

EPIDEMIC HEMORRHAGIC FEVER

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<u>TABLE OF CONTENTS</u>	<u>Page</u>
DEFINITION: . . . . .	1
HISTORICAL BACKGROUND . . . . .	1
DISTRIBUTION . . . . .	2
ETIOLOGY . . . . .	2
ANIMAL EXPERIMENTATION . . . . .	2
EPIDEMIOLOGY . . . . .	3
PATHOLOGY . . . . .	4
Kidney . . . . .	4
Heart . . . . .	5
Liver . . . . .	5
Spleen . . . . .	5
Lung . . . . .	6
Brain . . . . .	6
Thymus . . . . .	6
Skin . . . . .	6
Lymph Node . . . . .	6
Bone Marrow . . . . .	6
Pituitary . . . . .	6
Gastrointestinal Tract . . . . .	6
Pancreas . . . . .	6
Testicle . . . . .	6
Adrenal . . . . .	6
Thyroid . . . . .	7
Eye . . . . .	7
CLINICAL COURSE . . . . .	7
LABORATORY FINDINGS . . . . .	9
Urine . . . . .	9
Blood . . . . .	9
Cinical Chart . . . . .	9-a
Blood Chemistry . . . . .	10
Serology . . . . .	10
Cerebrospinal Fluid . . . . .	10
DIAGNOSIS . . . . .	19
PROGNOSIS . . . . .	10
DIFFERENTIAL DIAGNOSIS . . . . .	11
BIBLIOGRAPHY . . . . .	12

## EPIDEMIC HEMORRHAGIC FEVER

### DEFINITION:

Epidemic hemorrhagic fever is an acute infectious disease of virus etiology characterized by an abrupt onset with high fever, headache, myalgia hemorrhagic diathesis, albuminuria, and a leukemoid leukocytosis. It is said to be transmitted to man by the mite, Laelaps Jettmari Vitzthum. The host of the mite and probable reservoir of the disease is the field rodent, Apodemus agrarius.

The disease has been known by a variety of names since the first recognition in the Songo district of Northern Manchuria in 1939. It was then called Songo Fever. Later, after subsequent outbreaks, it was variously called Kokka Disease and Korin Fever, depending upon the Japanese name for the district in which the disease occurred. Still later, it was found to be identical with Nidoko Disease, which was first reported from the Nidoko district of Northeastern Manchuria in 1938. In February 1942 it was officially recognized as a disease entity and designated Epidemic Hemorrhagic Fever (Ryukosei Shukketsu Netsu) by the medical department of the Japanese Army.

### HISTORICAL BACKGROUND:

In August 1939 one of the cavalry companies of the Imperial Japanese Kwantung Army was ordered to the Shokako (Sung-hua) River at a point about 40 km below Harbin in the Songo (Sun-wu) district of Northern Manchuria. The mission of the company was to practice river-crossing techniques and the bivouac area was in the swampy regions near the river banks. Between September and December 1939 over 20 soldiers in that company contracted a disease of unknown etiology characterized by abrupt onset with high fever, hemorrhagic diathesis, and albuminuria. Of these 20 patients, 6 died. In the absence of a specific diagnosis, the disease was called Songo Fever.

A similar disease broke out in Japanese troops in the autumn of 1941 in the districts of Songo and Kokka (Hei-ho) in Northern Manchuria. In this outbreak, 26 of 236 patients died. Then, in the beginning of October 1942 in the Korin (Hu-lin) district of Northeastern Manchuria, another similar disease outbreak occurred in troops stationed there. The mortality in this instance was 15 out of 102 patients.

It has since been established by Ibuki that several disease outbreaks which occurred in Japanese troops in Northern and Northeastern Manchuria since 1935 and which were reported variously as hemorrhagic purpura, typhus, atypical scarlet fever, acute nephritis, etc., were in fact cases of epidemic hemorrhagic fever. The so-called Nidoko Disease, which broke out in a cavalry regiment camped along the Sui-fen River in Northeastern MANCHURIA in 1938, especially resembled this disease. Other instances of this nature were the "fever disease" which broke out in the artillery regiment after it had returned to Botanko from maneuvers in the swamps along the southwestern part of the Sairin River in 1936 and the "scarlet fever" which was prevalent in the troops stationed at the Doki (Tang-ho) station of the Suinning Railroad in May 1937.

