PAPERS AND ORIGINALS

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Outbreak of Marburg virus disease in Johannesburg

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Summary

The first recognised outbreak of Marburg virus disease in Africa, and the first since the original epidemic in West Germany and Yugoslavia in 1967, occurred in South Africa in February 1975. The primary case was in a young Australian man, who was admitted to the Johannesburg Hospital after having toured Rhodesia. Two secondary cases occurred, one being in the first patient's travelling companion, and the other in a nurse. Features of the illness included high fever, myalgia, vomiting and diarrhoea, hepatitis, a characteristic maculopapular rash, leucopenia, thrombocytopenia, and a bleeding tendency. The first patient died on the seventh day from haemorrhage resulting from a combination of disseminated intravascular coagulation and hepatic failure. The other two patients were given vigorous supportive treatment and prophylactic heparin and recovered after an acute phase lasting about seven days. During this period one developed pancreatitis, the serum amylase remaining raised until the 32nd day after the onset of the illness. The other developed unilateral uveitis after having been asymptomatic for two months. This persisted for several weeks and Marburg virus was cultured from the anterior chamber of the eye.

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Introduction

In February 1975 a young Australian man who had been hitch-hiking through Rhodesia died in the Johannesburg Hospital after an acute haemorrhagic, feverish illness. Shortly afterwards his travelling companion and then one of the nurses who had looked after him fell ill with the same disease. The girls recovered, and virological studies on all three showed that the illness was caused by the Marburg virus. The only previously described outbreak of Marburg virus disease occurred in 1967 in Marburg and Frankfurt, West Germany, and Belgrade.[1] Vervet monkeys (*Cercopithecus aethiops*) imported from Uganda for scientific purposes were the source of the infection, the primary patients all having had direct contact with blood, organs, or cell cultures from these animals. Secondary cases occurred among medical, paramedical, and lay contacts of the primary patients. In all, 31 people contracted the disease and seven of them died. The virus was isolated in laboratories in Germany, England, and South Africa and was shown to be different from all previously known viruses.[2-4]

The Johannesburg outbreak provided a unique opportunity to study the epidemiology of Marburg virus disease in its natural setting, and detailed epidemiological and virological reports will follow in due course. In this paper the clinical presentation in the three patients is described and is compared with that found in the previous epidemic. In addition, the rationale underlying the management of the two survivors is discussed.

Case 1

A 20-year-old Australian draughtsman was admitted to the Johannesburg

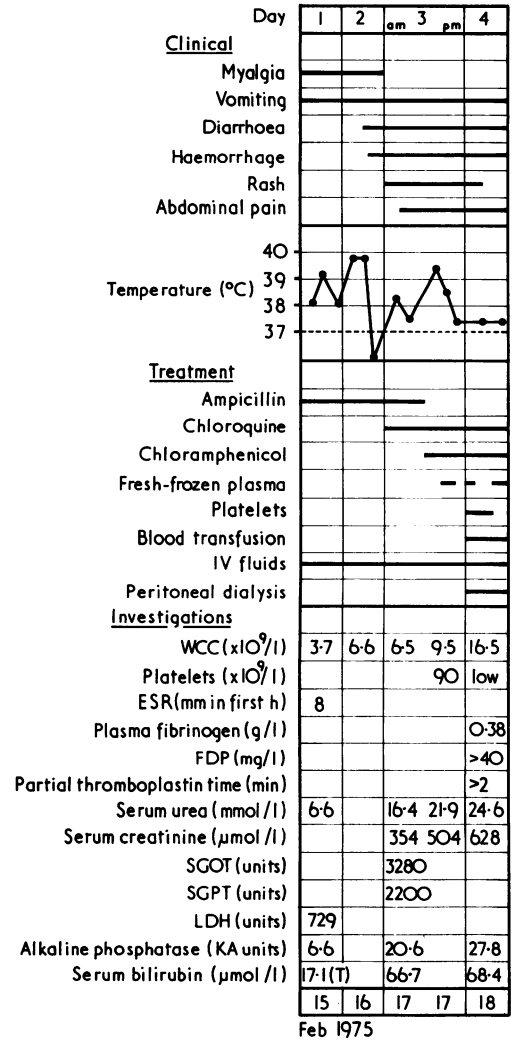

FIG 1—Clinical and laboratory data in case 1.

