A nosocomial outbreak of Crimean-Congo haemorrhagic fever at Tygerberg Hospital

Part III. Clinical pathology and pathogenesis

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Summary

Crimean-Congo haemorrhagic fever (CCHF) was diagnosed in 8 patients; 7 were staff members at Tygerberg Hospital who had been infected by a patient in whom the disease had not initially been diagnosed. Two patients, the initial case and a staff member, died and 4 became seriously ill. The immunopathogenesis of CCHF appears to be multifactorial. Certain features were common to all patients — leucopenia, thrombocytopenia, elevated liver enzyme values and low serum total protein levels. Ultrastructural changes in and around skin capillaries, including intracytoplasmic endothelial tuboreticulated bodies, were found. Virus-like particles were found on electron microscopy. Important individual factors related to prognosis were identified. The patients who survived all mounted a good antibody response, and manifested no coagulation defect extensive enough to explain the haemorrhagic tendency. In the patients who died no evidence of antibody production was detected; both developed diffuse intravascular coagulation and in 1 evidence of immune complex formation and complement consumption was found. Hepatorenal failure and cardiovascular collapse characterized the terminal period. Early clinical recognition of CCHF with specific attention to factors amenable to treatment may vastly improve the prognosis.

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Crimean-Congo haemorrhagic fever (CCHF) is one of the viral haemorrhagic fever diseases — a potentially lethal group of conditions in which immunological, haematological and biochemical factors play a vital role in the diagnosis and treatment.[1,2] These factors were studied during a nosocomial outbreak of CCHF at Tygerberg Hospital and were related to prognostic features by which patients were placed into one of three categories.[3]

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The pathogenesis subsequent to infection with CCHF has not been described, but fragmentary data on the pathogenesis of other members of the viral haemorrhagic fever group may be relevant. The role of 'leaky capillaries' as a factor which contributes to the haemorrhagic tendency of the specific group of diseases has been based largely on clinical observations and experimental animal work.[4,5] Earle[6] described widespread abnormalities of the blood vessels in patients with Korean haemorrhagic fever. These changes did not fulfil the histopathological criteria for vasculitis, and were nonspecific. We established that vessel damage of a vasculitic nature does not occur in CCHF, but did find evidence of virus-induced lesions of the endothelium. Activation and consumption of complement have been described in dengue and Argentine haemorrhagic fever, and immune complex-induced endothelial damage and enhanced capillary permeability in Korean haemorrhagic fever.[6-8] In the present study, evidence of complement consumption in 2 patients and circulating complexes in 1 patient were found. These appeared to be coincidental and not representative of the group as a whole.

A single clotting deficiency which could be held responsible for the haemorrhagic tendency in this particular group of diseases has not been identified. In 1967 McKay and Margaretten[9] concluded that disseminated intravascular coagulation (DIC) was central to the pathogenesis of the haemorrhagic fevers. More recent publications indicate that DIC is an occasional or late complicating factor.[10,11] Abnormalities in platelet aggregation and adhesiveness as a cause for the bleeding tendency in dengue haemorrhagic fever were suggested by Mitrakul.[10] In the present study clotting factor and haematological abnormalities were related to the onset and continuation of the haemorrhagic manifestations. The haemorrhagic tendency was preceded by a very marked leucopenia and thrombocytopenia.

Isolated deficiencies in clotting factors were identified but a specific pattern was not found. Immunological and biochemical features were monitored daily in 7 of 8 patients with diagnosed CCHF and were related to the clinical features of the disease. An attempt was made to identify immunopathogenic factors which determine prognosis. A feature of the immune response of the 2 patients who died was the absence of circulating antibodies.

Patients and methods

Eight patients with suspected CCHF were studied. Determinations of a specific immune response, i.e. presence of viral antigen and specific antibodies, were conducted on all 8 individuals. General parameters of the immune response were determined where possible in 7 patients. During the same period (17 - 30 September 1984) 115 people who had been exposed to diagnosed cases of CCHF and hospital staff members who presented with influenza-like symptoms were screened for a CCHF antibody response.

Virus isolation. Whole-blood specimens were sent to the National Institute for Virology, Sandringham, Johannesburg. Day-old mice were inoculated intracerebrally as well as cultures of Vero cells in microslide culture chambers. Mice died on about day 8 and brains were assayed for CCHF virus by complement fixation tests. Vero cells were fixed and stained for immunofluorescence with antisera to CCHF. Positive reactions were recorded within 3 - 8 days after onset of symptoms.

Antibody determination. A specific CCHF antibody was determined by means of indirect immunofluorescence. For this purpose acetone-fixed infected tissue cultures were employed and sera from suspected cases which had been inactivated at 56°C for 30 minutes were examined for the presence of antibodies.

