WHAT YOU HAVE NOT HAD THE TIME TO FIND OUT BUT WHAT YOU OUGHT TO KNOW ABOUT THE VIRAL HAEMORRHAGIC FEVERS

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'The Viral Haemorrhagic Fevers make up a group of distinctive nosological entities of diverse aetiology which show certain clinical manifestations and pathogenic mechanisms'. *Pub Hlth Rev IV*, No. 1, 39-68, 1975.

Some clinical conditions are characterised by bleeding tendencies and haemorrhagic manifestations from all natural orifices, from man-made puncture and incision wounds, and into the organs and tissues of the body.

The aetiological causes of these conditions are many, and this syndrome is the end result of a multi-factorial phenomenon which is arguably sketchily and incompletely known, though many plausible and logical explanations within the bounds of our present knowledge have been put forward, such as the damage to the vascular endothelial lining, effects on platelets, tissue cell destruction and liberation of active chemical substances, damage to the liver which is the biological factory of so many coagulation factors, damage to megakaryocytes the precursors of the platelets, toxic antigen-antibody complexes, activation of the complement cascade and of the coagulation/fibrinolysis systems simultaneously, and replication in mononuclear phagocytic cells of the reticulo-endothelial system.

Some haemorrhagic fevers are caused by bacteria, as was, for example, the Black Death, so called no doubt because of the skin discoloration produced in plague patients attacked by *Yersinia (Pasteurella) pestis*, and Weil's disease caused by a thin long filamentous spiral bacillus which is called, because of its cork screw shape and its patho-physiological effects, *Leptospira ictero haemorrhagiae*.

A more bizarre haemorrhagic condition with an unexpected and surprising cause is the newly discovered Haemorrhagic Syndrome of Altamira (HSA) which affects newly arrived immigrant settlers along the newly constructed Brazilian Trans-Amazon Highway.

This highway cuts across vast areas of primeval forest and goes through a wide variety of environments. Some of the settlers, along the sections of the highway opened up for colonisation, were stricken with ecchymoses and petechiae all over their bodies, with bleeding from gums and nose, and with meloena; the platelets were very low ($10,000 \text{ mm}^3$; $10.10 \times 10^9/1$); retraction of the blood clot was deficient and the bleeding time was markedly prolonged.

Footnote: This paper is the Preface reproduced here from a book to be published next year, under the auspices of the Army Medical Department, Ministry of Defence, entitled: Exotic New Diseases: A Review of the emergent African Viral Haemorrhagic Fevers.

This HSA is believed to be caused by an allergic reaction as a result of bites by black flies (Simuliidae).

Colonisation of this amazing transamazonian region is continuing apace, and it is to be expected that diseases, infections and infestations hitherto unknown will be discovered.

When a party of Bolivian army recruits were flown in 1967 from the mountain heights of La Paz to the lowland areas for military training they too were bitten by black flies and they developed haemorrhagic vesicular lesions and ecchymoses. This condition was at first suspected of being haemorrhagic Smallpox and later on a typical form of Bolivian Haemorrhagic Fever but it is known to be neither of these infections, and it has been named the Haemorrhagic Exanthem of Bolivia.

Equally dramatic and known for a much longer time than the 'new' conditions described above are the haemorrhagic manifestations induced by some venomous snakes.

However, the haemorrhagic conditions which concern us in this essay are the Viral Haemorrhagic Fevers (VHFs), a term introduced in medical literature by investigators in the Far East to cover the bleeding disorders that have a viral agent as their cause, though it is a curious and unexplained fact of medicine, both human and veterinary, that one of the oldest known members of the VHF group, namely Yellow Fever (Yellow Jack or Vomitos Negros, a reference to black vomited blood) while present in Africa and America is not found amongst the teeming millions of the inhabitants of Asia, nor in the non-human primates of that continent.

