The Hemorrhagic Fevers of Southern Africa
with Special Reference to Studies in the
South African Institute for Medical Research

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In this review of studies on the hemorrhagic fevers of Southern Africa carried out in the South African Institute for Medical Research, attention has been called to occurrence of meningococcal septicemia in recruits to the mining industry and South African Army, to cases of staphylococcal and streptococcal septicemia with hemorrhagic manifestations, and to the occurrence of plague which, in its septicemic form, may cause a hemorrhagic state.

"Onyalai," a bleeding disease in tropical Africa, often fatal, was related to profound thrombocytopenia possibly following administration of toxic witch doctor medicine. Spirochetal diseases, and rickettsial diseases in their severe forms, are often manifested with hemorrhagic complications. Of enterovirus infections, Coxsackie B viruses occasionally caused severe hepatitis associated with bleeding, especially in newborn babies.

Cases of hemorrhagic fever presenting in February-March, 1975 are described. The first outbreak was due to Marburg virus disease and the second, which included seven fatal cases, was caused by Rift Valley fever virus. In recent cases of hemorrhagic fever a variety of infective organisms have been incriminated including bacterial infections, rickettsial diseases, and virus diseases, including Herpesvirus hominis; in one patient, the hemorrhagic state was related to rubella. A boy who died in a hemorrhagic state was found to have Congo fever; another patient who died of severe bleeding from the lungs was infected with Leptospira canicola, and two patients who developed a hemorrhagic state after a safari trip in Northern Botswana were infected with Trypanosoma rhodesiense. An illness manifested by high fever and melena developed in a young man after a visit to Zimbabwe; the patient was found to have both malaria and Marburg virus disease.

"Ex Africa, semper aliquid novi," is quoted so often that it sounds trite, yet recent findings have confirmed that the statement is as true today as when Pliny wrote it about two thousand years ago. Pliny, quoting the Greeks, was referring to animals gathered at water holes in the desert whose mixing, it was surmised, gave rise to new and strange hybrids. Today is applies to viruses. In the last decade and a half, several hitherto unrecognized viruses have been identified in Africa south of the Sahara, causing alarming outbreaks of disease associated with high mortality. Because of their potential, in this jet age, for spread far afield and their danger to the medical and nursing staff caring for patients with these infections, they have aroused worldwide interest.

The South African Institute for Medical Research has been concerned in the study of these outbreaks. The Institute was established in 1912 to undertake research into diseases prevalent in Southern Africa, especially those affecting the Witwatersrand

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gold-mining workers who were particularly liable to pneumonia and meningitis. Sir Spencer Lister discovered that there were several serological types of pneumococci, a fundamental finding on which was based the production of pneumococcal vaccines used on a large scale to protect the miners.

It was also found that there were several serological types of meningococci. Vaccines were prepared but not used extensively at that time. Meningococcal infections became a serious problem in the early stages of World War II when the South African Army was being mobilized. Outbreaks occurred in most camps, manifesting often as a fulminant septicemia with a profuse purpuric rash. At the Ladysmith Military Camp in 1940 it was shown that “sulfa” drugs, as well as being lifesaving in cases of meningitis, eradicated the infection when administered to the entire military complement.

The value of mass chemoprophylaxis was later confirmed in the United States. Many cases of staphylococcal and streptococcal septicemia proved fatal until the introduction of penicillin opened a new era in the treatment of many bacterial infections.

Plague, endemic in rural areas of South Africa, periodically has given rise to epizootics affecting gerbils, the natural reservoir of the infection, and has often caused outbreaks of human cases. Some patients developed septicemia associated with a hemorrhagic state; many had pneumonia and were the starting focus of clusters of pneumonic plague cases. In one Eastern Cape Province outbreak, all 22 individuals on an affected farm died of pneumonic plague. Since then, the therapeutic effectiveness of sulfadiazine and streptomycin and the tetracylines in treatment has been established and plague is no longer the highly fatal disease that it once was.

Among exotic conditions investigated at this time was “onyalai,” a bleeding disease originally described as occurring in tropical Africa. Many patients were admitted to the Johannesburg Hospital with oral lesions associated with profuse bleeding. Patients often died from acute blood loss or cerebral hemorrhage. Once bleeding stopped, recovery was rapid. In several patients such symptoms followed ingestion of witch doctor medicine; profound thrombocytopenia was a characteristic feature and “onyalai” was considered to be a form of thrombocytopenic purpura secondary to exposure to an unidentified toxic constituent in the diet or medicine.

