CRC Handbook of Viral and Rickettsial Hemorrhagic Fevers

Editor

James H. S. Gear

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PREFACE

Within the last decades a number of hitherto unknown viruses have come to light in Africa, once again emphasizing that the well-known saying "Ex Africa semper aliquid novi" ("Out of Africa always something new"), is as true today as it was when Pliny wrote it about 2000 years ago. Pliny, quoting the Greeks, was referring to animals gathered at the water holes in the desert whose mixing, it was surmised, gave rise to new and strange hybrids. Today it is true of viruses, and they are much more real than Pliny's hybrid animals. These viruses have caused alarming outbreaks of disease manifesting as hemorrhagic fever associated with a high mortality. Because of their danger to the medical and nursing staff caring for the patients with these infections and because of their potential in this jet age for spread far afield, they have aroused world-wide interest and concern.

The first of these outbreaks occurred in 1967 when the laboratory personnel in two medical institutions, one in Marburg, West Germany and the other in Belgrade, Yugoslavia, were affected after handling the tissues of vervet monkeys which had recently been imported from Uganda. Of the 25 patients involved, seven died in a hemorrhagic state and there were six further cases among the medical and nursing staff attending to them after hospital admission. Studies carried out in West Germany, Britain, and South Africa revealed that the illness of these patients was caused by a hitherto unknown virus now named the Marburg virus and classified as belonging to the newly created genus of *Filoviridae*. The disease it causes is now known as Marburg virus disease and there is little doubt that the human patients contracted the infection from the vervet monkeys or their tissues.

In 1975 the first outbreak of Marburg virus disease to be identified in Africa affected two Australian students in South Africa after a trip through Rhodesia (now Zimbabwe) and a nursing sister who attended to them both. The boy died of the infection, but both girls ultimately made a good recovery. Since then, several other cases of Marburg virus disease have been recognized in Uganda and Kenya. The source of the infection remains to be determined.

In 1969 the first case in an outbreak of an illness now known as Lassa fever affected a nursing sister attending to patients in a mission hospital at Lassa in northeastern Nigeria. She was flown to Jos on the central plateau to be nursed in the hospital, where she died. The nursing sister who attended to her contracted the infection and also died. A third nursing sister, who attended to the second affected sister, in her turn contracted the infection and was flown to New York where she was admitted to the Presbyterian Hospital. After a severe illness she recovered.

From her blood and from the blood collected from the two patients who died in Nigeria, a hitherto unknown virus, named after the village where the first case contracted the infection as Lassa virus, was isolated in studies carried out in the Yale Arbovirus Unit in New Haven by Dr. Jordi Casals and Dr. Sonja Buckley. During the course of his studies Dr. Casals was infected and became seriously ill, but after receiving a transfusion of convalescent plasma collected from Lily Pinneo, the third sister involved in the Nigerian outbreak, he finally made a good recovery.

Several months later a technologist working in the same department was infected, but having gone home for Thanksgiving weekend to Pennsylvania, his illness was not reported to the Yale unit until relatively late and he died of the infection. Clearly a highly virulent virus was responsible for these fatal cases and no further studies were carried out in the Yale unit. The work was transferred to a special high security laboratory in the Centers for Disease Control in Atlanta, Georgia. Since then, further studies have incriminated a common field rodent, the multimammate mouse, *Mastomys natalensis*, as the main reservoir of the virus in nature. This animal commonly enters huts and houses and so may readily transmit the infection to the inmates. It seems likely that many cases of illness, which notoriously

followed the traditional rat hunt undertaken after the floods have receded and the reeds have dried out, were cases of Lassa fever.

Investigations have revealed that this infection is prevalent in the countries of West Africa. Indeed, it has been shown to be one of the most common causes of illness requiring hospital admission among the people living there. Several times patients who have contracted this infection in West Africa have traveled by air to Europe, England, and North America, and have become ill either on their way or soon after arrival, posing the difficult problem of their hospital care, for which special provision has been made in many countries. The occurrence of these cases emphasizes the importance of continuing vigilance and surveillance of air travelers from the endemic regions.