There are many viruses which can cause a VHF but the clinical pictures presented by the patients have much in common — thus we find fever, malaise, headache, generalised body pains and aches, nausea and vomiting, diarrhoea in the first few days and then the development of haemorrhagic manifestations seen in the full syndrome such as epistaxis, bleeding gums, haematemesis, haemoptysis, meloena, haematuria, bleeding from the uterine cavity, and petechiae, ecchymoses and haemorrhages in the skin. The worst afflicted patients slide into hypotension, irreversible shock, collapse, coma and death.

The reader will do well to take note of the fact that it is the tip of the viral disease iceberg that we see in VHF, and which is so dramatic and receives correspondingly the greater coverage in the professional medical press and publicity in the popular news media. Many persons, luckily for the human species, suffer a less severe illness or even a sub-clinical silent infection.

The spectrum of the clinical syndrome is similar, and so is the patho-physiology of VHFs. This statement is better expressed by reversing the sequence of these two sentences and observing that the patho-physiological mechanisms operating in VHFs and seen evolving in patients have the same common causative factors, from which it follows that the syndrome seen will be expected to be shared by all the VHFs, since it is after all the clinical expression and manifestation of these pathogenic mechanisms.

For the practical purpose of having some sort of orderliness when speaking

or writing about VHF, as well as to sift and sieve in one's own mind the possible aetiological agents when a patient is encountered with the signs and symptoms described above, it is convenient to categorise the VHF's according to their route of transmission such as mosquito-borne, rodent associated, tick-borne, respiratory route transmission, and unknown.

Mosquito Borne

(a) *Yellow Fever* has already been mentioned as an archetype of VHF's. It is the dreaded disease that, before the advent of one of our most effective viral vaccines, earned West Africa the nickname of The White Man's Grave.

'Beware my son the Bight of Benin
Whence few come out though many go in'.

The YF virus (a Flavivirus) circulates, in its ancestral strongholds in the high canopy of the tropical forests of Africa, between mosquitoes and monkeys. It has thus proved impossible to eradicate it, as it was once optimistically thought we could achieve, unlike the present position as regards smallpox which was declared eradicated in 1980 because it is believed that smallpox is a human disease and animal reservoirs do not exist.

The Yellow Fever virus-carrying mosquitoes (*Aedes* sp) were transported from Africa to the Americas as stowaways during that degrading period of man's history when slave trading between these two continents flourished to such an iniquitous extent; and thus Central and Southern America, in addition to Central Tropical Africa, became and remain enzootic areas.

Recent research incriminates ticks, (as well as mosquitoes) as possible natural vectors or reservoirs or both of the Yellow Fever virus. Because of their longevity and feeding habits on different hosts, including birds and bats, and transovarial transmission, these arthropods may play a considerable role in the perpetuation and transmission of the Yellow Fever Virus.

(b) *Dengue Fever* (DF) has been known for many years as break-bone fever and Dandy fever. It sprung into evil prominence in medical literature in the last two decades or so when it erupted as a severe Dengue Haemorrhagic Fever (DHF) in many South East Asian countries — the Phillipines, Burma, Thailand, Cambodia (Kampuchea), Indonesia, Malaysia, Singapore, Vietnam, Ceylon (Sri Lanka), India and in other places, e.g. Fiti Levu, the largest island in the Fiji Archipelago, and in other South Pacific islands. Since 1977 epidemics of DF have been reported recently from many islands in the Caribbean; to cite an example during the period June-October 1981 a total of 300,000 cases were reported in Cuba, 100,000 patients were hospitalised and 150 deaths occurred.

The Caribbean outbreaks probably led to the introduction of DF into Mexico in 1978. In the following year it spread northwards and 50,000 cases of DF were reported in 1980. Because of the extensive exchange of travellers and the prevalence of the mosquito vector (*Aedes aegypti*) in both Mexico and the USA the United States Health Authorities were not caught unawares when the first case of

the transmission of DF into continental territory since 1945 was reported from Texas in September 1980.

A feature attributed to the severe form of DHF, as compared with the less malignant DF, is that it has been thought to occur in patients who had already suffered another previous infection by a dengue virus of a different strain, with the result that the body suffers a gross immunological insult which results in a VHF. Recent work however suggests that it may also be possible to have a primary DHF without a previous infection by another heterologous dengue virus strain.

