

Chapter XIII

Humoral changes in the blood in cases of malignant disease explained on the basis of limax amoebae infection

It has been concluded that in many manifestations of collagen and auto-immune disease there must be some abnormal substance circulating in the blood to produce such disturbances as Köbner's phenomenon, Henoch-Schönlein purpura and various disturbances of the hypothalamus, such as mental disease, paralysis agitans, thyrotoxicosis, diabetes, etc. *Limax amoebae* infection appears to be responsible for many of the bodily disturbances associated with malignancy and substances derived from the organism must exist in the blood in such circumstances. Nakahara and Fukuoka (1950) isolated from tumours a substance they called "toxohormone", apparently protein-like and heat stable, which affected the liver catalase in mice and disturbed protein metabolism. This could well be derived from *limax amoebae* in the tumour. Again, in many cases of leukaemia there may be abnormal bleeding and petechial haemorrhages with a positive cuff test (symptomatic purpura). Allen et al. (1949), Barnard (1948) and others found these phenomena resembled the effects of heparin administration and the bleeding time was prolonged and the clotting time decreased. They found that the bleeding tendency ceases and the bleeding and clotting times may return to normal after intravenous administration of an antiheparin, such as toluidine blue or protamine sulphate. The author confirmed this as in the following case:-

Case 99 Female, aged 50 years, suffering from chronic myeloid leukaemia with severe generalized petechiae and bleeding from nasal mucosa and gums. The bleed-

ing and clotting time were determined before and two hours after the slow intravenous injection of 1 ml. of 1 per cent protamine solution. On the first occasion the readings were as follows:-

Bleeding time (Dukes method)	Before injection	2 hours later
Normal		5 minutes
2-5 minutes	9 minutes	10 seconds
Clotting time (Wrights method)		
Normal	5 minutes	9 minutes
6-12 minutes	20 seconds	

There was immediate cessation of the bleeding and appearance of petechiae for 8 days, when both returned. The injection was repeated with the following result:-

	Before injection	2 hours after
Bleeding time	9 mins. 35 secs.	4 mins.
Clotting time	3 mins. 50 secs.	6 mins. 15 secs.

Since protamine and toluidine blue neutralize mucopolysaccharides like heparin, this suggests that such a substance exists in the blood in this condition. It will be recalled that *limax amoebae* give a strongly positive PAS stain indicative of the presence of mucopolysaccharides in the cytoplasm. It may well be that the substance in the blood in the above situation is a mucopolysaccharide derived from *limax amoebae*.

Intravascular clotting and cancer

Earlier it was pointed out that a tendency to intravascular thromboses was a feature of rheumatoid disease, that is *limax amoebae* infection, while in advanc-

ed cases of malignant disease there exists in the blood a mucopolysaccharide heparin-like substance, which decreases the clotting time and must tend to favour the occurring of spontaneous intravascular clotting in such circumstances. A tendency to recurrent thrombophlebitis of various vessels may be observed in cases of lymphomata, leukaemia and myelomatosis and malignant disease of various organs (Wintrobe, 1967) including carcinoma of the pancreas, bronchus, gall-bladder, stomach, ovaries, uterus, etc. (see Evans, 1966; Wintrobe, 1967; Willis, 1967). The tendency for thrombophlebitis to affect a number of vessels in succession has been given the name thrombophlebitis migrans, but this is unsatisfactory as not only are veins subject to thromboses, but there is also a widespread thrombotic occlusion of

small arteries, friable vegetations on the heart valves, later giving rise to verrucose endocarditis and infarctions of various organs (Smith and Yates, 1955; Rohner et al., 1966; Zuffa et al., 1972). The endocarditis may eventually be indistinguishable from that occurring in rheumatic heart disease. Histologically the affected vessels exhibit an inflammatory change in their walls with numerous lymphocytes and often giant cells and often with well-marked periphlebitis. There may be considerable proliferation of the endothelium. The changes may be related to the vasa vasorum and the accompanying nerve bundles may also be affected. It is tempting to suppose that this phenomenon could be due to the heparin-like substance derived from limax amoebae in the tumours and elsewhere.