FIG. 2—Histological section of brain showing perivenous demyelination with cellular infiltration. (Loyez myelin preparation. $\times 350$).

vaccination against smallpox (Brain and Walton, 1969). This type of lesion when due to viral infections and prophylactic vaccination appears to have an allergic basis (Miller *et al.*, 1956; Greenfield and Norman, 1963). There is evidence that the inflammatory reaction with oedema and perivascular cuffing results from a combination of Coombs's type 2, 3, and 4 reactions (Webb, 1969). Peripheral neuropathy, probably of an allergic origin, has been documented after preventive inoculation against typhoid fever (Greenfield and Norman, 1963). Thus the acute encephalomyelitis in this patient, like the occurrence of a Guillain-Barré syndrome as a complication of typhoid fever (Chanmugam and Waniganetti, 1969), probably

resulted from an allergic process in the nervous system due to infection with *S. typhi*.

Studies on viral encephalitis have indicated that severe viraemia and the late appearance of antibodies, resulting in an excess of antigen over antibody, may be of importance in the pathogenesis of the disease (Webb, 1969). Interestingly our patient had a septicaemia late in the course of his clinical illness with a poor antibody response.

Though metabolic disturbances, toxæmia, hyperpyrexia, vitamin deficiency, and non-specific cerebral changes such as oedema and vascular lesions have been postulated as the pathogenesis of the neurological complications in typhoid fever (Wilson and Bruce, 1954; Aita, 1972) there appears to be little doubt that in some cases acute disseminated encephalomyelitis could be the cause. The present case also illustrates that bacterial infections, like viral infections, can produce neurological manifestations due to the occurrence of an acute disseminated encephalomyelitis.

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Hypofibrinogenaemia as a Cause of Bleeding in Chronic Myeloid Leukaemia

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Hypofibrinogenaemia is an occasional, well-documented complication of acute leukaemia (Rosenthal, 1963; Didisheim *et al.*, 1964; Hirsh *et al.*, 1967; Rand *et al.*, 1969; Goldman, 1974) and is seen most characteristically in patients with acute promyelocytic leukaemia. Excessive fibrinolysis was originally postulated as a cause of hypofibrinogenaemia but recent evidence has shown that fibrinogen utilization is secondarily increased as part of the process of disseminated intravascular coagulation.

We report here the first example of hypofibrinogenaemia secondary to chronic myeloid leukaemia.

Methods

Standard haematological investigations were carried out using a Coulter S electronic blood cell counter or by the methods of

Dacie and Lewis (1968). Additional coagulation tests included estimation of the kaolin cephalin clotting time (Proctor and Rapaport, 1961), factor V assay (Kappeler, 1955), factor VIII assay (Pool and Robinson, 1959), fibrinogen titre and fibrinolysis estimation (Sharp *et al.*, 1958), and assay of fibrinogen degradation products (Pitcher, 1971). Studies of fibrinogen turnover using ^{125}I -labelled fibrinogen were performed by the method of Jeyasingh *et al.* (1970).

Platelet aggregation studies were performed by the method of Born (1962) using adenosine diphosphate (ADP) at a final concentration of 5 mg/l, adrenaline at 5 mg/l, and thrombin at 500 U/l. Collagen was prepared by extracting 750 mg equine collagen (Sigma Chemicals Ltd.) with 10 ml 0.15M sodium chloride. A 0.1-ml sample of the extract was added to 1 ml platelet-rich plasma.

The Philadelphia chromosome was identified by using the method of Woodliff (1971).

Case History

A 69-year-old woman was admitted to this hospital in January 1973 complaining of spontaneous skin bruising and nose bleeds for eight weeks. Examination showed massive confluent bruising over her abdomen, chest, back, and limbs with multiple bilateral flame-shaped fundal haemorrhages. The liver was palpable 6 cm below the right costal margin and the spleen was enlarged 22 cm from the left costal margin. Her temperature was normal and there were no signs of infection. Haemoglobin concentration was 5.7 g/dl, W.B.C. $216 \times 10^9/\text{l}$. (polymorphs 51%, basophils 8%, metamyelocytes 8%, myelocytes 17%, promyelocytes 7%, myeloblasts 2%), and platelet count $490 \times 10^9/\text{l}$. Bone marrow aspiration showed a cellular marrow with an excess of myelocytes and metamyelocytes but without an excess of myeloblasts (<5%). Myeloblasts were negative for periodic-acid Schiff and Sudan black and contained no Auer rods. Promyelocytes (8%) were present in slight excess and most showed heavy cytoplasmic granulation. The Philadelphia

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Results of Coagulation Studies at Presentation (January 1973) and after Busulphan Therapy. Figures in Parentheses Represent Control Estimation or Normal Value for Investigation Shown.