An interesting phenomenon has also been detected in dengue infections which may explain the pathogenesis of the severe forms of the infection as seen in infants. A serum factor (antibody) has been detected which is not helpful to the patient in that it acts as a virus enhancement factor helping the replication of the virus in the host's mononuclear phagocytes.

Thus in experimental work, monkeys who had been infected with Dengue Viruses type 1, 3 and 4, on subsequent challenge with Dengue Virus type 2 (D2V) actually produced more virions than non-immune monkeys, which were similarly challenged as controls. In vitro experimental work also shows that cultures of peripheral blood leucocytes were very permissive to the replication of dengue viruses if the virus enhancement factor was added to the culture medium.

Applying the knowledge of this phenomenon to affected infants, it can be surmised that in highly endemic dengue areas the mother will pass over to her offspring maternal virus neutralising antibodies, which will specifically protect the child in the early days of its existence, but whereas these protective antibodies will in the process of time wane to low titre and decay, the pathogenic virus enhancement antibody will still remain effective in high dilutions. Hence the affected infant will suffer a severer form of a primary infection on exposure than it would have suffered if it had not inherited any maternal antibodies.

Recent work also suggests that genetic susceptibility may be an important factor in the development of (Dengue Shock Syndrome); a positive association is seen for the histo-compatibility antigens HLA-A2, and a negative relationship is seen for HLA-B13.

(c) *Rift Valley Fever (RVF)* is, like DHF and DSS, another example of a VHF which is currently extending its domain as well as causing a more virulent haemorrhagic manifestation in human populations.

Originally observed in 1913, RVF broke out again in 1930 on a farm on the shores of Lake Naivasha in the Rift Valley in Kenya, where it killed and caused abortion of thousands of lambs and ewes. The massive necrosis of the liver, which was observed on examining the internal organs of the dead animals, earned it its descriptive appellation of Enzootic Hepatitis. On epidemiological investigation it was discovered that all those farm labourers who had handled the infected carcasses had suffered from a dengue-like disease characterised by fever, rigors, headaches and body pains.

Subsequently various epizootics occurred in East and South Africa which caused

great economic losses to those engaged in animal husbandry but an ominous feature began to emerge in 1975, when unusually heavy rains favoured the vector mosquito population explosion in South Africa, and this led to a very severe epizootic, as was to be expected. Animal handlers again suffered numerous casualties but for the first time haemorrhagic manifestations, especially gastro-intestinal haemorrhages, caused a number of deaths.

In 1977-1978, RVF appeared practically on the shores of the Mediterranean Sea, in the south eastern region of the Nile delta where a severe epizootic affecting sheep, goats, cattle and camels was reported for the first time ever. Man and beast in Egypt presented an ideal immunologically virgin population for the virus, and in the areas affected 70 to 95 per cent of the human population was infected with approximately 600 fatalities.

The vector incriminated in the Egyptian outbreak is a mosquito belonging to the *Culex pipens* complex. Man is infected either by a mosquito bite or by handling infected carcasses.

RVF was brought into Egypt possibly by the 60,000 camels which annually cross over from the Sudan through the eastern desert, without going into quarantine, or by viraemic persons, or even by haematophagous insects carried by wind currents northwards from the Sudan. It is feared that Egypt may become a stepping stone to further the spread of RVF to other areas of the Middle East.

In a letter to the Veterinary Record of the 2nd June 1979 (vol 104, p 511) a veterinary surgeon, Mr A. Shimshony, draws attention to the close parallel that seems to exist between this epizootic and epidemic of RVF in Egypt, believed to be the first time that the RVF virus has appeared in Egypt and affecting camels and cattle, mosquitoes and humans, with biblical events which happened 4,000 years ago and which are described so dramatically in Exodus, where it tells of the fourth plague of Pharaoh, i.e. a grievous swarm of flies appeared in the land of Egypt; followed by the fifth plague which afflicted cattle, horses, camels and sheep; and finally the last plague which afflicted the first born of both man and beast.