Nonspecific immune response. Serum C3, C4 and C-reactive protein (CRP) levels were measured by radial immunodiffusion using immunoplates from Behring Diagnostics. Total haemolytic complement levels were measured in agarose gel containing sensitized sheep erythrocytes according to the method of Truedsson *et al.*[12] In 7 patients circulating immune complexes were determined by a competitive binding conglutinin enzyme immunoassay using commercial kits from Farmitalia Carlo Erba. The presence of endotoxin was determined in 2 of the patients by a chromogenic *Limulus* lysate assay method obtained from MA-Bioproducts. The presence and ratio of B cells, T cells and null cells and the helper/suppressor ratio were determined in 1 patient using the method of Brain *et al.*[13]

Haematology and clotting factors. Leucocytes and platelets were counted by means of a Coulter or Hemalog D counter. Coagulation studies were done by routine methods.

Histopathology. Skin biopsy specimens were removed from 2 patients with haemorrhagic skin lesions, and a percutaneous liver biopsy specimen was taken from 1 patient immediately after death. The tissues were fixed in buffered formalin and buffered glutaraldehyde and routinely processed for light and electron microscopy respectively.

Liver functions. The γ-glutamyl transferase (GGT) value will be reported as representative of all liver enzymes serially measured in 6 patients. Serum total protein and sporadic serum albumin values were determined at the same time.

Results

Patients are classified in Table I according to the severity of their disease. Patients A1 and A2 died. Patients B1 - 4 were severely ill and C1 and 2 had an attenuated form of the disease.

Patients A1 and A2 were admitted late (4 - 5 days) after onset of symptoms and diagnosis was delayed for a further 2 days. By the time of admission the haemorrhagic tendency had set in. Viraemia persisted throughout the course of the illness, and no virus-specific antibody production was evident (Table I). On admission, clinical jaundice and elevated bilirubin as well as liver enzyme values were recorded. Normal or elevated white blood cell counts (7,8 and 17,8 x 10^9/l respectively) were recorded and low platelet counts (14 and 37 x 10^9/l respectively) were present in both patients. Blood urea and serum creatinine levels on admission for patient A1 were 36,3 mmol/l and 355 mmol/l respectively.

A CCHF viraemia was detected in 5 of the 6 survivors shown in Table I. A rising titre of antigen-specific antibody confirmed the diagnosis in the remaining patient (C2). In the patients who survived, the viraemia disappeared at between 3 and 8 days (mean 5,2 days) after onset of symptoms. In all cases this was associated with a rising antigen-specific antibody titre. In patients B1-3, who were all under surveillance at the onset of symptoms, antibody production preceded or coincided with the onset of haemorrhagic manifestations. In patients B4 and C1, determination of antibody levels was delayed and this may explain why the haemorrhagic manifestations preceded onset of antibody production by 3 - 4 days.

Haematological values in relation to onset of signs and symptoms

Leucocyte values showed one of three patterns (Table I). Total counts on admission were normal (cases A1 and C1), low (cases B1, 2, 3, 4 and C2) or raised (case A2). However, in all cases counts fell sharply, reaching a nadir on day 3-11 of the illness (mean: day 6). In all cases where a different count was available, lymphopenia was present from the outset (counts on the Hemalog D ranging from 164 to 830 x 10^6/l). Thereafter, lymphocyte counts rose slowly, reaching values above 1 200 x 10^6/l by day 10.

Of interest was the variation observed in the monocyte count during the first week of the illness. In 3 cases in which a Hemalog D differential count was available the monocyte count was 100 x 10^6/l or lower on days 3 - 5, falling to as low as zero in 1 case on day 4. Monocyte counts then started to rise on day 6 and reached normal levels by day 8. In a single case (A2) in which leucocytosis was observed, toxic granulation of the neutrophils was marked, although no left shift, no Döhle bodies, and no degranulation or vacuolization were noted.

There were a moderate number of atypical lymphocytes, and an occasional neutrophil or eosinophil myelocyte and scanty normoblasts. In all cases there was a rapid and steep fall in the neutrophil count, reaching leucopenic levels in all except case A2. Neutropenia was seen in all cases on day 5, but returned to levels above 2 000 x 10^6/l by day 10.

On admission to hospital, platelet counts were very low in cases A1, 2 and B4, 129 and 107 x 10^9/l in cases B1 and 3, respectively, and normal in cases B2, C1 and 2 (Table I). In all cases but B2, platelet counts fell to levels between 14 and 53 x 10^9/l, reaching lowest values between days 4 and 8 (mean: day 6). Case C2 retained a normal platelet count almost throughout the disease, except for a slight fall from 238 to 195 x 10^9/l on day 6. It was noteworthy that irrespective of the platelet count, all patients except case C2 presented with purpura. This may imply that at least in some patients the purpura was of a non-thrombocytopenic nature. Platelet volumes ranged from 6,2 μm^3 to 9,1 μm^3 (mean 8,1) in the patients in whom platelet studies were done. Haemoglobin values declined in all patients except case C2, who was only mildly affected. It is probable that this reflected haemorrhage into tissues or external loss, as described elsewhere in this issue (Part II: Management of patients). Torrential haemorrhage was observed in the fatal cases, 1 of whom received no less than 33 units of blood in 3 days.

