of the Kuppfer cells (60%). These hyaline masses were also seen in the spleen (10%) and lungs along the alveolar sac (10%).

The general picture of Philippine haemorrhagic fever is that of systemic vascular involvement with a variable degree of haemorrhagic manifestations. Deaths occurring in the fifth to tenth days (85%) of the disease were due to haemorrhage from the stomach, lungs and adrenals (85%). The rest, showing no moderate or massive haemorrhage, succumbed to peripheral vascular failure as was evidenced by the finding of petechial haemorrhages or moderate to severe congestion of visceral, thoracic or cranial organs with apparent loss of plasma and red blood cells (15%).

The pathogenesis of haemorrhagic fever, based on the pathological findings, may be analysed by asking the following question: What causes generalized hyperaemia and thrombocytopenia? The generalized acute hyperaemia is produced by the action of either the virus toxin or the virus itself on the nerve endings or ganglion cells of the blood vessel. This is followed by vascular dilatation and loss of plasma and red blood cells due to increased endothelial permeability or rupture leading to shock. This is further enhanced and complicated by the lowered platelet production which cannot plug such damaged blood vessels. It is in the febrile stage that a widespread physiological abnormality affects the parenchymatous small blood vessels. Actual capillary rupture will produce moderate to massive haemorrhage, some showing slight inflammatory reaction. This will be followed by lowered blood pressure, and later by shock. The toxin or the virus itself appears also to be the factor that produces thrombocytopenia. It appears to inhibit maturation and release of platelets in the bone marrow. The action of antibodies produced by the reticulo-endothelial proliferation and the lack of adrenaline-like factor may be considered too. The findings in the spleen, liver or lungs are not sufficient to explain it in all cases. The reticulo-endothelial activity is only present in 30%. The changes in the glands are not sufficient to explain the absence of adrenaline-like factor except in two cases where diffuse haemorrhage was present.

Pathogenetic Studies on Thai Haemorrhagic Fever: Immunofluorescent Localization of Dengue Virus in Human Tissue*

NATTH BHAMARAPRAVATI & VIJITR BOONYAPAKNAVIK

It has been shown that severe cases of haemorrhagic fever in Bangkok are invariably associated with dengue virus infection, yet dengue viruses were isolated from the tissue in fatal cases in extremely rare instances. This prompted the authors [1] to attempt to identify and localize dengue antigen in the tissue of fatal cases by the immunofluorescent technique, using the direct method of staining. Blocks of tissue from liver, spleen, thymus, lungs, lymph-nodes, kidney, intestines, adrenals, skin and heart were obtained from 21 children who died with clinically diagnosed acute haemorrhagic fever and from six children who died of other causes. Positive staining for dengue antigen was demonstrated in only one case of haemorrhagic fever, in the lymphoid cells of the spleen and thymus. The inability to demonstrate dengue viral antigen in the tissue of most humans who died of haemorrhagic fever in this series is probably not due to a denaturation of the antigen after death since dengue virus survives for many days in human blood specimens or dead mice kept at 4°C. The technique should be sensitive enough to demonstrate a minute amount of antigen in an infected cell if it is present. It is possible that the viral antigen may be fixed in certain types of cells in the presence of excess antibody blocking all available reactive antigenic sites. Evidence supporting this hypothesis includes the demonstration of an increased number of lymphocytoid cells and plasmacytoid cells with pyroninpositive cytoplasm and containing gamma-globulin in the spleen and lymph-nodes; there is also a high titre of circulating antibody against dengue virus in a large percentage of fatal cases at the time of

* From the Department of Pathology, Siriraj Hospital Medical College, Bangkok, Thailand. Originally issued as document IR/Haem.Fever/Sem.1/WP/14.

[1] Bhamarapravati, N. et al. (1964) *Arch. Path.*, 77, 538-543.

death. In the case where positive staining was obtained there was a marked reduction in the number of cells with pyronin-positive cytoplasm, perhaps indicating less active antibody formation and perhaps leading to fixation of dengue antigen at the stage where there is antigen excess.

1784

Physiological Disturbance in Thai Haemorrhagic Fever *

SOMBODHI BUKKAVESA [1]

The physiological disturbance in Thai haemorrhagic fever begins with the virus or its products affecting the capillaries: the permeability of the capillary walls increases and the tourniquet test becomes positive. The erythrocytes can pass through the injured capillary walls to produce petechiae, purpura and ecchymoses on the skin and also haemorrhage in the internal organs. Involvement of the liver causes slight elevation of serum transaminases and slight enlargement of the liver. Involvement of the bone marrow causes arrest of the maturation of the megakaryocytes, thus producing thrombocytopenia.

Since the virus could rarely be isolated after shock or after the fourth day of disease and since the immunity response was very quick, it is probable that the virus dies after the fourth day of disease. Dying virus or its products may produce an endotoxin-like substance that causes constriction of the liver venules, thus leading to the pooling of blood in the splanchnic area. Shock develops because of the reduction in the circulating blood volume. Thereafter all the pathophysiological changes are similar to those of the septic-shock or the endotoxin-shock syndrome. As the blood pressure is low in the shock state, the tissues become toxic from anoxia and acidosis develops. The capillaries also suffer further injury, and intravascular fluid and low-molecular-weight colloids seep into the serous cavity. The plasma volume is thus reduced, while the red cell volume remains the same. The blood is concentrated, as shown by elevation of the haematocrit and haemoglobin values, and pooling of blood in the splanchnic area causes further enlargement of the liver. Anoxia of the liver causes further impairment of liver function—for example, deficiencies in the prothrombin complex (Factors II, VII, IX and X) and in Factor V, which aggravate haemorrhage, particularly in conjunction with thrombocytopenia and increased capillary permeability. Thus, a vicious circle is created and if it cannot be broken the patient will die from tissue anoxia and/or haemorrhage.

* Originally issued as document IR/Haem.Fever/Sem.1/WP/17.

[1] Department of Pediatrics, Faculty of Medicine and Siriraj Hospital, University of Medical Sciences, Bangkok, Thailand.

1785

Dengue Infection in Thai Children: A Pathophysiological Study *

MAYUREE BALANKURA,[1] AREE VALYASEVI,[2] CHAIYAN KAMPANART-SANYAKORN [3] & SANFORD COHEN [4]

Clinical material

117 patients, aged 5 months through 17 years, were admitted to the Thai Haemorrhagic Fever Study Centre with a tentative diagnosis of "Thai haemorrhagic fever". Of these 117 children, 94 had a serological diagnosis of acute dengue infection. Twenty-one of these dengue patients developed the shock syndrome during the course of the illness.

* A preliminary report from the Thai Haemorrhagic Fever Study Centre, Bangkok, Thailand. Originally issued as document IR/Haem.Fever/Sem.1/WP/28.

[1] Lieutenant-Colonel, Medical Corps, Royal Thai Army; Director, Thai Haemorrhagic Fever Study Centre, and Senior Paediatrician, Royal Thai Army Hospital, Bangkok, Thailand.

[2] Director, Thai Component, SEATO Clinical Research Centre, Bangkok, Thailand.

[3] Faculty of Public Health, University of Medical Sciences, Bangkok, and US Component, SEATO Medical Research Laboratory, Bangkok, Thailand.

[4] Captain, Medical Corps, US Army; US Component, SEATO Medical Research Laboratory and SEATO Clinical Research Centre, Bangkok, Thailand.