μmol/l (4 mg/100 ml) and the urea level to 16·4 mmol/l (99 mg/100 ml). WCC was 6·5 × 10^9/l and platelets were 90 × 10^9/l. SGOT and SGPT were 3280 and 2200 units respectively, alkaline phosphatase was 20·6 King-Armstrong (KA) units, and the serum bilirubin, which had been 17·1 μmol/l (1·0 mg/100 ml) on admission, was 66·7 μmol/l (3·9 mg/100 ml).

Despite the failure to find malaria parasites on repeated peripheral blood smears a course of chloroquine injections was begun. Atypical lymphocytes were present and some polymorphonuclear leucocytes showed the features of an acquired Pelger-Huët anomaly. These findings were thought to suggest a viral infection. Blood cultures and agglutination tests for typhoid fever, brucellosis, and rickettsial infections gave negative results. Stool examination

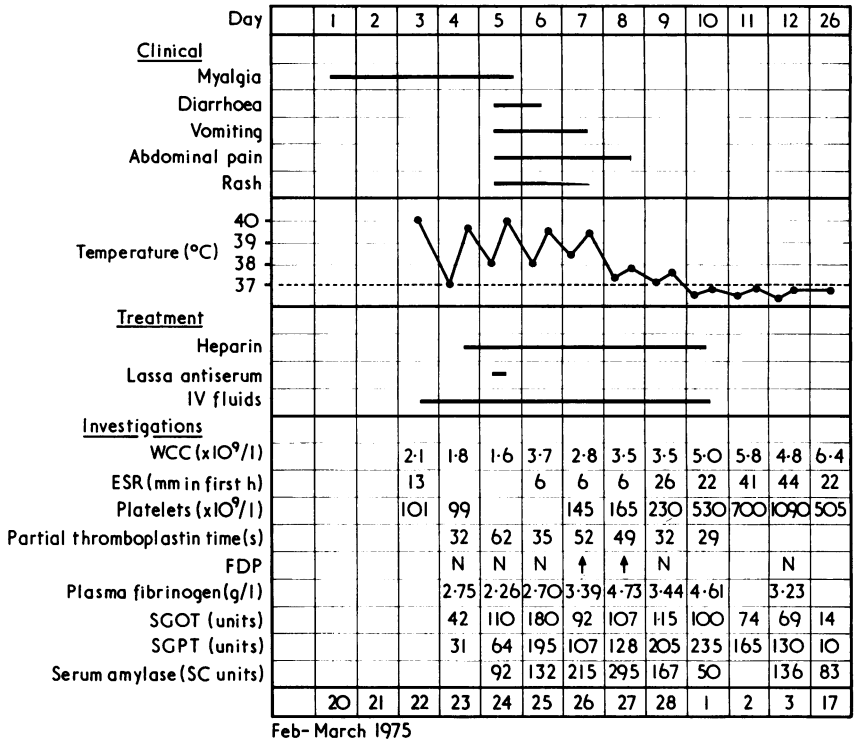

FIG 2—Clinical and laboratory data in case 2. For fibrinogen degradation products N = normal; vertical arrows indicate raised values.

Hospital on 15 February 1975 (fig 1). He had been ill for four days, complaining initially of malaise, rigors, and profuse sweating. Two days later frontal headache, nausea, and vomiting began, and on the day of admission he developed severe myalgia, which was generalised but affected mainly the lumbosacral region, and painful eyes.

During the first nine days of February he and his companion had travelled widely throughout Rhodesia, often by hitch-hiking, visiting Salisbury, Kariba Dam, Victoria Falls, Gwaai River, Bulawayo, Zimbabwe, and Beit Bridge. On their return to South Africa they visited Margate on the Natal coast, where the patient became ill. He had previously had good health.

Examination on admission showed an ill-looking young man with an oral temperature of 39°C, a pulse rate of 100/min, and a respiratory rate of 24/min. There was no pallor, cyanosis, or jaundice and the blood pressure was 120/70 mm Hg. The conjuctivae were injected and the throat showed the features of an acute pharyngitis. Slight lymphadenopathy was present in the left axilla. The lungs and heart were normal, the liver was not enlarged, and the spleen was not palpable. An erythematous, tender papule was present on the right flank. On direct questioning he remembered being stung or bitten by an unknown agent in that region six days before the onset of his illness while sitting on a roadside near Wankie. The rest of the examination showed nothing abnormal.