	January 1973	March 1973	June 1973	August 1973
Bleeding time (min)	4	3		
Whole-blood clotting time (min)	6-7	8		
One-stage prothrombin time (s)	16.0 (12.5)	13.5 (13)	14 (14)	13 (14)
Kaolin cephalin clotting time (s)	43 (38)	41 (37)	33.5 (37)	39 (39)
Prothrombin consumption index (%)	75 (<20)	33 (<20)	37 (<20)	24 (<20)
Thrombin clotting time (s)	14 (12)	12 (12)	13 (12)	13 (14)
Fibrinogen titre	$\frac{1}{2}$ (1/32-1/128)	1/128	1/128	1/128
Fibrinogen degradation products (assay) (mg/l)	160 (<20)	<20	<20	<20
Platelet count ($\times 10^9/l$)	490	260	105	110
Platelet aggregation with:				
ADP	Normal		Normal	
Adrenaline	Grossly impaired		Normal	
Thrombin	Absent		Normal	
Collagen	Absent		Normal	
^{125}I -fibrinogen turnover (h)	20 (72-96)		88 (72-96)	
Fibrinolysis	Not increased			

chromosome was identified in all cell preparations from the bone marrow. No other chromosomal abnormality was seen. Indices of liver function were normal and remained so throughout. Blood cultures were sterile.

Busulphan 6 mg daily by mouth was started after transfusion to a haemoglobin concentration of 11.7 g/dl. No further bruising or bleeding occurred and bruising had completely resolved 12 days later. As the W.B.C. fell towards normal busulphan was reduced to a maintenance dose of 1-2 mg daily. The liver and spleen slowly reduced in size and were not palpable in June 1973, by which time the blood count had returned to normal in all respects. A repeat marrow aspiration sample was normal apart from a persistence of the Philadelphia chromosome. The patient remained in excellent health.

Coagulation Studies.—Results of investigations at the time of presentation (January 1973) and after two months, five months, and eight months of busulphan treatment are shown in the table. The initial hypofibrinogenaemia was associated with a rapid rate of fibrinogen turnover. The high level of fibrinogen degradation products suggested that the primary process was a disseminated intravascular coagulation. With the exception of an increased prothrombin consumption index all the coagulation values including fibrinogen turnover had returned to normal by the time the patient had reached a clinical and haematological remission (June 1973). Immunoelectrophoresis of her plasma against antihuman fibrinogen at the time of presentation showed no evidence of dysfibrinogenaemia.

Comment

Hypofibrinogenaemia in association with leukaemia was first noted by Croizat and Favre-Gilly (1949) but its particular association with acute promyelocytic leukaemia was not realized for about 15 years, when Rosenthal (1963) and Didisheim *et al.* (1964) reported several cases, and by infusing fibrinogen into their patients showed an increase in fibrinogen turnover. This disorder is associated with severe and prolonged haemorrhage, and in addition to hypofibrinogenaemia the presence of fibrin degradation products in the serum can often be detected.

Though a bleeding diathesis associated with a low fibrinogen titre has been noted after blast-cell transformation (Hirsh *et al.* 1967) the present case is the first well-documented example of hypofibrinogenaemia due to chronic myeloid leukaemia. The patient showed the clinical and laboratory features of disseminated intravascular coagulation, the only contradictory finding being a platelet count at the time of presentation of $490 \times 10^9/l$ (Deykin, 1970). It is not clear why platelet aggregation was abnormal (see table) but a similar defect has been noted in patients with myeloproliferative disease (Gilbert, 1973) and in patients with disseminated intravascular coagulation (Kowalski *et al.*, 1964).

The coagulation defect in our patient resembled that produced by aspirin, but careful questioning of the patient excluded this possibility. A further consideration was the possibility that the abnormal granulocytes were contributing directly to the coagulation defect. By incubating leucocytes from the patient's peripheral blood with normal plasma we examined them for procoagulant or fibrinolytic activity. Neither was increased when compared with normal leucocytes. While this single observation must be interpreted cautiously it is at variance with the suggestion made by Sultan *et al.* (1973) that a thromboplastin-like material may be released from granulocytes in patients with similar bleeding disorders. However, our observation suggests that further studies, particularly of bone marrow granulocytes, are needed before their hypothesis can be accepted.

In view of the fact that virtually all patients with chronic myeloid leukaemia will respond to busulphan therapy in the initial stages of the disease it seemed logical to try to reverse our patient's coagulopathy by this method. We were able to reverse bleeding within a few days of starting treatment, and with the exception of the prothrombin consumption index all the coagulation values returned to normal once she entered remission of her disease (June 1973). The abnormality in the prothrombin consumption index had returned almost to normal two months later (see table) and it is likely that the defect on the three previous occasions reflected abnormal platelet function.

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