Coagulation and clotting factors

The prothrombin time ratio (PTR) (normal 1,0 - 1,3 in our laboratory) was at the low end of the normal range throughout, with the exception of case B2, in whom the PTR on presentation was 1,23 but thereafter remained under 1,0. The activated prothrombin time (APTT) was normal on admission in all cases except in case A2, who presented with evidence of liver failure. Thereafter this test was modified by the intravenous administration of heparin in a standardized dose of 10 000 U/24 h by continuous infusion pump. Fibrinogen degradation products (FDP) as measured by the latex particle technique were raised in 5 cases, including the 2 fatal ones (Table II). Fibrinogen levels were low in cases B1, 3 and 4 and very low

TABLE I. KEY POINTS OF THE INFECTION, HAEMATOLOGICAL CHANGES AND CLINICAL COURSE

	September 1984	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
A1	Viraemia				+				+															
	Antibody levels				–				–															
	Leucocytes			7,8	6,7	4,8	3,7	3,15																
	Platelets			14	42	68	68	133																
	Bilirubin (total)				41	62		53																
	GGT				125	96		148																
	Total protein/ albumin					41/23																		
	Signs & symptoms	——		- - -	- - -	- - -	- - -	- - -																
A2	Viraemia														+		+							
	Antibody levels														–		–							
	Leucocytes														17,8	10,3	4,3							
	Platelets														37	106	103							
	Signs & symptoms										——				- - -	- - -	- - -							
B1	Viraemia											+	+	+	–	–	–							
	Antibody levels											0	16	128	128	128	256	256	256	512	512	512	512	512
	Leucocytes											2,7	1,57	1,54	1,85	2,48	2,9	5,3	4,0	3,7	3,9	3,0	4,6	4,4
	Platelets											129	89	62	96	72	40	63	60	33	57	120	104	109
	Enzymes											9	12	49	124	128	168	180	192	156	136	162	156	118
	Protein														61	59	62	58	44	57	55	67	72	73
	Signs & symptoms									——	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
B2	Viraemia											+	+	+	–	–	–							
	Antibody levels											0	64	128	128	128	256	128	128	256	128	128	128	128
	Leucocytes									4,1	4,5		2,7	1,28	254	3,21	3,90	6,83	10,2	7,5	3,9	3,9	4,51	6,1
	Platelets									264	209		107	70	55	124	56	137	178	136	139	181	226	280
	Enzymes										12		8	17	59	80	83	81	108	96	90	84	108	108
	Protein										73				58	60	61	56	49	61	62	64	75	64
	Signs & symptoms										——	- - -	- - -	- - -	- - -	- - -	- - -	- - -						
B3	Viraemia											+	+	+	–	–	–							
	Antibody levels											0	0	4	128	32	128	256	256	256	512	256	128	128
	Leucocytes											3,3	4,07	2,09	2,46	3,15	4,8	7,7	6,0	6,0	5,8	6,5	7,9	8,5
	Platelets											107	67	55	96	76	75	155	126	104	136	136	199	230
	Enzymes												14	20	67	105	120	105	138	150	138	123	162	156
	Protein														66	69	75	60	42	59	55	56	71	58
	Signs & symptoms									——	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -						
B4	Viraemia								+								+							
	Antibody levels																64	512	512	2 048	2 048	1 024	512	1 024
	Leucocytes																2,6	4,51	4,7	3,6	3,8	4,1	6,57	
	Platelets																15	91	115	123	106	138	166	
	Enzymes																136	141	162	192	288	136	498	
	Signs & symptoms									——	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
C1	Viraemia																+	+	–					
	Antibody levels																32	128	128	128	512	512	512	512
	Leucocytes											5,4					2,1	3,04	4,2	5,1	3,5	2,8	4,99	4,9
	Platelets											208					25	60	103	158	149	193	211	228
	Enzymes																120	129	120	102	90	90	138	138
	Protein																62	65	58	72	73	74	75	72
	Signs & symptoms									——	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
C2	Viraemia															–		–						
	Antibody levels																	64		128	128	64	64	64
	Leucocytes																		3,8	3,7	4,3	4,0	6,4	6,1
	Platelets																		238	195	211	228	260	269
	Enzymes																			18	24	15	19	24
	Protein																			68	68	65	68	69
	Signs & symptoms																		- - -	- - -	- - -	- - -	- - -	- - -

Clinical onset: ——— **Haemorrhage:** - - - - -

Normal values: leucocytes 4 - 11 x 10^9/l, platelets 150 - 400 x 10^9/l, total bilirubin 1 - 17 μmol/l, GGT 0 - 32 U/l, serum total protein 60 - 80 g/l, serum albumin 38,4 - 48 g/l.

TABLE II. FIBRINOGEN DEGRADATION PRODUCTS

Case	Value on admission (μg/ml)	Positive < 40 μg/ml
A1	<10	<40 (D12)
A2	<10	<40 (D7)
B1	10	<40 (D5)
B2	<10	<40 (D6)
B3	10	<40 (D4)
B4	10	—
C1	10	—
C2	10	—

D = day after onset of illness.

TABLE III. FIBRINOGEN LEVELS

Case	Value on admission (mg/dl)	Lowest recorded value (mg/dl)
A1	73	73 (D8)
A2	108	50 (D7)
B1	240	180 (D3)
B2	265	245 (D7)
B3	162	110 (D4)
B4	190	190 (D8)
C1	215	215 (D7)
C2	195	180 (D10)

Normal 200 - 400 mg/100 ml.
D = day after onset of illness.

in the 2 fatal cases (73 mg/dl in case A1 and 50 mg/dl in case A2) (Table III).