Because of the high incidence of this disease in Japanese troops stationed in Manchuria, the Kwantung Army dispatched research and investigative groups to the various districts where it was prevalent. This work resulted in the conclusion that the disease was a specific entity of virus etiology.

#### DISTRIBUTION

Epidemic hemorrhagic fever is known to occur only in Northern and Northeastern Manchuria. However, Kitano reports having read in Soviet medical literature about disease outbreaks occurring across the Siberian border in which the clinical and pathological pictures closely resembled this disease. There are no other known endemic areas, but inasmuch as the geographical range of the field rodent, Apodemus agrarius, covets the entire Korean peninsula, it may be presumed that the disease is at least enzootic in Korea. The presence in Korea of the mite, Laelaps jettmari Vitzthum, has not been established.

#### ETIOLOGY:

The specific causative agent of epidemic hemorrhagic fever was shown by Kitano et al to be a filterable virus capable of passing Chamberland candles L<sub>2</sub>, L<sub>3</sub>, L<sub>5</sub>, and L<sub>9</sub> and Seitz EK filter.

Animal experimentation showed that infected citrated blood when kept at -3°C., remained infective for at least 8 days. However, an emulsion made from the organs of an experimental animal at the height of the fever, when kept at a temperature of -70°C., retained its viral potency for 81 days. This property is not shared by the protozoa or spirochaetal organisms.

Japanese workers have not been able to establish immunological relationships between this and other virus disease.

#### ANIMAL EXPERIMENTATION:

In November 1942 Japanese investigators caught 40 Apodemus agrarius in the Songo District of Northern Manchuria. From these rodents they were able to recover 203 Laelaps jettmari Vitzthum. The mites were ground up, suspended in normal saline, and 1.0 cc of this mixture was injected subcutaneously into the thigh of a monkey. After a period of 19 days, a moderate infection with a fever of 39.4°C. was noted. A second monkey was injected with blood from the first monkey taken at the height of the fever and after an incubation period of 12 days, fever and albuminuria developed. Postmortem dissection revealed what the Japanese call the "EHF Kidney" and other supposedly typical pathological findings. It is important to note that the blood is capable of the greatest degree of infectivity when collected at the height of the fever, and is non-infectious when the fever returns to normal.

In a further experiment, 0.5 cc of infectious serum was injected intraperitoneally into a Apodemus agrarius. This rodent was observed for 25 days and did not develop clinical manifestations of the disease.

Furthermore, the viscera presented a normal picture at autopsy. The liver, kidneys, and spleen were ground up and emulsified with 10 parts of Ringer's solution and 1.0 cc of this mixture was injected intradermally into a monkey. After an incubation period of 11 days, the monkey developed a fever of 40.2°C. and moderate clinical manifestations of the disease. Blood withdrawn from this monkey at the height of the fever was then injected into a second monkey which, in turn, developed the disease. Thus, it is felt that experimentally the host rodent, Apodemus agrarius, is capable of harboring an inapparent infection of this disease.

Repeated attempts have been made to culture bacteria from the blood, stool, urine, cerebrospinal fluid, and throat secretions of patients and infected experimental animals on all types of media, both aerobically and anaerobically, but the results have been consistently negative. In addition, numerous smears of infected blood and organ suspensions were examined under the darkfield microscope with no positive findings except that in a few cases "Theileria-like" bodies were found in the blood of patients suffering from epidemic hemorrhagic fever.