In 1976 great concern was felt when reports of a serious outbreak of hemorrhagic fever were received from the southern Sudan and northeastern Zaire. The outbreak in southern Sudan was centered on the Maridi Hospital and the one in Zaire on the Yambuku Hospital. The most disturbing feature of these outbreaks was the very high death rate and the infection of the nursing and medical staff at the hospitals, many of whom died in a hemorrhagic state. Other outbreaks of this disease, now known as the Ebola virus disease, have since occurred in the same region, but the ecology of the virus, which has been shown to be closely related to the Marburg virus, remains to be determined.

In 1977, reports were received from Egypt of a widespread epizootic causing the deaths of thousands of domestic animals including cattle, buffaloes, sheep, goats, and camels. This epizootic was associated with a severe epidemic in human beings among whom many thousands of cases occurred with several hundred deaths. The cause of the epizootic and epidemic was identified as Rift Valley fever. This was the first time that this disease was identified in the present era in a north African country. Previously widespread epizootics associated with epidemics, as well as the occurrence of sporadic human cases, have only been reported from sub-Saharan Africa. The extension of the infection to North Africa suggests that Rift Valley fever may spread further afield, possibly into the countries of the Middle East and those bordering on the Mediterranean Sea and beyond.

These epidemics of severe, often fatal, virus disease manifesting commonly with a hemorrhagic state emphasized the importance of these exotic African viruses in causing hemorrhagic fever. However, the name hemorrhagic fever had been given previously to an illness which came to light when affecting American and Allied soldiers at the front during the Korean war. This illness, characterized by serious involvement of the kidneys and the development of a hemorrhagic state, became known as Korean hemorrhagic fever. In spite of intensive efforts to isolate its cause, it took many years before it was finally identified as a virus in the tissues of a field mouse of the genus *Apodemus*. It is now known that related viruses cause hemorrhagic fevers occurring in Asia and Europe, including the Scandinavian countries. Collectively these diseases are now grouped together as hemorrhagic fevers with renal syndrome.

Even before this, an illness affecting the Russian soldiers in the western Crimea during World War II was characterized in many of the patients by severe bleeding from the mucous membranes and into the skin. An infective agent was identified by Chumakov in the blood of patients by the inoculation of human volunteers, and later the virus was isolated and characterized by the inoculation of newborn mice. The virus so isolated was shown by Dr. Jordi Casals to be similar to the Congo virus isolated by Courtois in 1956 from a patient in Stanleyville, now Kisangani. Since then, this virus, the Crimean-Congo hemorrhagic fever virus, has been shown to be widespread in southeastern Europe, Asia, tropical Africa, and more recently in South Africa.

In 1953 to 1954 an illness characterized by fever and hemorrhagic manifestations affected farm workers on the Argentine pampas. The cause of this illness, now known as Argentine hemorrhagic fever, was identified in 1958 and has become known as the Junin virus. In

1959 a similar hemorrhagic fever was observed in Bolivia and from these cases the virus now known as the Machupo virus was isolated. These two viruses and the Lassa virus have been found to be related to the lymphocytic choriomeningitis (LCM) virus. They have similar characteristics and on electron microscopy the virions have dense granules resembling grains of sand, and together they form a group of the *Arenaviruses*.

All these infections have come to light in the last three decades, but for centuries before this, the best known of the hemorrhagic fevers, yellow fever, had become notorious for the epidemics it caused. It was especially feared by the early mariners from Europe on their voyages of exploration along the west coast of Africa, the Atlantic coast of America, and among the islands of the Caribbean Sea. They knew that if the disease broke out on board ship most of the crew would be infected and about a quarter of them would die. Epidemics of yellow fever often decimated the British and French garrisons on the Caribbean islands and at intervals swept the Atlantic coast of North America, claiming thousands of victims. The story of the conquest of yellow fever is one of the best known and most inspiring in the history of medicine. It began with the incrimination of *Stegomyia fasciata*, now *Aedes aegypti*, as the important vector of the virus by Walter Reed and his team of the U.S. Army Yellow Fever Commission. It culminated in the development of the highly effective 17D yellow fever vaccine by Max Theiler, Hugh Smith, and their colleagues in the laboratories of the Rockefeller Foundation of New York. It perhaps is not as fully appreciated that the methods and techniques developed in the studies of the yellow fever virus have been applied with success to the investigation and elucidation of many other virus infections and to the development of a number of other virus vaccines.