En passant, the reader will take note of the difficulties of differential diagnosis facing physicians in Africa. Dr Jeannette Troup detecting the new Lassa fever outbreak in 1970 at the tail end of an extensive Yellow Fever epidemic in northern Nigeria; and the eruption of Ebola Fever in south west Sudan in 1976 when an epizootic of RVF was in progress in a more northern area of the country.

Tick Borne

A tick borne VHF was discovered by Russian army physicians towards the end of World War II affecting agricultural workers in the Crimea (Crimean Haemorrhagic Fever = CHF). It was described as an acute epidemic febrile illness with severe haemorrhagic manifestations. Later it was observed in other areas of the USSR round the Black Sea and the Caspian Sea and even in the central Asia republics of Tadzhik, Uzbek and others and was called the Central Asian Haemorrhagic Fever.

Like Lassa Fever in West Africa, CHF had probably occurred unrecognised for many years! A Dr Menderer had described a fever a century before (1825)

occurring in southern Russia with features which included debilitating diarrhoea, severe copious bleeding, rash, ulcers in the mouth, cramp, convulsions and drowsiness.

CHF is a tick borne disease of considerable public health importance in East European countries and the USSR; the virus has a variety of hosts such as cattle, hedgehogs, horses, hares, etc.

In 1968 Dr Jordi Casals (one of the discoverers of the Lassa Fever virus two years later) found the CHF virus to be identical to another virus (the Congo virus), first isolated from two patients in 1956, which causes a similar infection to CHF in African countries (Zaire, Uganda, Kenya, Nigeria, Senegal). More recently (1976) yet another similar virus to these two has been found to be active also in Asia; a nosocomial outbreak struck down unsuspecting medical and paramedical personnel in Pakistan. Similar episodes have also been reported from Dubai (1979) and Iraq (1979), and in February 1981 the first patient suffering and dying from Crimea Congo Haemorrhagic Fever was reported from South Africa thus emphasising the wide distribution of the virus.

The pattern which this tick borne haemorrhagic fever takes of causing a VHF in three continents is rather unusual in its vast geographic extent, especially when compared with other area-restricted tick borne viruses of this group such as Kyasanur Forest Haemorrhagic Fever discovered in 1957 and Omsk Haemorrhagic Fever discovered in 1947, the former being found in the tropical forest of Shimoga District, Mysore State, Southern India and the latter in the Siberian steppes of Omsk and the Novosibirsk Oblasts in the USSR.

The cause of the widespread distribution of the tick borne CCHF has been attributed to migratory birds which act as hosts and vectors of ticks infected with this obviously very adaptable virus.

Rodent Associated

(a) As regards the rodent associated VHF I shall deal fully with all the aspects of Lassa Fever, which first came to light in 1969 in West Africa, in the first section of the book, of which this paper is the preface.

(b) An identical picture had been seen before on the other side of the Atlantic, in Argentina (1959) amongst the workers gathering the maize (mal de los rastrojos) near the town of Junin and a similar syndrome suspected at first to be a form of murine typhus (el tifu negro: black typhus) affected the rural workers in Bolivia (1959).

These two South American Haemorrhagic Fevers are called Argentine Haemorrhagic Fever (AHF) and Bolivian Haemorrhagic Fever (BHF) and are caused by morphologically identical but antigenically different viruses, the Junin virus and the Machupo virus, so named after a town in Argentina and a tributary of the Amazon in Bolivia respectively.

(c) One other infection which has a rodent reservoir is the haemorrhagic fever which affected the United Nations troops fighting in Korea during the spring

and summer of 1951 when more than 2000 casualties from this disease were affected. It was described and reported under many names such as Epidemic Haemorrhagic Fever, Korean Haemorrhagic Fever, Far Eastern Fever and other clinically descriptive titles such as Haemorrhagic Fever with Renal Syndrome (HFRS) and Haemorrhagic Nephroso-Nephritis (HNN) alluding to the marked kidney pathological process.