#### EPIDEMIOLOGY:

Infection is acquired by the bite of the mite, Laelaps jettmari Vitzthum, usually without the victim being aware that he has been bitten. The virus is thought to pass from the salivary gland of the mite into the skin puncture during the biting process. However, in contrast to scrub typhus, no biting marks can be observed on the skin, the mites are not engorged with lymph, and evidence of blood-sucking is lacking. The mite retains the virus throughout its life cycle. Ibuki believes that the body louse, Pediculus humanus corporis, may also be a vector. The reservoir is the field rodent, Apodemus agrarius, and the infection in these rats apparently produces no clinical disease. In view of the preponderant incidence of epidemic hemorrhagic fever in the cavalry end in troops otherwise closely associated with horses, it must be borne in mind that the horse is a possible additional reservoir of this disease. Also, Japanese veterinarians have reported increased incidence of "influenza" and "acute infectious anemia" in horses in localities where epidemic hemorrhagic fever is endemic and during the same months of peak incidence of the disease in man. However, the method of transmission from the horse to man is not known.

The months of peak incidence of the disease are May and June and, again, in October and November. These are the months during which the multiplication of mites takes place at the greatest rate. However, the disease is known to have occurred throughout the year and generally recurs in any given endemic area during the same months of each year. The highest mortality was encountered by the Japanese in the cases occurring during the autumn months.

Epidemic hemorrhagic fever is especially prevalent in areas along river banks and in swampy marshlands where the grass grows high and is unattended. This type of terrain is apparently the ideal habitat of Apodemus agrarius. It is, however, also seen in hilly and forest areas.

In most cases, infection takes place when troops are in bivouac rather than when they are stationed in more permanent camps. The infection has a tendency to be localized within one room or one company or one specific area. For instance, in a two-story building, the outbreak would be limited to the first floor. In this respect it is characteristic of most mite-borne infections. In 1941 two companies of Japanese troops attached to the same cavalry regiment and stationed near San-shin Fu received hay for their horses from two different sources at approximately the same time. Epidemic hemorrhagic fever broke out in the company receiving hay from nearby Ryu-sin, but did not occur in the other company to which the hay had been shipped by rail from another area.

Person to person infection probably does not occur as there have been no proven cases recorded among attendants, nurses, doctors, and research workers. However, precautions should be taken at all times when in contact with these patients.

#### PATHOLOGY:

The most predominant pathological feature seen in epidemic hemorrhagic fever is a marked diffuse disturbance of the peripheral circulation. This involves paralysis of the peripheral capillaries, stasis, hemorrhage, and transudation. These disturbances occur primarily in the capillaries, decreasing in extent as the size of the vessels increases. Hemorrhage follows dilatation and subsequent stasis in the vessels and these changes are seen in all the organs. Parenchymatous degeneration of a diffuse type is seen in the kidneys as nephrosis and of a discrete type in the liver, pituitary, etc. as focal necrosis. Diffuse edema of the organs is due to these circulatory disturbances and varies with each organ. Serous inflammation (sic), for instance, usually affects the liver and adrenals.

Because of the apparent affinity of the virus for the capillaries, a form of capillary toxicosis ensues, resulting in vasomotor disturbances and destruction of endothelial cells. Thus, static hemorrhage follows vasomotor paralysis and pericapillary edema of the organs results from the endothelial damage. If hemorrhagic necrosis and atrophy due to stasis are present, serous inflammation and edema of the organs results in parenchymatous degeneration. The focal necrosis closely resembles the nodules of typhoid and typhus fevers.

Vasomotor paralysis and stasis are always present so that hemorrhage naturally ensues. Capillary bleeding is usually hemorrhage per diapedesis, but there is also the possibility of hemorrhage per rhexis and there need not necessarily be any associated morphological changes. This hemorrhagic tendency differs in extent with each case, but the areas of involvement are specific for each organ; for example, the outer area of the medulla and the surface of the cortex in the kidneys, the sub-capsular surface of the liver, the right atrium of the heart, the zona reticularis of the adrenal cortex, and the ciliary body of the eyeball.

Kidney: Macroscopically, the kidney is markedly swollen and may be double its normal weight (200 gm or over). Following severe hemorrhage, rupture of the organ may be seen. The cut surface of the cortex is dull and slightly yellowish, showing intense swelling and cloudiness.

In contrast, the medulla is a vivid deep-red color, making the cortico-medullary boundary sharply distinct. This is characteristic of the "EHF Kidney".