Relapsing fever was once widespread in South Africa and during World War II outbreaks occurred in several military camps. Many patients developed a severe form of the disease associated with hepatic abnormalities and a hemorrhagic state. On the other hand, relapsing fever is a cause of tropical thrombophlebitis which sometimes involves the visceral and cerebral veins. The infection has now been virtually eliminated from South Africa but remains endemic in Central Africa.

In the early years of this century a condition known as black fever associated with a high mortality rate was prevalent in rural districts of South Africa. The name was derived from the black appearance of the tongue and skin associated with petechial hemorrhages. Following introduction of the Weil Felix test in 1918 it was shown that this condition was typhus fever. Studies since then have revealed that four rickettsial diseases—epidemic louse-borne fever, endemic murine flea-borne typhus, the variety of tick-borne typhus known as tick-bite fever, and Q fever—are endemic in South Africa. Following the introduction of long-acting insecticides, louse-borne typhus fever has become a minor problem. However, tick-bite fever remains wide-
spread; usually mild, the illness is more severe in elderly patients and may be complicated by a hemorrhagic state. Q fever is also common and several cases of rickettsial endocarditis manifesting with petechial hemorrhages have been identified.

Coxsackie B viruses have been found to cause severe infections, especially in newborn babies, associated with severe myocarditis, fulminating hepatitis, and a fatal hemorrhagic state.

The classic prototype of a viral hemorrhagic fever is yellow fever, a disease feared for centuries. In the islands of the Caribbean Sea, epidemics often claimed thousands of lives, especially in military camps, as vividly described in the autobiography of Sir Harry Smith who took part in the Peninsular War. In describing a voyage to Jamaica he wrote, “Soon after we landed, the crew, all but one man, an old German carpenter, died of yellow fever and in the harbour commenced one of those awful visitations to the islands which swept off hundreds. The disease spread to our troops to an appalling extent. In six weeks we buried 22 officers and 668 soldiers. I resolved to move the 84th from Fort Augustus to bivouac at Stony Hill... So soon as they were ready I marched the Corps and from that day the yellow fever ceased.” The camp in the hills of Jamaica still stands as a monument to the intuitive wisdom of this great soldier.

As is well known, the conquest of yellow fever began when the United States Army Commission showed that the disease was caused by a filter-passing agent transmitted by the mosquito Stegomyia fasciata. Eradication of this mosquito resulted in elimination of yellow fever from Cuba and then from the “seed beds” in the big urban centers in tropical America. Later it became apparent that yellow fever was endemic in the forests and there was no hope of eradicating the infection by mosquito control.

Fortunately, at this time, a team led by Dr. Max Theiler (a South African) and Dr. Hugh Smith, in the laboratories of the International Health Division of the Rockefeller Foundation, succeeded in producing the 17D strain vaccine. The successful use of this vaccine has removed the threat of yellow fever from millions of people living in tropical America and tropical Africa. However, its administration has not been free from risk. During World War II an epidemic of yellow fever occurred in the Sudan, a region where military operations were about to be undertaken by British and South African Armies against the Axis forces in Abyssinia. There was urgent need for yellow fever vaccine to protect the troops, and its production was undertaken by the South African Medical Corps. In 1942, one of the officers of this Corps was seconded to the laboratories of the International Health Division in New York to take part in the investigation of the outbreak of hepatitis which affected the soldiers of the United States Army following the administration of yellow fever vaccine. There were about 30,000 cases, with about 100 deaths and many of the severe cases manifested hemorrhagic tendencies. The source of the infection was traced to the human serum ingredient of the vaccine. It was also found there was an antigenic component in the acute phase serum of patients which reacted in the precipitin test with a component, presumably an antibody, in the convalescent phase serum. This antigen seems identical to that later described and called the “Australia antigen.” It was suggested then that chronic hepatitis following on the acute attack in some cases resulted from an auto-allergic reaction involving liver cells which had been made antigenic by the virus infection. This was one example of what it was suggested should be called the hyper-reactive auto-allergic diseases. Other examples were to be found in every system and one of interest in the present context is immunothrombocyto-
penic purpura. Since then the validity of this hypothesis of the pathogenesis of many hitherto obscure conditions has been confirmed in other studies.