The risk of infection precluded extensive study of bone marrow aspirates, but in the single case studied (A2) the aspirate was hypercellular and all elements were represented. Megakaryocytes were present in increased numbers.

Nonspecific immune response

In the index case (A1) evidence was found of serum complement consumption including fractions C3 and C4. Values for total complement, C3 and C4 of 0%, 25 mg/dl and < 6 mg/dl respectively were recorded. Normal values in our laboratory are 80 - 120% for total complement, 52 - 120 mg/dl for C3 and 20 - 50 mg/dl for C4. Circulating immune complexes of 56% (normal 0 - 37%) inhibition and abnormally elevated CRP levels of 45 μg/ml were registered. In patient B3 temporary depression of the total complement and C3 levels (68% and 46 mg/100 ml respectively) were recorded, which after 1 week reverted to normal (98% and 76 mg/dl). No circulating immune complexes were detected in this patient and the CRP value was weakly positive. In the remaining patients no evidence of complement consumption or circulating immune complexes was recorded.

Endotoxin was not found and the T and B cells as well as the helper/suppressor T-lymphocyte ratios remained normal in patients in whom determinations were done.

Liver function

Serum GGT values were employed in all patients as representative of the liver enzymes. The GGT value became elevated on the second day after appearance of the haemorrhagic tendency in patients B1, 2 and 3 (Table I). This relationship could not be established for cases B4, C1 and 2 as early liver function determinations were not done. The GGT value (normal 0 - 32 U/l) remained excessively high for 10 - 11 days before the turning point was reached and decreases in the values were recorded (Table I). Peak enzyme values were associated with a drop in the serum total protein level, indicating that another liver function had been affected (Table I). Occasional albumin values were recorded and paralleled the total protein values.

Histopathology

The pathological changes observed under light microscopy consisted primarily of a diffuse extravasation of red blood cells into the interstitium, resulting in haemorrhagic lesions in the skin and liver respectively (Figs 1 and 2).

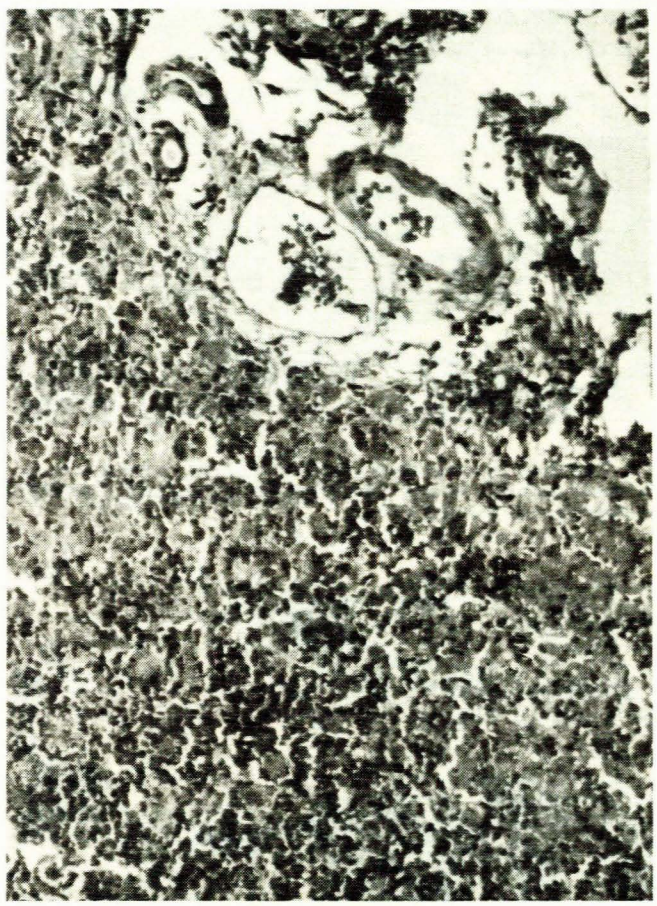

Fig. 1. Photomicrograph to illustrate the diffuse interstitial haemorrhage in the liver, effacing architecture. Note the relatively normal portal structures (H and E x 200).

Morphological evidence of reaction of the tissues to haemorrhage in the form of a cellular response, haemosiderin-containing macrophages or vascular proliferation was never encountered.