The glomeruli show slight to medium degeneration and the walls of the loop are swollen and have indistinct borders. They may fuse and then show irregular morphology and atrophy. The epithelium of Henle's loop and the epithelial cells of Bowman's capsule sometimes undergo vacuolization and granular degeneration and destruction. The cavity of Bowman's capsule contains the same albuminous products as the tubules. In general, the findings are those of glomerulitis with an increase in the glomerular nuclei as a result of inflammation.

All of the capillaries and loops which form the Malpighian corpuscles are flooded with blood. The interstitial connective tissue is edematous and loose and characterized by cellular infiltration and hyperplasia (interstitial edema). The entire vascular system, especially the capillaries, shows a diffuse and high degree of dilatation, stasis (hyperemia and congestion), and hemorrhage. The involvement in the cortex is to a much lesser degree than in the medulla. The periarteriolar and perivenular accumulation of round cells is a characteristic finding. Occasionally, hemorrhagic rupture may be seen on the subcapsular surface of the cortex.

Heart: The myocardial cells undergo albuminous, hyaline, or waxy degeneration and show a tendency to atrophy. The interstitium, especially perivascularly, shows serous permeation and hyperplasia of the connective tissue fibers. At times localized or slightly diffuse infiltration and hyperplasia of histiocytic monocytes can be seen. The endocardial epithelium shows slight hyperplasia and hydropic degeneration is seen in the subendocardial connective tissue.

The dilatation, congestion, and hemorrhage of the vascular system is the same as in the other organs. Often the whole structure of the right auricle shows a diffuse permeation of blood. The walls of even the smallest branches of the coronary artery show histolysis and edema. At the same time, the pericardium shows hyperplasia of the loose connective tissue fibers and histiocytes.

Liver: There is some swelling and increase in weight (1200 -1500 gm). The liver cells undergo albuminous and hydropic degeneration. The chordae undergo separation and necrosis, swelling and compensatory hypertrophy, and a tendency towards disintegration. At times, there are seen localized small necrotic foci or small granulomatous cellular nodes scattered throughout the lobular parenchyma. The Kupffer cells are not always increased and occasionally undergo degeneration. In Glisson's sheath, lymphocytic and histiocytic infiltration can usually be seen. Dilatation, hyperemia, congestion, and small hemorrhages are always present, mainly involving the capillaries. In some cases, there is a pericapillary edema associated with a degeneration of the arenchymal cells.

Spleen: The cells of the reticulo-endothelial system of the spleen usually show a slight to medium increase, a reactive hyperplasia. The Malpighian corpuscles are slightly atrophied. The vascular changes follow the same pattern as in the other organs and the follicular arteries often show edema or hyalinization, but this finding is not characteristic,

Cellular infiltration can usually be seen below the endothelial cells of the trabecular arteries. The distribution of blood varies, but the blood volume is usually increased.

Lung: Dilatation, congestion, and small hemorrhages may be present in the interstitial tissues. There are also inflammatory changes of the alveolar septal walls and a serous flooding of the alveoli due to congestion and hyperemia.

Brain: There are circulatory disturbances as in other organs, especially in the capillaries of the membranes and parenchyma. Degeneration of the nerve cells is not noticeable and hyperplasia of the glia cells is not extensive. Serous permeation is often present in the pericapillary area. Subarachnoid hemorrhage rarely occurs and a fair degree of lymphocytic and histiocytic infiltration can be seen in the pia mater. Nerve cells show a slight degree of cloudy degeneration and the small vessels are hyperemic and have a tendency to hemorrhage.

Thymus: There is the usual fat replacement seen in adults.

Skin: The corium shows the same circulatory disturbances seen in the other organs. There is some pericapillary cellular infiltration.

Lymph Node: There is hyperplasia of the reticulo-endothelial system. There are also the characteristic circulatory disturbances of the vascular system.

Bone Marrow: There are varied changes which are not consistent from bone to bone or even in different parts of the same bone. Sometimes the marrow is red and sometimes it is yellow. The red marrow shows the characteristic capillary circulatory disturbances.

Pituitary: The characteristic circulatory pattern is seen in all the lobes, but more so in the anterior lobe. The parenchymal cells of the anterior lobe lose their staining properties. The hemorrhagic tendency is so great that the gland resembles a hematoma and may attain a weight of 2 gm.