Following on the success with yellow fever, the Rockefeller Foundation decided to extend studies to arthropod-borne viruses in general. After discussions with Dr. Theiler, then Director of the laboratories of the International Health Division, and Dr. Smith, it was decided to support a unit in South Africa in the laboratories of the Poliomyelitis Research Foundation.

Under the auspices of this unit a serological survey was undertaken, which indicated that yellow fever did not occur south of the Zambesi and Cunene River valleys, and that over 30 mosquito-borne viruses were prevalent in South Africa. These included Rift Valley fever, Wesselsbron, and chikungunya viruses. The last agent, originally identified in Tanzania and in South Africa, has been incriminated as an important cause of hemorrhagic fever in India.

**RECENT CASES OF HEMORRHAGIC FEVER**

In 1975, the staff of the South African Institute for Medical Research undertook investigation of cases of hemorrhagic fever which presented in February and March of that year. The first episode involved two Australian students, MH and DO, who were on a holiday visit to South Africa. After a tour through Rhodesia, MH became ill in Natal and on his return to Johannesburg was admitted to hospital where he developed a hemorrhagic state from which he died. Then his traveling companion, DO, and a week later a nursing sister, MC, who had cared for MH and DO, became ill, but both recovered. In considering the diagnosis, a list of possible causes was drawn up and most could be excluded on clinical grounds. Laboratory studies performed in the United States identified the disorder as that of Marburg virus disease. Intensive studies to find the source of the infection are still in progress.

At the same time an extensive outbreak of Rift Valley fever occurred in South Africa. Seven fatal human cases were investigated; these patients developed a hemorrhagic state with profuse fatal gastrointestinal hemorrhage. Virus was recovered in mice inoculated with suspensions of the liver from three cases and identified as the virus of Rift Valley fever. In 1977 an extensive epizootic of Rift Valley fever in Egypt was associated with an epidemic affecting the human population; thousands of cases developed, and several hundred deaths occurred.

Cases of hemorrhagic fever now attract attention with increasing frequency and the help of the staff of the National Institute for Virology is often requested to determine their etiology.

**BACTERIAL INFECTIONS**

The most frequent cause of hemorrhagic fever remains the bacterial infections of which the most common is meningococcal septicemia. Several patients with staphylococcal septicemia were also investigated. One such patient, a 26-year-old female school teacher in Beira, Mozambique, received medication, later found to be barbiturates, for the relief of pain after dental work. She developed fever and petechiae, some of which coalesced into blood blisters. The patient was flown to Johannesburg and admitted to the Fever Hospital as a suspected case of hemorrhagic fever. Hematologic studies revealed a leucocyte count of about 1,000 with few neutrophil leucocytes present. Cultures of blood and blister fluid gave profuse growths of *Staphylococcus aureus*. She responded well to antibiotic treatment and her agranulocytosis, presumably the result of the administration of barbiturates, resolved.
RICKETTSIAL DISEASES

Several patients with tick-bite fever, all of whom were suspected of possibly having one of the severe African virus hemorrhagic fevers, were admitted to the Fever Hospital. All had a profuse hemorrhagic rash; two elderly patients developed gangrene of their fingers and toes. The diagnosis in these patients was made after their admission to hospital, and although desperately ill by that time, most responded well to treatment with tetracyclines. However, one patient was moribund and died soon after admission. The serious nature of these patients' illnesses emphasizes a need for early diagnosis which usually has to be based on clinical findings. In some patients, the presence of rickettsiae may be shown in skin biopsies by immunofluorescence techniques originally described by Dr. T.E. Woodward in the diagnosis of Rocky Mountain spotted fever and Q fever.

VIRAL DISEASES

A 34-year-old athletic man, who had been traveling through the northern Transvaal and the south coast of Natal, became ill with high fever and died soon after being admitted to the H.F. Verwoerd Hospital in Pretoria, where he developed a hemorrhagic state with severe bleeding from his mucous membranes. Herpesvirus was isolated from his urine and blood cultured in hospital and then from post-mortem organ specimens. Histologically there was extensive necrosis of the parenchymal cells of the liver which microscopically showed intranuclear inclusions typical of Herpes simplex virus infection.