Investigations showed haemoglobin 13·2 g/dl; leucocyte count (WCC) 3·7 × 10^9/l; erythrocyte sedimentation rate (ESR; Wintrobe) 8 mm in the first hour; blood urea and serum creatinine levels normal; no malaria or trypanosomal parasites on peripheral blood smears; cerebrospinal fluid and chest *x*-ray films normal.

A provisional diagnosis of typhoid fever was made and treatment with intravenous ampicillin begun. Next morning severe watery diarrhoea without blood or excess mucus developed, and later that day the vomitus became obviously blood-stained. The temperature remained raised. During the next day the patient's condition deteriorated alarmingly. Profuse vomiting and diarrhoea persisted, and both vomitus and stools contained large amounts of blood. He complained for the first time of diffuse abdominal pain and was found to be lethargic and drowsy. A confluent, non-itchy, erythematous maculopapular rash appeared on the trunk, neck, face, and arms. At the time urinary output was low and the serum creatinine level had risen to 354 showed numerous bipolar Gram-negative rods compatible with, but not diagnostic of, *Yersinia pestis*. This together with the fact that the patient had visited an area in Rhodesia endemic for plague suggested the possibility of septicaemic plague. As neither plague nor typhoid fever was excluded at this stage chloramphenicol was added to treatment. Fresh-frozen plasma was given for the bleeding.

By the next morning bleeding from the bowel was life-threatening. The plasma fibrinogen was 0·38 g/l (normal 2·0-4·0 g/l),[5] fibrinogen degradation products (FDP; Thrombowellcotest) were over 40 mg/l (normal under 10 mg/l), activated partial thromboplastin time (PTT; Thrombofax) was longer than 120 s (normal 29-40 s), and the prothrombin index was 51% of normal. The findings were thought to be those of disseminated intravascular coagulation, probably aggravated by failure of synthesis of clotting factors by the liver. Fresh blood, fresh-frozen plasma, and platelet-rich infusions did not lessen the bleeding. He was now anuric with a serum creatinine of 628 μmol/l (7·1 mg/100 ml) and a urea of 24·6 mmol/l (148 mg/100 ml). Peritoneal dialysis was begun. That evening a massive haematemesis and haemoptysis was followed by cardiorespiratory arrest. Resuscitation was unsuccessful.

Necropsy confirmed the immediate cause of death as profuse gastrointestinal haemorrhage and bleeding into the lungs. The spleen and lymph nodes in the left axilla were slightly enlarged. The liver was pale but not enlarged. Microscopically the liver showed patchy but extensive degeneration of hepatocytes, most pronounced in the midzones of the lobules but also affecting the centrilobular and periportal areas. The affected cells showed severe eosinophilic change and eosinophilic masses resembling the Councilman bodies typically found in yellow fever. There was little fatty change, and clearly defined intranuclear inclusions were not prominent. Sections of the spleen showed relatively acellular pulp and depletion of the lymphocytes of the Malpighian corpuscles. Many lymphocytes showed pyknosis and fragmentation of the nuclei, and many round or oval bodies, possibly pyknotic fragments, and much nuclear dust were seen. Similar changes were noted in the lymph nodes. Kidney sections showed pronounced tubular necrosis and some fibrin deposition in the glomeruli.

Although the cause of the fulminant haemorrhagic illness was not known then, the clinical presentation, natural history, and liver histopathology, together with the fact that the patient had visited an area in Rhodesia where

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the rodent reservoir of Lassa fever, *Mastomys natalensis*, was known to be prevalent, raised the possibility that we might have been dealing with Lassa fever. When his travelling companion (case 2) became ill she was therefore looked after using the strict barrier-nursing techniques recommended by the World Health Organisation.[6] In addition, all the primary contacts of case 1 —35 doctors and nurses—were isolated in the Johannesburg Fever Hospital, and less close contacts were kept under daily surveillance.

Case 2

This patient, a 19-year-old girl, was the travelling companion of case 1. She had been at his side constantly from the onset of his illness until his death. Two days after he died she became ill with malaise, headache, and backache, mainly in the lumbosacral region. She had previously been well (fig 2).