Gastrointestinal Tract: In those cases showing severe intestinal hemorrhage, the entire tract is a deep purplish-red color. There is hemorrhage in the capillary loops of the villi and in the plexi of the submucous layer.

Pancreas: Interstitial hyperemia and bleeding. At times, small hemorrhages are seen in the islets of Langerhans.

Testicle: There is noticeable injection of the small vessels of the interstitium.

Adrenal: There is hyperemia and hemorrhage at the boundary between the cortex and medulla. Parenchymal and, sometimes, vacuolar degeneration

are characteristically seen in the zona fasciculata of the cortex.

Thyroid: There is interstitial hyperemia and hemorrhage.

Eye: The uvea shows congestion and there is frequent hemorrhage in the ciliary bodies.

#### CLINICAL COURSE:

The incubation period is 2 to 3 weeks, but may be as short as three days or as long as one month. There is no painful eschar with resulting regional lymphadenopathy (as in scrub typhus) at the site of the original entrance of the virus from the bite of the infected mite. As a matter of fact, the patient frequently is not aware that he has been bitten. In most instances, the onset is sudden with tremors, chills, fever, severe frontal headache, anorexia, nausea, and vomiting. However, there may be prodromal symptoms lasting from 1 to 7 days consisting of fatigue, anorexia, general malaise, and slight myalgia with moderate lumbago. The temperature rises to a peak of about 104 to 105° F. by the 3rd day and then falls gradually but precipitously, so that it is normal or below normal by the 5th or 6th day. It is extremely important to realize that this defervescence has no bearing upon the prognosis of the disease. After the temperature returns to normal, usually by rapid lysis, but in more severe cases by crisis, other manifestations of the disease increase in severity and death, when it occurs, takes place one or two days after the temperature falls.

A petechial rash becomes manifest on about the 3rd day, involving the neck, anterior and posterior axillary folds, upper arms, and thorax. This eruption has been described as morbilliform, individual lesions being scattered and ranging in size from that of a pin-head to a millet-seed. It frequently takes the form of linear striations rather than of a petechial or macular rash and is most often slight in extent, although it may become more widespread and severe as the disease progresses. Associated with this eruption is a generalized flush about the face and neck. In most instances, this flush is an almost imperceptible deepening of the suntan normally acquired by soldiers in the field. Sometimes, however, it is a distinct reddening of the skin and resembles a newly-acquired sunburn. (Description is the appearance in Oriental patients - Ed.) Mucosal and conjunctival hemorrhages nearly always occur along with severe injection of the corneal vessels. There is a redness periorbitally and over the cheekbones which is apparent even over the so-called "sunburn flush". There is no pericral blanching and rarely herpetiform rash. However, dermographism is present and a slight edema of the face results in a characteristic vapid or stupid expression. Edema of the limbs is sometimes marked, but most often slight or inapparent.

Headache, nausea, vomiting, thirst, muscle and joint pains, insomnia, and signs of cerebral damage may occur throughout the course of the disease but usually increase in severity shortly after defervescence. Paroxysms of hiccoughing are common and temporary myopia frequently occurs. The

tongue usually has a thin yellow coating and there is an unpleasant odor to the breath. Constipation and diarrhea may be alternately present or completely absent from the clinical picture. The pulse is relatively slow, but in serious cases, tachycardia develops. The blood pressure drops just before and after the temperature starts to decline. There is very little tendency to diaphoresis and, although there is no inflammation of the pharynx, the patient frequently complains of painful deglutition.

In more severe cases, hemoptysis, hematemesis, hematuria, and melena may appear. No organ system is spared in the hemorrhagic diathesis characteristic of this disease. Extensive renal involvement may lead to anuria and uremia and intensified cerebral symptoms may cause delirium, stupor and coma.

Under more favorable circumstances, there is a general and gradual change for the better. The hemorrhagic eruption and the characteristic albuminuria first disappear and then the nausea, vomiting, and hiccoughing soon follow. The patient makes a complete recovery in about two weeks after the onset of the disease and there is usually absolute freedom from residual manifestations. However, in some cases, low-grade fever, palpitation, insomnia, anoxemia, and slight hemorrhagic tendencies may reappear in cycles after the patient has made an apparent recovery.

