Laboratory Sections of the American Public Health Association at the Eightieth Annual Meeting in Cleveland, Ohio, October 22, 1952.

nosis is based on (1) history of exposure in an endemic area, (2) symptoms of fever, chills, malaise, headache and backache, and (3) signs of a flushed face and injection of the conjunctiva and mucous membranes.

The blood elements are normal except for occasional moderate leukopenia. Between the third and fourth days, a petechial rash appears, commonly on the palate and axillary skin folds; and transient episodes of hypotension may occur, particularly after exertion or periods of extreme restlessness. About the fourth day, the typical patient develops albuminuria. This is generally sudden and severe. Indeed, within a few hours after the patient provides a specimen with a trace or 1-plus albumin, he frequently excretes urine which boils solid and contains casts. This albuminuria is one of the characteristic signs of the disease, and it usually provides the first definitive clinical evidence which permits one to make the diagnosis "Hemorrhagic fever—confirmed."

The period from the third to the sixth day is of particular importance. Some of the less severely ill patients begin their recovery and have an uneventful convalescence with rather prompt defervescence, followed by a period during which diuresis replaces the oliguria and albuminuria. During this crucial period, certain of the more seriously affected patients develop marked changes in the blood.[10, 12, 16] In most cases, thrombocytopenia occurs. When this is severe, purpura, hematemesis, gross hematuria, and melena can be encountered. Others develop marked leukocytosis with counts of 20,000 to 100,000 and a predominance of young cells of the myelocytic series. Episodes of hypotension and shock are common during the latter part of the first week and probably constitute the greatest hazard to survival. Following the onset of oliguria and albuminuria, the blood nonprotein nitrogen and creatinine values mount, and in the severely ill patients reach extremely high levels during the ensuing week. In some of the patients, blood potassium levels are sufficiently elevated to produce electrocardiographic changes.[10, 15]

Even the severely ill patients are usually out of danger by the tenth or twelfth day. In those who survive, there are rare residuals. Ordinarily, the capacity to concentrate urine remains diminished for a variable period of time.

The treatment of epidemic hemorrhagic fever is symptomatic.[11] To date, none of the specific antibiotic and chemotherapeutic agents have proved of value in this disease. Probably the most important aspects of the acute illness from the point of view of treatment and mortality are the hypotension and shock. Experience has shown that these patients have an extremely poor tolerance for exertion and rough handling. Therefore, their care during the early days of the illness is directed toward obtaining adequate rest and protection from trauma.[13] This starts with the early, tentative diagnosis within the first 24–36 hours, prompt evacuation by helicopter to the "Hemorrhagic Fever Center" within a few miles of the hyperendemic area, the liberal use of sedatives to obtain rest and relaxation, and the administration of adequate *but not excessive* amounts of fluid orally.

During the critical period at the end of the first week, when episodes of hypotension are occurring, the treatment is still conservative. For transient shock, the foot of the bed is elevated, the legs are wrapped in elastic bandages, and sedatives are given. In many instances, such conservative treatment of shock is sufficient, and the episode passes after a few hours. Even in those individuals with protracted hypotension and progressive shock, plasma expanders, especially concentrated albumin, and vasoconstrictors are used cautiously and in relatively small amounts. The usefulness of noradrenaline is being determined

currently. Experience has shown that the enthusiastic treatment of these patients in shock with large amounts of fluids has prompt untoward effects. The majority of patients with severe azotemia can be carried through on conservative treatment; however, for some of the most severely affected ones, particularly those with hyperpotassemia, ion exchange resins and the artificial kidney have been employed. With the onset of diuresis, the patient has usually passed the last milestone and will recover.

The mortality in epidemic hemorrhagic fever has varied from time to time during the past year. From mid-April to mid-July, approximately 500 United Nations troops were treated at the 8228 Mobile Army Surgical Hospital (MASH). In this group, the mortality was less than 5 per cent. The majority of deaths occur late in the first week or early in the second week of the illness, usually following a protracted period of shock. A few deaths occur during the third or fourth week, associated with prolonged renal failure. In those who die early in the course of the disease,[3, 9, 14] the most striking lesions found at autopsy are in the kidney where the medullary tissue is sharply demarcated because of the extensive hemorrhages into this region. Other hemorrhagic manifestations are observed in various organs, but particularly in the pituitary, the adrenal, and the right auricle of the heart.

The histopathology[2, 3, 9, 14] consists primarily of capillary dilatation, hemorrhage, focal necrosis, and mononuclear cell infiltration of parenchymatous tissue. As might be expected from the gross lesions, such microscopic changes are most prominent in the kidney, pituitary, and adrenal. However, small areas of focal necrosis are found at times in the liver, heart, and other organs. Moreover, interstitial myocarditis and pancreatitis are occasionally encountered, as well as small perivascular infiltrations in various other tissues.

Epidemic hemorrhagic fever in Korea is a "place" disease, not a contagious disease.[17, 18] The epidemic area extends as a belt across the peninsula with the southern border at the level of Seoul and the known northern border at the present main line of resistance. Within this general area the disease is seeded in sharply defined foci in rural areas. Most cases occur as isolated events but small outbreaks are encountered which appear to result from almost simultaneous infection of the members of the group. The greatest numbers of patients are seen during two periods of the year, that is, the late spring-early summer period and the late fall-early winter period. However, scattered cases occur throughout the remainder of the year.

Both the Japanese[1, 21] and Russian[4] scientists were of the opinion that the etiological agent of epidemic hemorrhagic fever was maintained in nature through a cycle involving rodents and arthropods. However, the two groups were inclined to incriminate different rodents and different arthropods. The American studies during the past summer produced similar opinions regarding the importance of rodents and arthropods, but the findings led this group to suspect trombiculid mites as the most likely vectors of the disease.[20] It will be recalled that this general group of mites provides the vector for scrub typhus, another classical example of a "place" disease. It may be emphasized that definitive information on the mode of transmission of epidemic hemorrhagic fever to man and the natural cycle of the disease in rodents and arthropods will not be obtained until the agent can be readily handled in the laboratory and used in crucial tests on this phase of the problem.

There are many lines of investigation which hinge upon the theoretically simple procedure of finding a suitable

laboratory host for the agent. Thus, the development of satisfactory diagnostic procedures, the preparation of vaccines, the undertaking in the laboratory of careful chemotherapeutic screening tests, all demand a susceptible laboratory host. Both the Russian [5] and Japanese [22] workers demonstrated that the disease could be transmitted from man to man by inoculation of body fluids obtained during the first few days of the febrile illness; moreover, they demonstrated that the agent was filterable.[1, 5] However, neither of these groups was able to establish and maintain the agent in a common laboratory animal. Since the disease was first encountered among UN troops, extensive and laborious efforts have been made to find the answer to the crucial question of a suitable laboratory host. Such studies to date have been no more fruitful in American hands [19, 23] than were the earlier ones of the Japanese and Russians. Needless to say, this problem is still under intensive investigation.

This presentation has been an interim report covering certain phases of the rapidly developing knowledge regarding a disease with which we had no experience before the year 1951. It is apparent that a considerable amount of information has been accumulated in this brief time on certain features of the disease. On the other hand, virtually no definitive data are available regarding other equally important aspects of the malady.

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