The most striking finding on admission two days later (22 February) was a temperature of 40 C. Pulse was 92/min, and blood pressure 110/70 mm Hg. Specifically, there was no pallor, jaundice, cyanosis, rash, conjunctival injection, or enanthema on the soft and hard palates. She was tender in both axillae but the lymph nodes were not enlarged. The heart and lungs were normal, the liver was not enlarged, and the spleen was not palpable.

Investigations showed a haemoglobin 15·0 g/dl; WCC 2·1 × 10^9/l (74% neutrophils); platelets 101 · 10^9/l; ESR 13 mm in the first hour. The peripheral smear showed atypical "viral" lymphocytes, and some polymorphonuclear leucocytes showed the acquired Pelger-Huët anomaly. She was thought to be suffering from the same illness as case 1.

Next day the fever persisted and she continued to complain of painful muscles and joints. The WCC remained low and a direct Coombs test result was positive. Serum fibrinogen, FDPs, and PTT were normal. Nevertheless, in view of the severe disseminated intravascular coagulation that had developed in case 1 an intravenous loading dose of 2000 units heparin was given prophylactically, followed by a constant infusion of 10 000 units over the first 24 hours. Thereafter the dose was monitored according to the PTT. Blisters developed on her buttock and thigh but these were thought to be due to the use of a hot-water bottle before admission. The next day she developed upper abdominal pain, nausea, vomiting, and watery diarrhoea without blood or excess mucus. In addition she became more lethargic and drowsy. Rebound tenderness was elicited in the epigastrium and to the right of the umbilicus. Acute pancreatitis was suspected and was confirmed by a serum amylase level of 92 Street-Close (SC) units. The serum transaminase levels (SGOT and SGPT) were also moderately raised. Because of the possibility that she may have been suffering from Lassa fever she was given 250 ml Lassa fever antiserum intravenously, which had kindly been provided by the Hospital of Tropical Diseases, London, through Professor A W Woodruff. Shortly afterwards a maculopapular erythematous rash appeared on the trunk and arms. This lasted for 48 hours, and some days later slight desquamation occurred at the sites of the rash.

During the next two days the patient remained feverish, diarrhoea and vomiting persisted, and the epigastric pain became progressively worse. The serum amylase level rose to 295 Street-Close units. Serum FDP levels were raised and ^{125}I—fibrinogen was injected to determine the rate of fibrinogen clearance.[7] This was studied over 200 hours starting on day 7 and found to be normal (five days; normal range four to six days). The dose of heparin was raised and by the next day the FDPs had returned to normal. Fifty-two hours after receiving the specific antiserum her temperature returned to normal. Firstly the diarrhoea and then the vomiting settled, and apart from persistent epigastric pain she began to feel better. Thereafter there was a steady clinical and biochemical improvement, the serum transaminase levels and amylase level returning to normal on days 16 and 32 respectively. Heparin was discontinued on the 10th day. She felt completely well 10 days after becoming ill but was not discharged for another 30 days for public health reasons and because of the raised serum amylase levels.

Vigorous supportive treatment was given from the day of admission. Parenteral fluids (± 4 l daily) were administered from the outset and serum electrolytes and urinary output were maintained within normal limits throughout the illness. During the period of symptomatic pancreatitis nasogastric suction was also applied. Fever was controlled by fanning and tepid sponging. Hydroxyzine was used as a sedative and antiemetic and pentazocine as an analgesic.

Day-to-day management was provided by the nurses and doctors who had been exposed to case 1 and who were already isolated in the fever hospital. It was from this group that the third case came.

Case 3

A 20-year-old nursing sister on the staff of the Johannesburg Hospital looked after the first patient on the penultimate and ultimate nights of his illness. Barrier nursing was not practised during the initial two hours of the first night but thereafter a gown, gloves, and mask were worn at all times. She did not recall handling a bedpan or urine or blood specimens from the patient during the unprotected period. She was present during the attempted resuscitation, which included endotracheal intubation, bronchial suctioning, and external cardiac massage, but wore protective clothing. After the patient died she attempted to console his companion (case 2), and during this time, while not wearing gloves, handled several wet facial tissues that had been used by her. Eight days later she nursed this patient for one six-hour shift, wearing protective clothing, including goggles. After working for about five hours she fainted and then vomited. She then felt better and completed the duty (fig 3). Twenty-four hours later, while on night duty, she complained of malaise and lower backache, which caused her to go off duty at midnight.