No specific vascular lesions could be discerned in the skin on light microscopy. Electron microscopy confirmed the diffuse extravasation of red blood cells and showed marked pericapillary oedema (Fig. 3). Reduplication of the basal lamina of endothelial cells and the presence of intracytoplasmic tubuloreticulated bodies within the endothelial cells were noted (Fig. 4). Due to autolysis the ultrastructure of the liver cells was difficult to interpret. A moderate number of tubuloreticulated

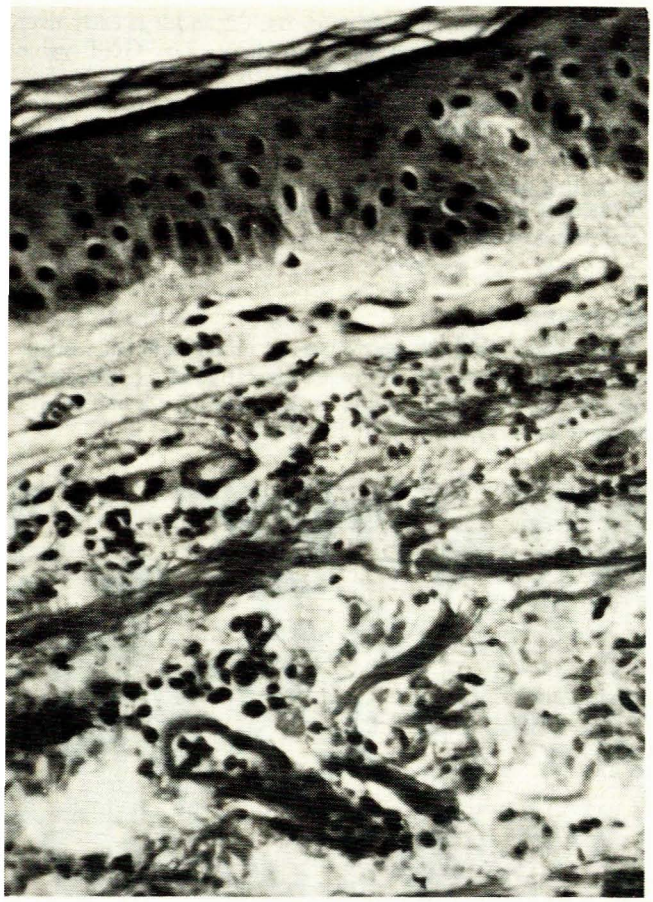

Fig. 2. Diffuse extravasation of red blood cells in the dermis in haemorrhagic skin lesions. The epidermis and vascular structures appear normal (H and E x 400).

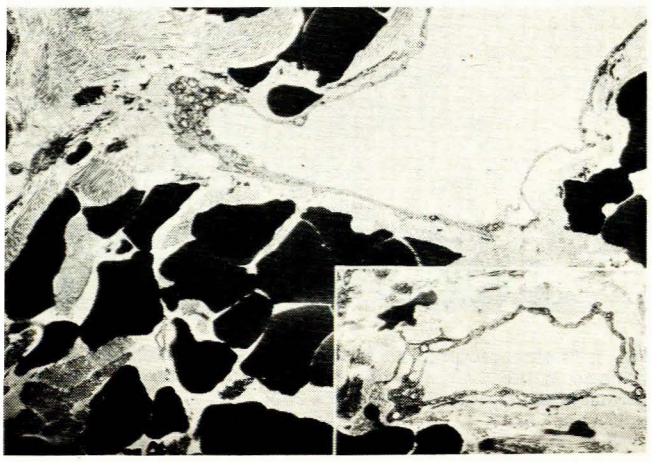

Fig. 3. Electron photomicrographs showing extravasated red blood cells in the pericapillary area. Inset illustrates the attenuated cytoplasm of endothelial cells with the accumulation of oedema-fluid in the subendothelial zone (x 2 400; x 7 000).

bodies as well as 90 - 100 nm virus-like particles were seen in the cytoplasm of endothelial cells of the sinusoids and portal vessels (Fig. 5). The virions measuring 90 - 100 nm in diameter (Fig. 5, inset) consisted of an electron-dense core surrounded by a unit membrane — a size consistent with that of CCHF virus.[14]

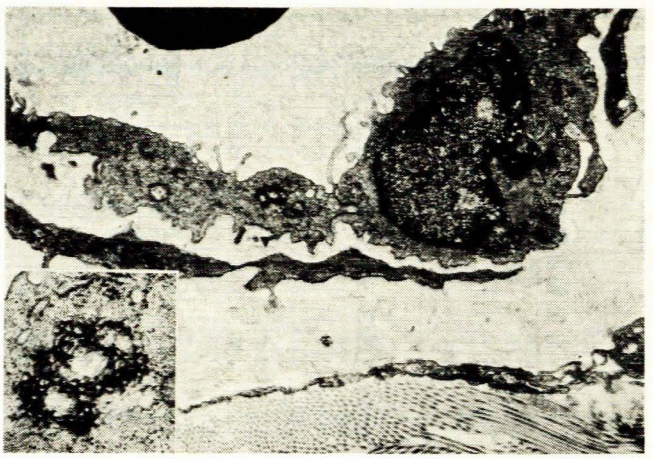

Fig. 4. A small venule in the dermis showing reduplication of the basal lamina in the subendothelial space. Inset shows an intracytoplasmic tubuloreticulated body in the endothelial cell (x 100 000; x 40 000).