Although the means for controlling yellow fever are available, the disease still smoulders in tropical Africa and tropical America and still on occasion flames into epidemics, and thus still demands the attention of medical scientists and public health authorities.

The means for the treatment and control of the rickettsial diseases have also been developed, but in one form or another these infections still give rise to problems in most countries of the world. They too still merit the attention of physicians and those concerned with the public health, especially as they are important causes of the hemorrhagic state.

Although fever and hemorrhage are a striking feature of many cases of these viral and rickettsial infections, the hemorrhagic state may complicate a number of other infections including bacterial, spirochetal, and protozoal infections. When presented with a patient developing a hemorrhagic state the other conditions have to be considered carefully in the diagnosis. Many, indeed most, of these nonvirus conditions respond well to specific treatment, emphasizing the importance of an early and accurate diagnosis. In many cases the clinical findings give a clear clue to this, but in others it is only with the help of laboratory investigations that an accurate diagnosis can be made.

High security laboratories have been established in many countries to provide special facilities and safe working conditions for the staff engaged in the study of these diseases, which are emerging as important causes of morbidity and mortality in many regions of the world. There clearly is a need for a comprehensive account of the hemorrhagic fever viruses and the diseases they cause, as well as of the conditions which may simulate them. There is also a need for an account of the methods for their study and prevention. It is trusted that this handbook will help to meet this need.

THE EDITOR

Dr. James H. S. Gear, M.B.Ch.B., F.R.C.P. (London), D.P.H., D.T.M. and H., is honorary Professor of Tropical Medicine at the University of the Witwatersrand.

Dr. Gear graduated from the University of the Witwatersrand in 1929 and, after serving as a resident medical officer in the Johannesburg Hospital, joined the staff of the South African Institute for Medical Research where he has remained since, except for the war years of 1940 to 1945 when he served as Officer Commanding the Medical Laboratory Services of the South African Medical Corps.

He was granted the Diploma in Public Health at the University of the Witwatersrand in 1932 and the Diploma of Tropical Medicine and Hygiene at the University of London in 1933. He was then appointed Lecturer in Tropical Medicine in the University of the Witwatersrand in 1938.

During the war he was responsible for the courses in Tropical Medicine given to the medical officers of the South African Medical Corps and to the medical officers of the Royal Navy serving east of Cape Town.

He was appointed Honorary Professor of Tropical Medicine in the University of the Witwatersrand in 1960. He was appointed Deputy Director of the South African Institute for Medical Research in 1950 and in 1960, Director. In 1969 to 1970 he was Visiting Professor of Tropical Health in the School of Public Health of Harvard University and in 1972 Visiting Professor in the Department of Medicine in the University of Maryland, Baltimore.

In 1953 he was appointed Director of Research of the Poliomyelitis Research Foundation, a position he held until 1976. In this Institution in addition to the studies of poliomyelitis, Coxsackie viruses, and other enterovirus infections, he was engaged in the study of the arbovirus infections and brought to light the occurrence of Rift Valley fever in southern Africa in 1951, calling attention to the first fatal cases of this disease in 1975. He led the team which reported the first outbreak of Marburg virus disease recognized in Africa and was responsible for the recognition of the first case of Crimean-Congo hemorrhagic fever in South Africa in 1981. He has since then taken a special interest in the hemorrhagic fevers occurring in Africa and has described his findings in a number of articles and papers.

Among other honors he was awarded the Chalmers Medal of the Royal Society of Tropical Medicine in 1949 in recognition of research of outstanding merit contributing to our knowledge of tropical medicine, in 1952 the Bruce memorial medal and lectureship of the American College of Physicians, and in 1959 the silver medal of the South African Medical Research Council. In 1977 he was awarded the Manson medal of the Royal Society of Tropical Medicine and Hygiene.