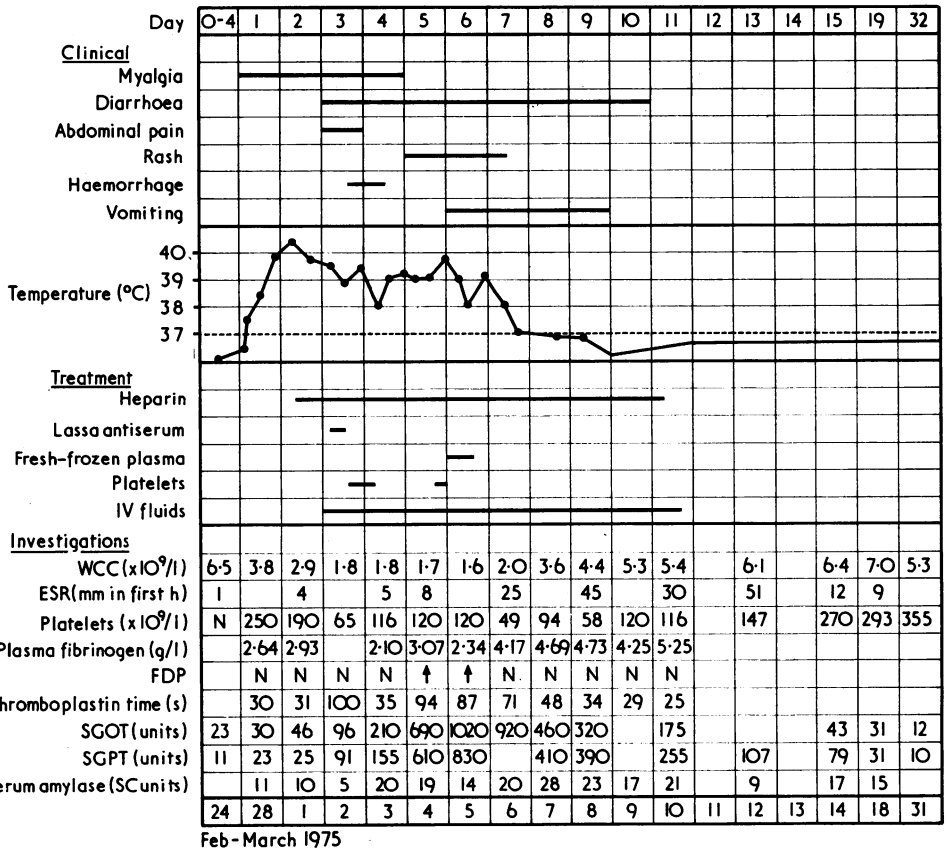

FIG 3—Clinical and laboratory data in case 3. For fibrinogen degradation products N = normal; vertical arrows indicate raised values.

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By the next morning (28 February 1975) the backache was severe and other muscles were also slightly painful. She felt cold and had a mild headache.

On examination her oral temperature was found to be 37·5 C (it rose to 38·5°C during the morning), pulse was 82 beats/min, and blood pressure was 110/70 mm Hg. The muscles of the right shoulder girdle were tender to palpation and the joints painful on movement, particularly the knees. The conjunctivae were injected but there was no rash or enanthema. There was no jaundice, pallor, or cyanosis. Slight tenderness was noted in both axillae, and the lymph nodes in the left axilla were slightly enlarged. The liver was not enlarged and the spleen was not palpable.

"Baseline" blood tests four days before admission had shown normal values. On admission there was a moderate leucopenia (WCC 3·8 $\times$ 10^9/l; 79% were neutrophils) and the ESR was 5 mm in the first hour. Platelet count was 250 $\times$ 10^9/l. Peripheral smears showed atypical "viral" lymphocytes, and an acquired Pelger-Huët anomaly of the polymorphonuclear leucocytes was observed. Serum amylase, transaminase levels, and the coagulation profile were all normal. As in case 2 the direct Coombs' test result was positive. It was thought that the patient was suffering from the same disease as cases 1 and 2. The following day her temperature remained above 38°C, leucocytes fell to 2·9 $\times$ 10^9/l, and the SGOT began to rise. In view of the apparent success with heparin in preventing a severe disseminated intravascular coagulation syndrome in case 2 a similar regimen was instituted. Initially, satisfactory prolongation of the PTT was achieved with about 14 000 units daily.