Temperature: The fever usually lasts from 2 to 7 days, but averages 5 to 6 days. It reaches its peak (104 to 105°F) on about the 3rd day and then gradually falls to normal by the 5th or 6th day. In most cases, as the fever drops, the general symptoms worsen and there is very little sweating during the pyrexial period.

Circulatory System: The systolic pressure drops just before and after defervescence, thus lowering the pulse pressure. In severe cases, the radial pulse is almost imperceptible, especially when the fever drops. The heart is slightly enlarged during and just following the pyrexial period. The heart sounds are weak and a soft systolic murmur is heard at the apex. The EKG shows myocardial degeneration when taken at this time. After recovery, there is usually a slightly elevated blood pressure.

Respiratory System: The respiration is usually normal throughout. In the end stages of serious cases, dyspnea and tachypnea are present. The appearance of severe hemoptysis is an unfavorable prognostic sign.

Facies: Slight edema of the face results in the characteristic vapid or stupid expression of the patient. There is a redness periorbitally and over the cheek-bones, but no perioral blanching.

Skin: Dermographism is present. Petechiae occur on the neck, anterior and posterior axillary folds, thorax, and upper arms. These may frequently take the form of linear striations and may not be very marked. The face and neck may appear flushed. The Rumpel-Leede phenomenon is positive for 2 to 3 days, but may be seen throughout the course of the disease in more severe cases.

Eyes Subconjunctival hyperemia and hemorrhage are associated with

chemosis. The tiny hemorrhagic spots in the iris surrounding the pupil seen in Weil's disease are not apparent in epidemic hemorrhagic fever. However, the outer vessels of the iris are injected. There is a temporary myopia at this time. Papilledema may be present, but there is rarely fundal bleeding.

Digestive System: There is anorexia, nausea, and vomiting from the beginning. The patient complains continually of thirst. The epigastrium is tender and sore. Severe abdominal pain may be present throughout or when the fever drops. This pain may be as intense as the pain of renal colic. Hematemesis and melena appear in serious cases.

Liver and Spleen: Hepatomegaly and splenomegaly are not characteristic. Clinical jaundice is rare. It is difficult to measure the extent of liver function because of the severe disturbances in the kidneys.

Nervous and Skeletal Systems: There is not especially severe pain in the limbs (scurvy) or in the back (purpura variolosa) or in the joints. There is no opisthotonus (cerebrospinal meningitis). Calf myalgia is rare (Weil's disease). The tendon reflexes are non-specific, being either increased or decreased. Severe hyperesthesia is not present, but increased olfactory sensitivity is noticeable.