He is an honorary member of the Infectious Diseases Society of America, of the American Society of Infectious Diseases, the American Society of Tropical Medicine, and the American Veterinary Epidemiological Society, and is a foreign associate of the National Academy of Sciences, Washington, D.C.

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Introduction

CLASSIFICATION OF HEMORRHAGIC FEVERS

J. H. S. Gear

The name 'hemorrhagic fevers' refers to conditions characterized as the name implies by fever and hemorrhage. These have a diverse etiology and those of an infective origin may be classified according to the etiological agent responsible for their development. At present it is known that the hemorrhagic state may result from the circulation in the bloodstream of viruses, chlamydia, rickettsiae, bacteria, fungi, spirochaetes, and protozoa, and even, though rarely, helminths. The infections, which are well recognized as sometimes leading to the development of a hemorrhagic state, are listed in Table 1.

Although the hemorrhagic state may develop in a variety of infections, the term hemorrhagic fever has recently acquired a more specific meaning, referring to certain arthropod-borne and certain rodent-borne infections. These are listed in Table 2 and it is with these that the following chapters are mainly concerned.

The arthropod-borne infections have been classified according to the antigenic composition of the viruses based on the results of hemagglutination inhibition, complement fixation, and neutralization tests. More recently, with the development of monoclonal antibodies, it has been possible to identify subtypes and varieties of viruses within each type. The recent advances in sequencing RNA directly make it possible to compare directly the genomes of closely related viruses. The arthropod-borne viruses have been classified into the following groups: (1) Togaviridae; (2) Flaviviridae; (3) Bunyaviridae. The rodent-borne viruses include the Arenaviridae.

The family Togaviridae has recently been circumscribed by the elevation of the *Flavivirus* genus to the status of a family of the Flaviviridae.[1]

The name *Togavirus* refers to the envelope and is derived from the Latin 'toga' — a Roman mantle or cloak. The family Togaviridae now comprises four genera, namely, *Alphavirus* with 26 species, *Rubivirus* (one species), *Pestivirus* (three species), and *Arterivirus* (one species). The virions are spherical, 40 to 70 nm in diameter, and mature by budding of nucleocapsids through plasma membranes. The virus envelope carries surface projections associated with two proteins, E1 and E2, that are usually glycosylated. E1 is the functional hemagglutinin for *Alphaviruses*. The envelope encloses the spherical nucleocapsid (diameter 28 to 35 nm) with icosohedral symmetry. The genome is a single molecule of single-stranded RNA with a molecular weight of about 4×10^6. The gene sequence of the *Alphavirus* genus has been determined.

The family Flaviviridae, only recently created, comprises the genus *Flavivirus* which at present contains 65 related species and two possible members.[2] The virions are small enveloped RNA viruses (diameter 45 nm) with peplomers comprising a single glycoprotein E embedded in host-derived lipid and is associated with a membrane-like protein M which surrounds the RNA encased in the core protein C. The gene sequence commences 5'-C-M-E..... The single strand of RNA is infectious and has a molecular weight of about 4×10^6. It functions as the messenger. The replication strategy and the mode of morphogenesis are distinct from those of the Togaviridae which are slightly larger but morphologically similar in some respects.

Most species are arboviruses in the biological sense. They infect a wide range of vertebrate hosts, causing a variety of diseases including yellow fever and dengue. Epitopes on the envelope protein E induce monoclonal antibodies which react with type, complex, or group specificity measurable by hemagglutination-inhibition or neutralization tests. Transovarial transmission of some species occurs in arthropods and transplacental transmission occurs in some mammals.

