Paroxysmal Nocturnal Haemoglobininurin and Leukaemia

Paroxysmal nocturnal haemoglobininuria is an uncommon and puzzling disease which has been the subject of considerable study and speculation by haematologists. It can be diagnosed in the laboratory by lysis of the erythrocytes when, in the presence of fresh normal serum, the pH of a sample of the patient’s blood is reduced to between 6.5 and 7.0 (the acidified-serum or Ham's test) or the blood is suspended in a medium of low ionic concentration (the sugar lysis test). These tests depend on a unique sensitivity of the cells in this disease to lysis by complement. A remarkable feature of this condition is that one group of cells is usually extremely sensitive to lysis, whereas the remainder of them are normal or only slightly more sensitive than normal. This suggests that there are two distinct populations of red cells circulating. The finding is consistent with evidence from cell-survival curves of two types of cell and the finding of a mixture of normal and structurally abnormal cells in electron-microscope preparations of blood from patients with this disease.

A relationship between paroxysmal nocturnal haemoglobininuria and marrow aplasia has been well established. It varies from patient to patient. Some have signs of moderate or severe haemolysis with strongly positive in-vitro tests at the same time as they show evidence of chronic marrow hypoplasia and pancytopenia. Others have transient attacks of marrow failure during the course of the disease. Conversely there are patients in whom aplastic anaemia has been the first diagnosis. They appear to be suffering from aplastic anaemia throughout their illness, but they produce a small number of red cells characteristic of paroxysmal nocturnal haemoglobininuria. Sometimes the haemoglobininuria becomes predominant, and it is this which may determine the eventual outcome rather than the aplastic anaemia. Paroxysmal nocturnal haemoglobininuria, or at least the production of a proportion of cells with the defect characteristic of it, probably occurs in 10–20% of patients with aplastic anaemia. It seems to occur irrespective of whether the marrow hypoplasia is familial, induced by a drug or toxin, or idiopathic.

The link between the two diseases might be the development of an abnormal clone of haemopoietic cells in a regenerating, previously aplastic marrow, or alternatively whatever induces bone marrow hypoplasia might also cause the abnormal clone.

The persistence of a damaged or mutated clone of abnormal cells in an otherwise normal marrow is consistent with the haematological findings, especially the two populations of red cells referred to above, though it is difficult to understand the phenomenon in those cases in which the abnormal clone remains as a minor population for a long time, perhaps for many years, without either extending or being eliminated.

The onset of acute leukaemia as a complication of aplastic anaemia has been known for a considerable time. It may develop after irradiation,
after chemical injury, especially benzene poisoning, and after chloramphenicol-induced aplasia. Here, too, it may be that an injury which induces hypoplasia of bone marrow is also leukaemogenic, or alternatively that leukaemia develops as a result of an abnormal hematopoietic cell line in a regenerating marrow. In 1967 W. Dameshek suggested that there might also be a link between leukaemia and paroxysmal nocturnal haemoglobinuria, possibly by the abnormal clone leading to the haemoglobinuria in one patient and leukaemia in another. This speculation of a relationship between the two is supported by recent reports from three different centres on the occurrence of acute granulocytic leukaemia in patients with paroxysmal nocturnal haemoglobinuria. In all three cases the latter condition was diagnosed beyond doubt on the basis of in-vitro tests and had probably been present for three to six years before leukaemia became apparent. In none of the cases had there been a pre-existing aplastic anaemia. A history of exposure to possible injurious substances was elicited in only one of the patients, a 58-year-old man who had been receiving isoniazid and p-aminosalicylic acid for pulmonary tuberculosis.

The publication of these reports has stimulated Dameshek to repeat his earlier speculation and to remark that the termination of paroxysmal nocturnal haemoglobinuria as acute leukaemia is reminiscent of a similar course in some cases of myelosclerosis, chronic granulocytic leukaemia, polycythaemia vera, and erythraemic myelosis. In this context it is, perhaps, significant that in paroxysmal nocturnal haemoglobinuria the defect is not confined to the red cells but that leucocytic alkaline phosphatase is unusually low, as it also is in chronic granulocytic leukaemia and in some cases of myelosclerosis with myeloid metaplasia. Dameshek postulates that paroxysmal nocturnal haemoglobinuria could be regarded as a myeloproliferative disorder of the same type as erythraemic myelosis. This interesting suggestion deserves study but requires more substantial evidence. But at least it might be worth while to do a screening serological test for paroxysmal nocturnal haemoglobinuria in all cases of acute leukaemia, and conversely patients with this haemoglobinuria should be closely supervised with the possibility in mind of leukaemia developing.

Poisoning Treatment Centres

In 1962 a committee set up by the Ministry of Health recommended the designation of district centres for the treatment of poisoning and one specialized poisoning treatment unit within each region. Each district centre was to have a physician in charge specially interested in this field, who could readily call on the services of a consultant anaesthetist or psychiatrist. Last year another official committee, the Hill Committee on the Hospital Treatment of Acute Poisoning, commented that though the district and regional centres had been designated "so far as we can tell, cases of poisoning continued to be received at any local accident and emergency centre." It also pointed out the inadequacy of the supporting laboratory services and the failure of physicians with a special interest in clinical toxicology to emerge except in a few centres. The report recommended that all accident and emergency departments should be staffed and equipped for dealing with cases of acute poisoning of both adults and children. The centres should also have psychiatric cover and adequate laboratory support.

The Department of Health and Social Security commended the report to regional hospital boards and boards of governors, stating that the full implementation of the recommendations might not be practicable immediately or in all areas, and in any case would be subject to the demands of other hospital services on available resources.

This week Dr. Henry Matthew and his colleagues report at p. 489 on the centre at the Edinburgh Royal Infirmary, which functions in the manner recommended by the reports. In fact, since the unit has been in existence for over 90 years, it is likely that the recommendations of both reports were influenced to a large extent by it. This paper should help hospital authorities even though no costing information is supplied. There do, however, appear to be certain developments in the management of these patients which might make a difference in the ease and speed with which regional hospital boards are able to implement the Hill report.

The report recommended that every designated poisoning treatment centre should have associated laboratory facilities for carrying out at least the detection and quantitative estimation of carbon monoxide, alcohol, barbiturates, salicylates and iron in blood, and phenothiazines in urine only qualitatively, at short notice throughout 24 hours. Matthew and his colleagues question the need for such a service for several reasons. Firstly, the actual demand for an emergency request is minimal (9 per month average). Secondly, the number of cases in which antidotes for the poisons are available is comparatively few. Thirdly, those cases that do require emergency pathological investigations need principally and preferably electrolyte and blood gas analyses. Fourthly, it is now possible to detect the two commonest drugs taken (barbiturates and salicylates) by simple "side-room" methods. It appears, therefore, that the normal laboratory services associated with accident and emergency departments are adequate to manage these patients.