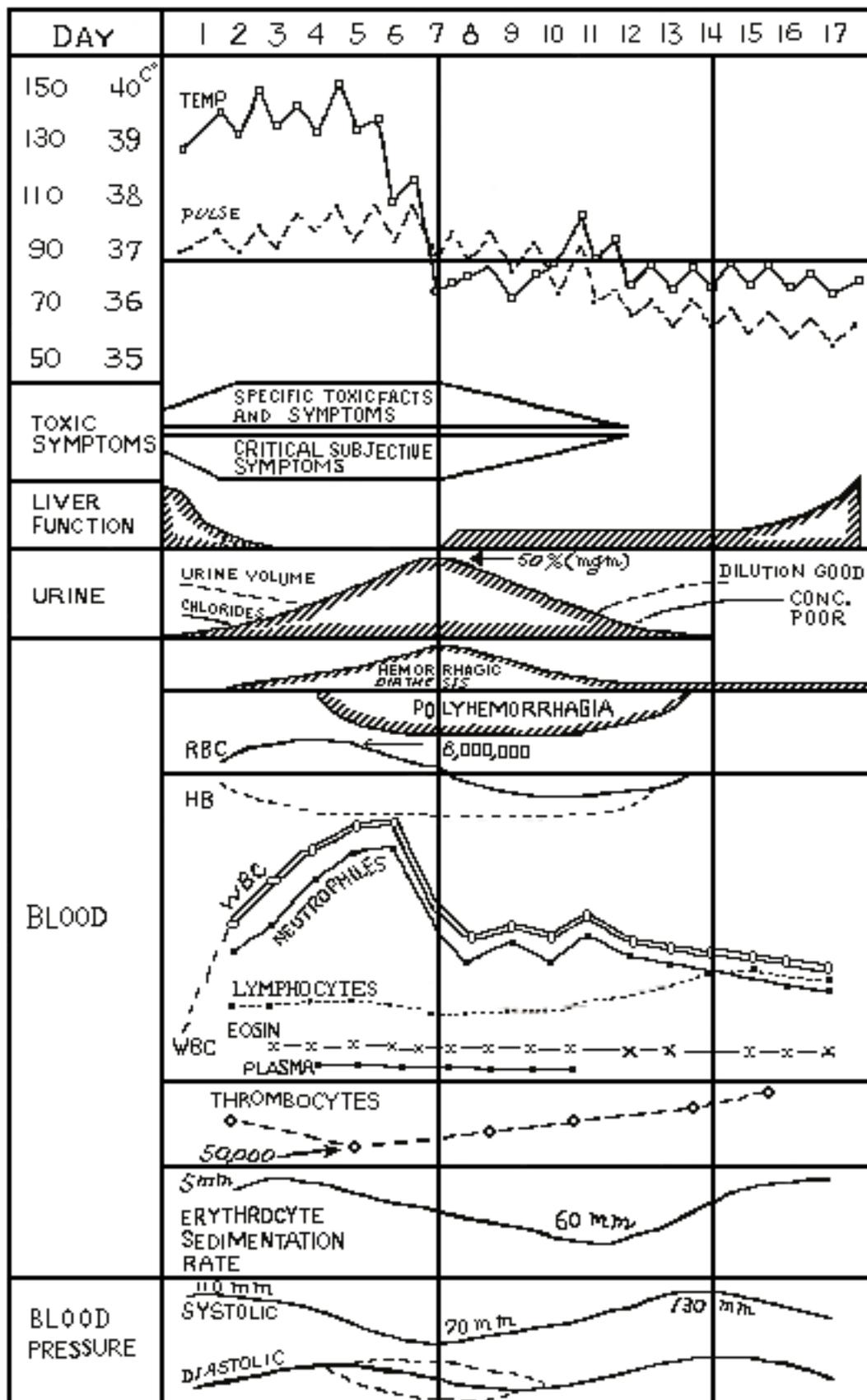
Tongue and Throat: The tongue has a thin yellow coating and the breath is unpleasant. Although the pharynx is not injected, the patient frequently complains of painful deglutition.

## Laboratory Findings

Urine: There is marked oliguria during the period of defervescence which may result in anuria in the more serious cases. Albuminuria is a constant finding from about the 3rd day and may reach above 10mgs%. The specific gravity is low and the chlorides are reduced. Gross hematuria is seen at times, but blood almost always appears microscopically. The sediment consists mostly of RBC, WBC, all types of casts, epithelial cells, and usually fibrin. Coagulation of fibrin may cause severe dysuria. The special casts (Sic), floccular material, and spirochaetes of Weil's disease are not found. The reaction is acid. The diazo, urobilinogen, and urobilin tests are irregular and not specific. However, the indican reaction is strong and the PSP excretion test is noticeably disturbed. With recovery, the urine volume increases, the albumin decreases, and the concentrating power, which had dropped, returns to normal. There are no signs of residual chronic nephritis.

Blood: The RBC are increased in the beginning of the disease, but are later decreased as the hemorrhagic diathesis takes place. The Hb follows the pattern of the erythrocytes and the color index remains at 1.0. Nucleated erythrocytes are present.