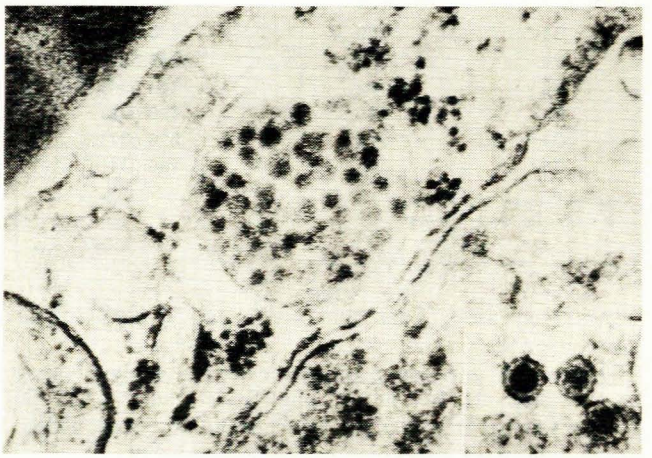

Fig. 5. High-magnification electron photomicrographs illustrating a cluster of virus-like particles in an endosomal structure within an endothelial cell of a portal tract vessel in the liver. Three virions (90 - 110 nm) with electron-dense cores and surrounding unit membranes are illustrated in the inset (x 60 000; x 120 000).

Discussion

Because of the infective nature of material obtained from patients with CCHF and the fact that it appears sporadically in remote parts of the world, little information exists on the pathogenesis of the disease. Swanepoel *et al.*[1] conducted an extensive study in which they determined antibody response to CCHF in 1 patient as well as 74 contacts. Antibodies were found in 5 of 74 sera, but none of these patients recalled having symptoms of the disease. None of the 115 contacts potentially exposed in the present study showed evidence of circulating virus or antibody production. The relationship between viraemia and circulating antibody was well documented in cases B1-3 (Table I) and suggests that the patient's ability to mount a specific immune response contributed to eradication of the circulating virus. This observation needs to be qualified, since hyperimmune serum was administered to these 3 patients on 11 September 1984. The possibility that it could have contributed to the first detection of circulating antibody on the following day in 2 of the patients cannot be excluded.

A relatively small amount of hyperimmune serum (250 ml — maximum titre 1:1 024) was administered, however, and a considerable dilution effect of the passively transferred antibody would have occurred. The rising antibody titres in patients B1 and 2 on the day after the transfusion suggest endogenous antibody production. The rise actually preceded the onset of the haemorrhagic manifestations by 2 days. In patient B3, no circulating antibody could be detected on the day after transfusion of hyperimmune serum. Endogenous antibody production may represent the most important single factor for survival. Patients B4 and C1 (Table I) received no hyperimmune globulin, and were discovered to have the disease relatively late after the onset of symptoms. One of these patients (C1) was relatively asymptomatic and the process of recovery was evident at the onset of the attenuated haemorrhagic manifestations of scattered petechiae and light vaginal bleeding.

In contrast, no endogenous antibody response was recorded in either of the patients who succumbed. Both presented in a preterminal phase of the disease, and at this point circulating virus was still detected in the absence of any endogenous antibody. The lack of antibody response in fatal CCHF has been documented by other workers.[1] This phenomenon has serious diagnostic and therapeutic implications. The diagnosis of CCHF in patients who are seriously ill and in danger of dying will, in the absence of circulating antibody, be delayed for periods of up to 1 week because culture for CCHF virus is a time-consuming process. This imposes a great responsibility on the attending physicians, since inadequate isolation procedures and careless handling of blood samples could have disastrous consequences. It is well known that antibody production in CCHF can be delayed in comparison with other viral haemorrhagic fevers.[15] Our data suggest that the absence of antibody production may also have serious prognostic consequences. An important therapeutic consideration for patients with this tendency would be the administration of scarce hyperimmune globulin in preference to those who have an endogenous antibody response. A massive viraemia could have been responsible for suppression of B-cell function — alternatively an immune deficiency before infection could have related to the degree of viraemia in the patients who died.

Leucopenia and thrombocytopenia were evident 1-2 days before or on the first day of haemorrhage in cases B1, 2 and 3 (Table I). It was also evident early during the haemorrhagic tendency in patients B4 and C1. It is worth nothing that 3 cases in the literature presented with leucocytosis.[2,16] These abnormalities in leucocyte counts are not diagnostic, since leucopenia and thrombocytopenia are of course common in severe infection. Lymphopenia from the outset was seen when leucocyte counts were normal or low on presentation. However, case A2, presenting with marked leucocytosis, had a normal lymphocyte count with neutrophil leucocytosis. The presence of toxic granulation and changes of DIC in this case increased the difficulty of diagnosis. A shift to the left in the neutrophil series was not marked, which is perhaps a pointer against bacterial septicaemia. Monocytopenia was noted in the 3 cases where Hemalog counts were done in the acute phase of the illness. At present the only recognized cause of monocytopenia is hairy-cell leukaemia.

Our data would suggest that CCHF needs to be listed as an infective cause of monocyte depression. The mean platelet volume was at the upper end of the normal range, inferring increased turnover with normal to high production. This impression was substantiated in the one bone marrow aspirate studied, in which megakaryocyte numbers appeared raised. This differs from the reduced number of megakaryocytes observed in bone marrow studies reported elsewhere.[16,17]

Evidence of DIC was found in the 2 patients who died. It provides evidence that this clotting deficiency has, when found in patients with CCHF, serious prognostic implications.[10,11] In the remaining patients it was our definite clinical impression that their haemorrhagic tendency was more marked than the thrombocytopenia and coagulation abnormalities warranted. No morphological evidence of specific vascular lesions, which could have contributed to the haemorrhagic tendency, could be demonstrated in our study.