This Korean Haemorrhagic Fever (KHF), HFRS or HNN though new to 'western' doctors had been recognised many years before by Japanese and Russian doctors in Manchuria and Siberia. Following an acute onset with influenza-like symptoms, haemorrhagic signs appear about the third day, with subconjunctival haemorrhages and thrombocytopenia; albuminuria is detected on the fourth day, followed by hypotension on the fifth day which can lead to irreversible shock in about 1 to 10 per cent of cases. Benign or severe renal insufficiency is the rule for several weeks.

The syndrome was described in 1930 in the USSR but the disease obviously existed much earlier than this date.

There is a focus of HFRS in the Far East: Eastern Siberia, China, Korea and Japan. There is also a western focus which extends from the Urals, the Upper and Middle Volta, to Scandinavia (where it is known as Nephropathia Epidemica). The aetiology of the Balkan 'endemic nephropathy' in Yugoslavia, does not appear to have been clearly elucidated as yet: however the presence of HFRS infection has been reported from Yugoslavia, Czechoslovakia, Bulgaria, Romania, Hungary and recently (1981) in the villages of northern Greece close to the Bulgarian and Yugoslavian borders.

In an investigation on sera from parts of the world where HFRS has not been reported in man as yet, one serum specimen from Alaska and two from Bolivia were reported to be positive by the immunofluorescent antibody technique against the KHF antigens to a titre of 128, 128, and 256 respectively. Positive results were also found in Gabon and the Central African Republic! I am reminded of the reported finding of antibodies against the African Ebola Haemorrhagic Fever virus in serum samples from Central America by my Belgian confrere Dr G van der Groen and his co-workers.

In Korea HFRS has a seasonal incidence, the maximum number of cases occurring from October to December. In the USSR the disease is endemo-epidemic in some foci, and in these areas it constitutes the most important haemorrhagic fever, with several hundred cases a year.

It is of interest to note that Korean and Russian investigators have put forward the suggestion that this HFRS is transmitted by rodents' excreta without invoking the need of an arthropod vector. This would bring HFRS in line with the arenaviruses such as Lassa Fever and AHF and BHF. The epidemiological data point to direct or indirect contact with field mice and voles (the field mouse *Apodemus agrarius* in Asia and the bank vole *Clethrionomys glareolus* in Europe respectively; other species of these rodents have also been incriminated recently namely *Apodemus sylvaticus* and *Clethrionomys rutilus*) which excrete the virus in the urine, while these rodents show no signs of being affected by the virus infection,

just as is the case of Lassa Fever and the silent association of the Lassa virus with its wild life maintenance host, the multi-mammate rat.

A great deal of research has been done in ascertaining the epidemiological features and the aetiological agent of this VHF. The USSR research investigators using fluorescent antibody tests reported positive results in locating the responsible antigen in clinical and experimental specimens but they could not identify the virus agent.

The USA research groups, who studied this disease intensively as a result of the Korean war, reported no success in their efforts to isolate the aetiological agent.

The present method of diagnosis of this disease has been the result of the investigations and techniques adopted by Korean workers who used slices of infected lung tissue from the rodent *Apodemus agrarius coreae*, which will give a positive fluorescent antibody test when tested against sera obtained from HFRS patients. To isolate the virus the patient's specimens are inoculated intra-pulmonary or intra-muscularly into this common field mouse. The agent of HFRS does not cause an illness in the inoculated rodent but here again its replication in the animal's tissue can be demonstrated by immuno-fluorescent (IFAT) tests.

Recently the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) scientists working in collaboration with Korean investigators have found a suitable cell culture line (A-549) which can be persistently infected with the virus agent of HFRS.

It has proved difficult to characterise the aetiological agent of HFRS but it is known that it does not cross-react with members of the Arenaviridae family. Korean research scientists who have been in the forefront of research in this field, have examined by thin-section and negative-contrast electron-microscopy virus-infected A-549 cell cultures, and they have concluded that the morphology and the morphogenesis of the HFRS virus are compatible with those of the orbiviruses. The virus is registered as the Hantann virus; it has no serological relationship with orbiviruses, nor with any known virus. However, it has now (1982) been discovered that the cultures used by the Korean scientists were unfortunately contaminated and not pure cultures. Groups of workers in the USA and in the USSR are of opinion that the HFRS virus is a bunyavirus.