In the beginning of the disease there may be a leukopenia. Severe cases show a decrease to 2300 per cmm. Then there is a true leukemoid



From: Ibuki: Report of a special committee on the investigation of Epidemic-Hemorrhagic Fever, Army Publication, 31 Jan 43.

leukocytosis, sometimes reaching 88,000 per cmm. However, some slight cases show no leukocytosis at all. The polymorphonuclear neutrophils show a marked shift to the left with the appearance of myelocytes and myeloblasts. The granulocytes show noticeable vacuolar degeneration. Eosinophiles are present throughout the course of the disease and the lymphocytes and large monocytes show changes typical of any acute infectious disease. Large plasma cells increase extraordinarily during the fastigium of the disease. Thrombocytes decrease from the beginning and by the 4th or 5th day reach a low point of 16,000 to 40,000 per cmm.

The sedimentation rate is not increased in the beginning, but by the afebrile period, there is a slight increase. In moderate cases it returns to normal by the 3rd week.

During the febrile and at the beginning of the afebrile periods, the maximum and minimum resistance (erythrocyte fragility) are both slightly decreased. The bleeding time varies between increase and decrease. The clotting time is normal or slightly increased. The clot retraction time is prolonged during the fastigium of the disease.

Blood Chemistry: The reduceable vitamin C is slightly decreased. The prothrombin time has a tendency to increase slightly. Serum bilirubin does not show a noticeable rise. Blood protein is reduced, but increases during recovery. The A/G ratio is usually within normal limits and the fibrinogen remains normal. The NPN increases to 200 to 300 mg% in severe cases. The blood chlorides show an early decrease. The pH is below normal (7.1).

Serology: The Weil-Felix is usually negative, but there may be some positive reactions. Some patients show a weakly positive Wasserman.

Cerebrospinal Fluid: The CSF generally remains clear and under normal pressure even in the face of cerebral symptoms. However, there is a tendency to xanthochromia and the pressure sometimes increases to 200-300 mm. The Takada-Ara test is usually positive during the fastigium.

#### DIAGNOSIS:

Epidemic hemorrhagic fever should be considered in any individual in an established or suspected endemic area presenting with acute onset of chills, fever, anorexia, and vomiting in association with the subsequent development of a petechial rash about the neck, chest, upper arms, and anterior and posterior axillary folds. Subconjunctival and corneal hemorrhage, hiccupping, albuminuria, and leukemoid leukocytosis in the presence of eosinophilia and nucleated erythrocytes would further lead the clinician to suspect this disease. The dissociation between febrile peak and the fastigium of the disease is also characteristic, as is the later development of hematuria, hemoptysis, hematemesis, and melena.

#### PROGNOSIS:

In general the prognosis is poor if there is bradycardia and hypo-

tension at the beginning of the eruptive period (3rd Day). Persistent hiccoughing is also a bad prognostic sign and cases developing frank pulmonary hemorrhage or severe cerebral symptoms nearly always have a fatal termination.

The case fatality rate in Songo fever was reported as 11%, in Korin fever as 14.7%, and in Nidoko disease as 14%. The average mortality from epidemic hemorrhagic fever, therefore, can be estimated at 13.2%. However, Ibuki estimates that the overall fatality in the Japanese cases was closer to the vicinity of 16%.

#### DIFFERENTIAL DIAGNOSIS:

Leptospirosis: The incidence of Weil's disease is exceedingly rare in Manchuria and Korea. The characteristic calf myalgia associated with this disease is not seen in epidemic hemorrhagic fever. Ordinary strains of leptospira may nearly always be seen in the urine by darkfield microscopy and be readily identified in tissue preparations. The mortality from anicteric leptospirosis is nil.

Relapsing Fever: In the absence of the secondary or recurrent bout of fever in Borrelia infections, it is most certainly a diagnostic possibility, particularly in view of its frequently hemorrhagic tendencies and of its great incidence in Manchuria and Korea. However, the organisms are readily found in blood smears, there is no noticeable thrombocytopenia, and the skin appears to be dirty-yellow and sweaty. There is no diaphoresis during the crisis in epidemic hemorrhagic fever as there is in relapsing fever.

Other diseases presenting common symptoms are:

Typhus  
Typhoid  
Atypical Scarlet Fever  
Scurvy  
Hemorrhagic Purpura  
Malignant Thrombocytopenia  
Hemophilia  
Anaphylactoid Purpura  
Subacute Bacterial Endocarditis  
Purpura Fulminans  
Purpura Variolosa

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