The presence of the viruses and virus-associated tubuloreticulated bodies within the endothelial cells, however, suggested that secondary functional abnormalities of the capillaries may have been responsible for the clinicopathological changes. It seems highly likely that several factors, including borderline clotting efficiency and enhanced capillary leakage, contributed to the haemorrhagic tendency (Figs 6 and 7). The fact that leucocyte and platelet deficiencies coincided with the presence of viraemia and rising specific antibody titres may be of more than chronological coincidence in the pathogenesis of 'leaky capillaries'. It is evident from Figs 6 and 7 that several factors could participate in causing this phenomenon. Endothelial damage, either directly by circulating virus or by leucocyte-induced factors, could contribute to enhanced capillary permeability. Endothelial abnormality could in turn contribute to the onset of thrombocytopenia.

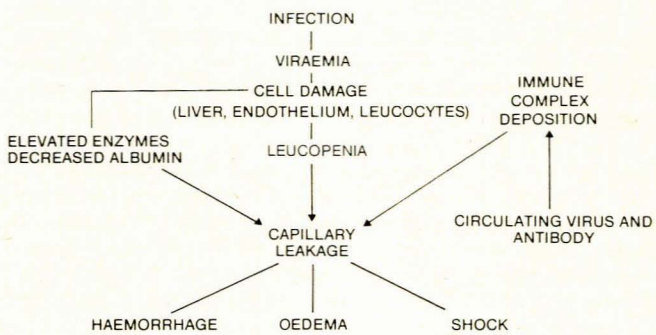

Fig. 6. Pathogenesis of CCHF.

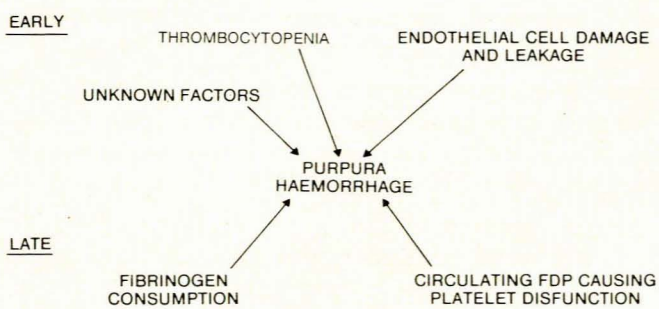

Fig. 7. Pathogenesis of haemorrhage in CCHF.

The contribution of immune complexes to endothelial damage in CCHF seems small from the data collected in this study. Evidence of complement consumption with circulating immune complexes was demonstrated in 1 patient who died (A1), and abnormally low complement levels in the absence of circulating immune complexes were present in a second patient (B3 — Table I). Complement activation in these patients may not be due to a CCHF virus-induced process. In fact no circulating antibody was detected in the blood of the patient in whom complement consumption and circulating immune complexes were recorded. It is conceivable that complement activation could have been induced by one of the many blood products of which both patients received larger quantities. The contribution of immune complex-induced endothelial damage in CCHF may, however, on the present evidence, be a

patient-specific phenomenon. The precipitous drop in the leucocyte count recorded before or on the 1st day of haemorrhage in patients B1-3 suggests that the leucocytes may be involved together with other factors such as a thrombocytopenia and viraemia in inducing endothelial damage. Either direct destruction of the leucocyte by the circulating virus or damage after phagocytosis of viral products may have contributed to its destruction with subsequent release of lysosomal enzymes in the capillary bed. In the event of a massive release of these enzymes and a subsequent relative lack of specific anti-enzymes, local capillary damage could have been enhanced. An early elevated CRP level was present in only 1 patient, indicating that the absence of CRP may be useful in differentiating CCHF from septicaemia.

The role of abnormal liver and renal function, which could compound the clotting deficit, needs to be considered. This factor could have contributed to the terminal haemorrhagic manifestation in the 2 patients who died. In the survivors hepatorenal failure was not present although clear evidence of disturbance of liver function was recorded in 5 of 6 patients in Table I. Rising enzyme levels, as represented by the GGT values, were recorded on the 2nd - 4th days after onset of the peripheral haemorrhagic tendency. This took place in the absence of marked elevation of bilirubin levels. A presenting clinical feature before onset of the haemorrhage was that of right upper quadrant tenderness. It is conceivable that cell damage and focal capillary haemorrhage in the liver could have taken place at an early stage in the clinical course. The extended elevation of enzyme levels coincided in all patients with a return of the peripheral leucocyte values to normal. At this point the patients were all convalescent, apyrexial and without any haemorrhagic tendency. We suggest that return of natural leucocyte numbers and function with resultant phagocytosis of damaged liver tissue, and proteolytic enzyme release by phagocytic cells, contributed to the extended abnormality of enzyme values.