An incident somewhat similar to the European outbreak of Marburg virus disease in 1967, when African Green Monkeys were brought into the laboratories at Marburg, Frankfurt and Belgrade, occurred five years before in Moscow (1962) when a large number of rodents were brought into a laboratory where research was being conducted on tick-borne encephalitis. About ten days later the laboratory staff, and also visitors to the laboratory, started to fall sick with signs and symptoms of HFRS and in the succeeding four weeks 113 patients were diagnosed as having been infected.

Two episodes of a typical VHF (high fever, severe malaise, diarrhoea, renal damage, thrombocytopenia, rise in serum transaminases, and one case of disseminated intravascular coagulation) have been reported recently amongst the staff of an animal-house laboratory in a Japanese medical school (Tohoku University

School of Medicine); and this led to the awareness that outbreaks of HFRS had been occurring in Japanese medical schools and colleges for some years. No person to person transmission has occurred. The epidemiological investigations have traced all the infections only to personnel handling laboratory rats, many of which were subsequently tested and proved by IFAT to be infected with the agent of HFRS.

In recent years cases of HFRS have been recorded in urban areas of China, Japan and Korea. The reservoir in these cases appears to be the household rat, presumably infected by rodents from surrounding rural areas. Outbreaks in Japan which have occurred around a railway station and a port suggest that infected rodents may have been imported from abroad. Seropositive rats have also been detected in the USA!

Therefore to prevent artificial dissemination of this disease, against which we have no drugs or vaccines, it is recommended that rodents from enzootic areas should be handled with due care, that breeding should be controlled and that rodents should not be exported from the enzootic areas unless strict precautions are taken.

As an interesting aside it may be mentioned that blood taken from patients suffering from HFRS was in the past injected into patients in whom it was desired

Fig. 1

Fig. 2

Research scientists handling cultures of the deadly viruses, the agents of the Viral Haemorrhagic Fevers, must either physically contain the viruses in gas-tight negative-pressure biohazard safety cabinets or isolate themselves individually in plastic suits like astronauts carrying their own life support systems. The first method is used at our maximum containment laboratory Centre for Applied Microbiology Research (the Lassa Suite) at Porton Down, Salisbury and the second method at Fort Detrick, USA. Figure 1 shows scientists at the United States Army Medical Research Institute for Infectious Disease, Fort Detrick in individual protective suits.

The transport and management of patients suffering from Lassa Fever, Marburg-Ebola Fever, and other Viral Haemorrhagic Fevers, demand special professional training and techniques. The Royal Air Force aero-medical evacuation team based at the RAF Princess Alexandra Hospital, Wroughton, Wilts may be called upon to repatriate such a patient. Figure 2 shows personnel of the RAF medical team practising the aero-medical transportation of a VHF patient who is isolated in a plastic, flexible-film, negative-pressure tent, fitted with High Efficiency Particulate Air (HEPA) filters; the air transit isolator ready for loading into an aircraft.

to induce a feverish reaction as part of the medical management of certain psychiatric conditions.

Air Borne

The VHF's associated with the respiratory route of transmission are the very familiar viral diseases but encountered in their most virulent forms such as smallpox, vaccinia, measles, rubella etc.

Unknown

Two VHF's whose provenance is still unknown at the moment of writing (August, 1982) constitute the subject matter of the second section of the book to which this paper is the Preface.

Fig. 3

The VHF patient is transported to a specially designated hospital or an infectious unit in such a hospital where he is managed, nursed and treated in a flexible-film tent — the patient bed isolator — which is a larger version of the air transit isolator. These flexible-film isolators have been developed by Professor Trexler, a veterinary research scientist, and are manufactured and marketed by Vickers Medical Engineering Division, Basingstoke. Figure 3 shows the management of a patient in 'Trexler Tent,' which effectively isolates the patient and affords complete protection to the medical and paramedical personnel in attendance.