Table 1
INFECTIONS SOMETIMES COMPLICATED BY A HEMORRHAGIC STATE

Condition	Causal Agent
Virus Infections, Common Virus Infectious Fevers	
Hepatitis A, B, non-A-non-B	Virus
Measles	Rubeola
German measles	Rubella
Chickenpox	Varicella
Vaccinia	Vaccinia
Herpes simplex	
Cytomegalovirus	
Infectious mononucleosis	Epstein Barr (EB) virus
Smallpox	Variola
Arthropod-borne virus infections	Refer to Table 2
Virus infections associated with rodents	Refer to Table 2
Chlamydial Infections	
Psittacosis, *C. psittaci*	
Rickettsial Infections	
Epidemic louse-borne typhus fever	*Rickettsia prowazeki*
Tick-borne typhus fever	*Rickettsia rickettsii*
Mite-borne typhus fever	*Rickettsia conorii*
	Rickettsia orientalis
Bacterial Infections	
Coccal	
Meningococcal septicemia	*Neisseria meningitides*
Staphylococcal septicemia	*Staphylococcus aureus*
Streptococcal septicemia	*Streptococcus pyogenes*
Bacterial	
Gram negative bacterial septicemia	*Pseudomonas* sp. *Klebsiella, Escherichia coli*
Septicemia plague	*Yersinia pestis*
Typhoid fever	*Salmonella typhi*
Anthrax septicemia	*Bacillus anthracis*
Fungal Infections	
Candidiasis[a]	*Candida albicans*
Histoplasmosis[a]	*Histoplasma capsulatum*
Spirochetal Infections	
Leptospirosis	
Weil's disease, infectious hepatitis, leptospirosis	*Leptospira icterohaemorrhagiae*
Swineherd's disease	*Leptospira pomona*
Canicola fever	*Leptospira canicola*
Relapsing fever	*Borrelia duttoni, B. recurrentis*
Protozoal Infections	
Malaria	*Plasmodium falciparum*
Trypanosomiasis	*Trypanosoma rhodesiense*
Toxoplasmosis	*Toxoplasma gondi*

[a] Only likely to develop in infections in immunosuppressed or immunocompromised patients.

Table 2
VIRUS HEMORRHAGIC FEVERS

Arthropod-Borne (Arbo) Virus Infections

Family	Genus	Disease
Togaviridae	Alphavirus	Chikungunya
		Sindbis
Flaviviridae	Flavivirus	Yellow fever
		Dengue types 1—4
		West Nile
		Congo fever
		Kyasanur forest
		Omsk
Bunyaviridae	Nairovirus	Crimean-Congo hemorrhagic fever
	Phlebovirus	Rift Valley fever

Rodent-Borne Virus Infections

Arenaviridae	Arenavirus	Argentine (Junin) hemorrhagic fever
		Bolivian (Machupo) hemorrhagic fever
Bunyaviridae	Hantivirus	Hemorrhagic fever with renal syndrome (Korean hemorrhagic fever)

Unknown

Filoviridae	Filovirus	Ebola virus disease
		Marburg virus disease

The *Flavivirus* genus includes several of the most important arboviruses causing hemorrhagic fever in human beings.

The family Bunyaviridae comprises over 200 viruses (serotypes, subtypes, and varieties) that infect vertebrates and/or invertebrates.[3] Four genera of viruses have been defined, namely *Bunyavirus, Nairovirus, Phlebovirus,* and *Ukuvirus*. The virions are mostly uniformly spherical, 80 to 110 nm in diameter, and possess a unit membrane envelope from which protrude polypeptide spikes 5 to 10 nm long. They have three helical nucleocapsids, often in the form of supercoiled circles, each consisting of a single species of single-stranded RNA, a major nucleocapsid polypeptide N, and in some cases a large polypeptide which may be a transcriptase component. The genome is composed of three species of RNA, L large, M medium, and S small, organized in end-hydrogen bonded structures. The viruses appear to mature primarily at smooth membrane surfaces and accumulate in Golgi vesicles and saccules. It has been shown that transovarial, venereal, and transstadial transmission in arthropods occurs in some members of the family.

Some viruses within a serogroup are capable of forming recombinant viruses by genome segment reassortment.

Transmission to vertebrates is usually by arthropod bite, but aerosol infection has been demonstrated in Rift Valley fever and transstadial transmission in Crimean-Congo hemorrhagic fever.