A schematic representation of factors which could contribute to capillary leakage with subsequent extravasation of intracapillary contents and the haemorrhagic tendency are shown in Figs 6 and 7. The drop in total serum protein, which coincided with the peak abnormality in enzyme determinations, suggests that a deficiency of liver function in relation to albumin production existed. Clinically, oedema was evident at this point in patients. It could therefore be reasoned that low intravascular osmotic pressure together with enhanced capillary permeability contributed to fluid loss into the tissue and to the clinical development of oedema.

In conclusion, it is evident that a uniform and well-defined pathogenesis of CCHF could not be identified. It is clear, however, that certain features are specific for individuals with the disease. These are the haematological, immunological and clotting factors, which are of great value in determining the prognosis of severely ill patients and therefore in planning rational therapy.

REFERENCES

1. Swanepoel R, Struthers JK, Shepers AJ, McGillivray GM, Nel NJ, Jupp BG. Crimean Congo hemorrhagic fever in South Africa. *Am J Trop Med Hyg* 1983; **32:** 1407-1415.
2. Gear S, Thomson TD, Hopp M *et al.* Congo-Crimean haemorrhagic fever in South Africa: report of a fatal case in the Transvaal. *S Afr Med J* 1982; **62:** 576-580.
3. Van Eeden PJ, Joubert JR, Van de Wal BW, King JB, De Kock A, Groenewald JH. A nosocomial outbreak of Crimean-Congo haemorrhagic fever at Tygerberg Hospital: Part I. Clinical features. *S Afr Med J* 1985; **68:** 711-717 (this issue).
4. Gajdusek DC. Viral hemorrhagic fevers. *J Pediatr* 1962; **60:** 841-857.
5. Callis RT, Jahrling PB, Depadi A. Pathology of Lassa virus infection in the rhesus monkey. *Am J Trop Med Hyg* 1982; **31:** 1038-1045.
6. Earle DT. Symposium on epidemic hemorrhagic fever. *Am J Med* 1954; **6:** 619-709.
7. Bokisch VA. The potential pathogenic role of complement in dengue hemorrhagic shock syndrome. *N Engl J Med* 1973; **289:** 996-1000.
8. Debracco MME. Argentine hemorrhagic fever: alterations of complement system and anti-junin virus hemorral response. *N Engl J Med* 1978; **299:** 216-221.
9. McKay DG, Margaretten W. Disseminated intravascular coagulation in virus diseases. *Arch Intern Med* 1967; **120:** 129-152.
10. Mitrakul C. Hemostatic and platelet kinetic studies in dengue hemorrhagic fever. *Am J Trop Med Hyg* 1977; **26:** 975-984.
11. Molinas FC, Debracco MME, Maiztegui JI. Coagulation studies in Argentine hemorrhagic fever. *J Infect Dis* 1981; **143:** 1-6.
12. Truedsson L. Sjöholm AG, Laurell AB. Screening for deficiencies in the classical and alternative pathways of complement by hemolysis in gel. *Acta Pathol Microbiol Immunol Scand* [C] 1981; **89:** 160-166.
13. Brain P, Cox J, Duursma J, Pudifin J. T and B lymphocytes in three population groups. *Clin Exp Immunol* 1976; **23:** 454.
14. Ellis DS, Soythee T, Lloyd G *et al.* Congo Crimean haemorrhagic fever virus from Iraq: I. Morphology in BHK_{21} cells. *Arch Virol* 1981; **70:** 189-198.
15. Centers for Disease Control. Viral hemorrhagic fever. *Ann Intern Med* 1984; **101:** 73-81.
16. Suleiman MN, Muscat-Baron JM, Harries JR *et al.* Congo-Crimean hemorrhagic fever in Dubai: an outbreak at the Rashid Hospital. *Lancet* 1980; **ii:** 939-941.
17. Al Tikritix, Al-Ani F, Jurji FJ *et al.* Congo-Crimean haemorrhagic fever in Iraq. *Bull WHO* 1981; **59:** 85-90.

Nuus en Kommentaar/News and Comment

Quos deus vult perdere

Those who consider that life is treating them unfairly may like to ponder the sad story of the man who, in trying to do a good deed, discovered that it was simply not his day (In England Now, *Lancet* 1985; **i:** 809).

He was on his way home when he discovered a mini stalled on a railway crossing. He helped the lady driver to push it clear, thereby straining his back, just in time before the barrier went down and an express train hurtled past. The lady promptly fainted, whereupon the Great Dane sitting in the back seat jumped out and grabbed him by the leg. He limped to the barrier and tied the dog up before returning to the lady to administer first aid. At this juncture, the barrier went up taking the dog with it, but not so quickly that it could not grab the reluctant Samaritan by the shoulder. The lady was aroused from her stupor by the shouts of anguish from mid-air, whereupon she screamed, the dog barked, and the hapless rescuer fell to the ground. As he got to his feet, a railway worker, who had seen all this, lowered the barrier again thereby hitting him on the head. The half-strangled dog slipped its lead, bit him on the buttock, and took to the hills. The lady then started berating the dazed man, hitting him with an umbrella and calling him a sadist and dog-hater. Eventually, two policemen ran him to the local hospital, but not before charging him with illegal parking, damage to railway property and breach of the peace.