The next afternoon the patient was given 250 ml Lassa fever antiserum (kindly supplied by the Centre for Disease Control, Atlanta, USA), which was well tolerated. The rate of ^{125}I-fibrinogen clearance, determined[7] over 120 hours starting on day 3, was found to be midly increased (three days). At about this time she developed watery diarrhoea and abdominal cramps. The abdomen was found to be slightly tender. That evening slight but persistent bleeding was noted from a venepuncture site, and small amounts of blood were present in both urine and stool. A rise in the level of FDPs suggested the presence of a disseminated intravascular coagulation in addition to the heparin effect. By midnight the platelet count had fallen to 49 $\times$ 10^9/l and she was given 7 units of fresh platelet concentrates during the night and 6 more the next day. In the morning the skin appeared suffused but there was no obvious rash. Fever, severe diarrhoea, mild nausea, and slight myalgia and arthralgia persisted. In addition there was biochemical evidence of worsening hepatitis. On the evening of the next day, the fifth day of her illness, a maculopapular erythematous rash appeared on the trunk and arms. Her conjunctivae remained injected and she complained of a painful scratchy throat; however, no enanthema was present. She was lethargic and somewhat drowsy. The next day she complained of severe nausea and began to vomit. A nasogastric tube was passed and suction instituted. Postural dizziness was present. SGOT was 1020 units.

On day 7 of the illness the patient began to improve and her temperature settled. By this time there was a strong suspicion, based on preliminary virological studies, that the illness was not Lassa fever but was due to the Marburg virus. A unit (250 ml) of specific Marburg virus antiserum (kindly supplied by Behringwerke, West Germany) was available, but in view of her improvement it was withheld. Vomiting and diarrhoea became less troublesome and stopped on the 10th day of the illness. The serum enzyme levels improved. After 21 days she was completely well and biochemically normal. She was discharged.

Two months later she developed a painful right eye. Uveitis was diagnosed and the Marburg virus was cultured from fluid aspirated from the anterior chamber. She was treated with steroid and atropine drops and the condition subsided over several weeks. A repeat viral culture 10 weeks later was negative.

Virus studies

Virus studies were carried out at the Poliomyelitis Research Foundation (PRF), Johannesburg, and at the Centre for Disease Control (CDC), Atlanta.

Throat swabs and blood were collected in case 1 on the day of the patient's admission to hospital. The suspensions prepared from them were inoculated at the PRF into baby mice and tissue cultures of vervet monkey kidney. At necropsy specimens of various organs were collected and suspensions of liver, spleen, kidney, and brain prepared at the PRF. These were inoculated on 20 February into tissue cultures of vervet monkey kidney. Histological sections were prepared from the same specimens and examined the following day. The liver showed patchy midzonal necrosis. Because of these findings Dr David Sencer, director of the CDC, was consulted by telephone. He immediately arranged to send special containers for the transport of aliquots of the tissue suspensions to Atlanta by air. The suspensions arrived at the CDC on 1 March.

On 3 March Dr Isobel Spence, of the PRF, on electron microscopical examination of tissue retrieved from paraffin blocks of liver, spleen, and lung, observed bodies and arrays in the cytoplasm of cells that resembled virus particles. On 4 March at the CDC Dr Herta Wulff obtained a negative fluorescent antibody test result for Lassa fever, and the next day structures indistinguishable from Marburg virus particles[8] were observed by Dr F A Murphy on electron microscopy of vero cell cultures inoculated with the original suspensions. Later the same day Dr Herta Wulff confirmed their identity using a fluorescent antibody technique. These findings were immediately transmitted to Johannesburg. On 6 March the coverslip preparations from the original tissue cultures stained with haematoxylin and eosin showed cytoplasmic inclusion bodies similar to those of Marburg virus infection.