The name Filoviridae has been suggested to include the genus *Filovirus* of which the type species is the Marburg virus and the other member is Ebola virus.[4] Another proposal is that both these viruses be included in the rhabdovirus group. However, it has been noted that

Table 3
TRANSMISSION

Vector	Family	Genus
Mosquito-Borne		
Chikungunya	Togaviridae	Alphavirus
Dengue	Flaviviridae	Flavivirus
Rift Valley fever	Bunyaviridae	Phlebovirus
Yellow fever	Flaviviridae	Flavivirus
Tick-Borne		
Crimean-Congo hemorrhagic fever	Bunyaviridae	Nairovirus
Kyasanur forest disease	Flaviviridae	Flavivirus
Omsk hemorrhagic fever	Flaviviridae	Flavivirus
Rodent-Borne		
Argentinian hemorrhagic fever (Junin)	Arenaviridae	Arenavirus
Bolivian hemorrhagic fever (Machupo)	Arenaviridae	Arenavirus
Lassa hemorrhagic fever	Arenaviridae	Arenavirus
Korean hemorrhagic fever (hemorrhagic fever with renal syndrome)	Bunyaviridae	Hantivirus
Unknown		
Marburg virus disease	Filoviridae	Filovirus
Ebola virus disease		

the major features which distinguish these viruses from the rhabdoviruses are the particle length, the unique proteins and a central axial channel of diameter significantly smaller than that of the rhabdoviruses. The classification is still under review.

The virion contains one molecule of single-stranded RNA with a molecular weight of approximately 4.2×10^6. Purified virions contain at least five polypeptides with the basic pattern being the same for both viruses. The proteins are designated VPO, VP1, VP2, VP3, and VP4. In both viruses the VP1 is a glycoprotein and probably is the major component of the virion spikes since it is removed by bromelain treatment. Lipid solvents destroy viral infectivity. Sugar is a component of one virion protein. The infectivity of the virus is stable at room temperature, but is destroyed in 30 min at 60°C. The virus is also inactivated by UV and gamma irradiation — by 1% formalin and β-propriolactone.

By electron microscopy the virus particles are pleomorphic, appearing as long filamentous forms, sometimes with extensive branching or as U-shaped, V-shaped, or circular forms. The particles vary greatly in length up to 14,000 nm, but have a uniform diameter of approximately 80 nm. There are spikes on the particle surface approximately 70Å in length and 100Å from one another.

Immunofluorescent studies have revealed that there is little or no antigenic cross reaction between Marburg virus and Ebola virus. Laboratory animals immune to Marburg virus are not protected against Ebola virus infection.

Virus-infected cells contain prominent cytoplasmic inclusion bodies consisting of viral nucleoprotein material. These inclusion bodies consist of a finely fibrillar or granular ground substance which condenses into tubular structures or nucleocapsids. Budding of completed virions takes place at cell membranes into which virion spikes have been inserted.

Both viruses are indigenous to Africa and cause hemorrhagic fever in man. Both are highly virulent for humans and several species of monkeys. Strains of Ebola virus isolated in Zaire and Sudan differ in virulence for monkeys and mice, the former causing uniformly lethal infection, and the latter rarely resulting in fatality.

Arenaviridae — the lymphocytic choriomeningitis virus has been well known for many years. More recent studies have revealed that it is related to the Machupo virus, the cause of Bolivian hemorrhagic fever, and to other members of the Tacaribe complex, and more recently to Lassa virus from West Africa. These viruses are grouped together in the family Arenaviridae.[5]

Members of this family have spherical or pleomorphic virions with a dense lipid bilayer membrane bearing surface projection. On electron microscopy, dense RNA containing granules 20 to 30 nm in diameter are observed. The name arenaviruses (from *arenosus*, Latin for sandy) was chosen to reflect the characteristic fine granules seen in the virion in ultrathin sections. The RNA is single stranded and consists of four large and one to three small segments. Virions are formed by budding from the surface membranes.

The infectivity is ether, acid, and heat sensitive. Most arenaviruses have a single rodent host in which persistent infections occur. Among the members of this group which may infect human beings are the Junin, Machupo, and Lassa viruses which may cause hemorrhagic fever in man.

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