A similar case involved a medical representative who had travelled through South Central Africa and was admitted to the Bloemfontein Hospital with a suspected diagnosis of African hemorrhagic fever. He, too, died soon after admission. The diagnosis of Herpesvirus infection was established, first by finding characteristic Herpesvirus particles on electron microscopy and subsequently by its isolation and identification in tissue culture. More recently, a woman in her sixth month of pregnancy was admitted to the Johannesburg Hospital in a hemorrhagic state from which she died and again Herpesvirus infection was identified in histological sections of her liver.

Herpes simplex virus infection is a well-known, often lethal infection affecting patients receiving immunosuppressive therapy or having immunodeficiency disorders. The occurrence of fatal cases in two previously healthy young men is somewhat unusual and suggests the infection may have been due to unusually virulent strains of virus.

Another patient, a 20-year-old Portuguese woman, was admitted to the Johannesburg Hospital a week after the onset of her illness in an incipient hemorrhagic state which then became full-blown. As she had been in contact with recent immigrants from Mozambique where a Lassa-like virus had been isolated from rodents, collected at Mopeia in the Zambesi Valley, she was placed in isolation with strict barrier nursing techniques. The patient eventually recovered, and laboratory tests showed an unusually high rubella antibody titer, suggesting that her illness was, in fact, rubella. However, liver biopsy revealed a picture of subacute active hepatitis. Patients with chronic active hepatitis have been found to have exceptionally high titers of antibody to rubella virus, the meaning of which remains an intriguing question.

During the extensive 1976 outbreak of Ebola virus hemorrhagic fever in the Sudan and Zaire and, similarly, during outbreaks of Marburg virus infection in Uganda and Kenya in 1980 and 1981, the help of the South African Institute for Medical
Research was requested for assistance in the investigation and the control of these infections.

Another case was that of a 13-year-old male camper who developed acute symptoms after spending a week in the western Transvaal; he had a high fever, developed a hemorrhagic state on the third day, and died on the sixth day after onset. A tick, identified as a species of Hyalomma, was found attached to his scalp. A provisional clinical diagnosis of Congo fever was confirmed by isolation of the virus in newborn mice inoculated with the patient's blood. Although known to occur in the tropical regions of Africa, this was the first identification of Congo virus as a cause of hemorrhagic fever in South Africa.

MISCELLANEOUS INFECTIONS WITH HEMORRHAGIC MANIFESTATIONS

1. A healthy young male, who had been swimming and fishing on an outing with his dogs, developed an acute illness, characterized by severe conjunctivitis, hepatitis, and pneumonitis associated with profuse hemoptysis, and acute respiratory distress syndrome from which he died. The cause of his fatal illness was found to be Leptospira canicola.

2. Two American visitors, after a safari trip through the swamps of Botswana, were admitted to the Fever Hospital with high fever and in an incipient hemorrhagic state. Their illness was due to Trypanosoma rhodesiense and responded well to specific treatment with Suramin.

3. Following a visit to Zimbabwe, an 18-year-old male developed an illness characterized by high fever and melena. Blood smears revealed the presence of malaria parasites, Plasmodium falciparum. In addition, laboratory studies demonstrated acquisition of immunofluorescent antibodies to Marburg virus between acute and convalescent phase serum samples. The patient had both malaria infection and Marburg virus disease and illustrates the difficulty in diagnosis of cases of hemorrhagic fever.

It is apparent from this account that the hemorrhagic state may result from a variety of infective agents, usually a severe infection with intense circulation of microorganisms and often extensive liver damage. Systematic consideration of the possible causes together with performance of appropriate laboratory tests usually have elucidated the etiology.

Many of these studies have been carried out in cooperation with the Yale Department of Epidemiology and Public Health. Indeed, this collaboration began during World War II and has continued to the present. The rubella unit in the laboratories of the Poliomyelitis Research Foundation was established with the help and advice of Dr. Dorothy M. Horstmann, a world-renowned authority on virus infections. More recently, the assistance of the Yale Arbovirus Research Unit was requested in the study of the Marburg virus outbreak in 1975 and most valuable advice was received; identification of this agent was carried out in the Center for Disease Control, which has now assumed responsibility for investigation of the dangerous African hemorrhagic fevers.