In the meantime the other two patients (cases 2 and 3) had become ill. Throat swabs, blood, urine, and faeces were collected at regular intervals during the course of their illness. Suspensions were prepared and inoculated into vervet monkey kidney tissue cultures, and after 14 days of observation the coverslips were collected, fixed, and stained with haematoxylin and eosin, and in each case inclusions similar to those produced by Marburg virus were observed.

Sera separated from the blood collected early in the illness in case 2 and before its onset in case 3 were compared by Mrs E Rossouw at the PRF in indirect immunofluorescence tests for antibody against the virus from case 1 in vervet monkey kidney coverslip preparations. These showed the absence of antibodies in early specimens and their presence in convalescent specimens of blood from cases 2 and 3 against the virus from case 1, thus confirming that all three patients had had the same virus infection.

Final confirmation that the outbreak was due to Marburg virus was obtained by Dr Herta Wulff when she showed that the results given by fluorescent antibody tests on sera taken from cases 2 and 3 at intervals after the onset of the illness showed an almost identical pattern of rise in titre against the virus from case 1 and against the Popp virus isolated in the original outbreak in Marburg.

Discussion

Apart from meningococcal, staphylococcal, or streptococcal septicaemia, which may occur anywhere, the diseases that should be considered as possible causes of an acute haemorrhagic fever contracted in tropical Africa include the viral infections yellow fever, chikungunya fever, Rift Valley fever, Lassa fever, and Marburg virus disease, the protozoal infections malaria and trypanosomiasis, and septicaemic plague. The clinical presentation in our three patients, together with the negative peripheral blood smears and blood cultures and the histopathological findings in the liver of the patient who died, strongly suggested that we were dealing with either Lassa fever or Marburg virus disease. Which of the two was not apparent early on in the outbreak, since the symptoms and signs associated with them are similar.[9] Both may cause hepatitis and hepatic necrosis, and both are often fatal. In view of the greater likelihood that the young Australians were exposed during their travels to the rodent reservoir of Lassa fever, *M natalensis*, than to the primary source of Marburg virus disease, *C aethiops*, Lassa fever was initially considered the more likely cause of the Johannesburg outbreak. During the course of the illness in case 3, however, preliminary results of the virological studies became available, which implicated Marburg virus as the cause; this was subsequently confirmed.

The incubation period of the illness in the 1967 outbreak was estimated to be three to nine days.[1] Probably our first patient contracted the disease during his trip through Rhodesia and infected his companion. Only in case 3 was it possible to get a reasonably accurate idea of the incubation period, which seemed to be seven or eight days. The clinical picture was remarkably uniform in the three patients and was in almost all respects similar to that in the 1967 epidemic.[1] Early complaints were malaise, headache, and myalgia, which was generalised but affected mainly the lumbosacral region. Nausea, vomiting, watery diarrhoea, and abdominal pain developed a few days later. A characteristic maculopapular rash against a background of pronounced erythema appeared on the trunk, face, and arms on the fifth or sixth day of the illness. This rash was not itchy and faded after three or four days in the two survivors, in one of whom it was followed some days later by fine desquamation.

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RASH AS DIAGNOSTIC FEATURE

As in the original description of the disease, the rash was a major diagnostic feature in the clinical recognition of the illness. A high fever was present at the time of admission in all three patients. It ran a remittent or continuous course and lasted five to seven days. The relative bradycardia noted in the earlier epidemic was again evident, as were the leucopenia and low erythrocyte sedimentation rate. The acquired Pelger-Huët anomaly of the neutrophils together with atypical plasmacytoid lymphocytes was a distinctive feature in all three patients. Lethargy, drowsiness, and postural dizziness were notable when the illness was at its height. Less striking manifestations were slight axillary lymphadenopathy and conjunctival injection. The dark red enanthema on the soft and hard palates that was consistently found in the 1967 outbreak was not seen in any of our patients. The first patient complained of a sore throat, but the appearances were those of an acutely inflamed pharynx rather than a dark red discoloration.

Profuse bleeding from the gastrointestinal tract and later the lungs occurred in the fatal case. It began on the sixth day, rapidly increased in severity, and was the eventual cause of death. Investigation showed the features of a severe disseminated intravascular coagulation, probably aggravated by failure of synthesis by the liver of coagulation factors. The other two patients were treated prophylactically with heparin intravenously from an early stage and showed only mild disseminated intravascular coagulation. There was, in addition, some indirect evidence of mild bone marrow suppression. Haemorrhage was prominent in seven of the 31 patients in the first epidemic of Marburg virus disease.[1] Profound thrombocytopenia was recorded in these patients, but no proof of disseminated intravascular coagulation was found in the limited coagulation studies reported.

Biochemical evidence of hepatitis was present in all our patients, with SGOT levels as great as or even greater than SGPT levels; this is similar to the earlier experience.[1] Only the patient who died was jaundiced, and at necropsy there was patchy but extensive degeneration of the hepatocytes. Obvious pancreatitis occurred in our second patient and was one of the dominant features of her illness. The serum amylase levels remained high for 32 days. Slightly raised serum amylase levels were found in the other surviving patient, and a low-grade pancreatitis may have contributed to her abdominal pain.

CONTROL OF HAEMORRHAGE

In view of the uncontrollable haemorrhage in case 1, it seemed important to attempt to prevent this complication in the subsequent patients. Disseminated intravascular coagulation is presumably initiated in this disease by virus-induced endothelial damage and disseminated cellular breakdown, resulting in the release of tissue thromboplastins.[10] At present it is not possible to prevent this from occurring, but it was hoped that by giving heparin early in the course of the disease consequent intravascular coagulation could be reduced in severity. In fact, both patients did at one stage of their illness develop evidence of disseminated intravascular coagulation, but in the first it was detectable only on laboratory testing, while in the second it manifested with a mild and short-lived bleeding tendency. The usefulness of heparin in established disseminated intravascular coagulation is the subject of controversy and results reported are equivocal.[11-14] It was nevertheless felt justifiable to use heparin prophylactically in the second and third patients in an attempt to prevent the full evolution of a consumptive coagulopathy similar to the one that had caused the death of the first patient. The degree to which this treatment modified their illnesses is not known. The relatively benign course of the disease in the two girls, however, was in striking contrast to the fulminant haemorrhagic illness to which the first patient succumbed. The results suggest that the prophylactic use of heparin in severe viral illnesses associated with haemorrhage may be warranted.

The increased serum amylase level for a month in case 2 raised the possibility of persistent viral infection in this patient. No virus, however, was cultured from her stools during this period. The third patient, who had appeared to recover completely, developed uveitis 80 days after the onset of the illness and Marburg virus was cultured from the anterior chamber. The condition settled over several weeks and a repeat viral culture two and a half months later was negative. In this context it is of interest that virus was cultured from the seminal fluid of one of the victims of the original Marburg outbreak 83 days after the onset of the illness.[9] These various observations indicate that the virus can persist for at least two to three months after the initial attack.

One final point merits comment. Limiting the Johannesburg outbreak of Marburg virus disease to three persons with two recovering was a team effort that spread far beyond the boundaries of the countries immediately involved. Particularly noteworthy was the way in which expert advice, precious antiserum, and virological laboratory support were immediately made available at short notice. The Centre for Disease Control in the United States; the London School of Tropical Medicine, and Behringwerke in West Germany all made invaluable contributions.

We wish to pay tribute to the members of the nursing staff who attended to the three patients and to the many members of the laboratory technical staff, who carried out their duties willingly and conscientiously despite the considerable risks. Unstinting back-up support was also provided by Dr J McMurdo, superintendent of the Johannesburg Hospital, and his administrative staff, by Professor A H Smith, medical officer of health, Johannesburg City Health Department, by the Secretary for Health and his regional Director in Johannesburg, and by Dr M Shapiro, director of the South African Blood Transfusion Service. We also thank Professor A W Woodruff, of the Hospital for Tropical diseases, London, for expert advice and for supplying Lassa antiserum, and Professor W Mohr, who, through the good offices of Professors R Siegert and G A Martini, arranged for the supply of Marburg antiserum by Professor H G Shrick, of Behringwerke. For their decisive help in the elucidation of the cause of the illness we are indeed grateful to Dr David Sencer, director of the Centre for Disease Control in Atlanta, and his staff. In particular, we are indebted to Drs W R Dowdle, R Hufakker, and F H Murphy, to Dr Herta Wulff, who identified the infectious agent as Marburg virus, and to Dr Lyle Conrad for his invaluable co-operation in the epidemiological studies of the outbreak.

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