HEMPAS

An important mechanism of anaemia is reduced production of red cells by the bone marrow. This can be due to a reduction in the number of erythropoietic cells, as in aplastic anaemia, leukaemia, and myelosclerosis. Conversely production of red cells may fail despite an abundance of erythropoietic marrow, a state termed ineffective erythropoiesis or dyserythropoiesis.[1] It is characterized by a rapid iron turnover; intramedullary death of developing red cells, giving rise to increased production of bilirubin and reduced delivery of cells to the blood; and often abnormalities in shape, size, and function of circulating cells, so that their survival is moderately shortened.

Dyserythropoiesis is a major factor in the anaemia due to deficiency of vitamin B_{12} and folic acid, and in thalassaemia and sideroblastic states.[1] A dyserythropoietic component of lesser degree also occurs in aplastic anaemia, myelosclerosis, and iron deficiency anaemia.

A group of congenital refractory anaemias is characterized by erythropoietic hyperplasia of the bone marrow with a large proportion of morphologically abnormal and multinucleate erythroblasts together with dyserythropoiesis. These congenital dyserythropoietic anaemias appear to be rare but it is possible that more cases remain to be recognized. It has been suggested[2] they should be considered in the differential diagnosis of refractory anaemias, especially macrocytic anaemias not responding to folic acid or vitamin B_{12}, primary sideroblastic anaemias, atypical thalassaemia, and atypical hereditary haemolytic anaemias.

H. Hempel and F. Wendt[3] have divided the congenital dyserythropoietic anaemias into three main types—I, II, and III. Type II, designated Hereditary Erythrocyte Multinuclearity associated with a Positive Acidified Serum test and abbreviated to the acronym HEMPAS, has been particularly well studied.

The clinical, haematological, and serological features of HEMPAS have recently been reviewed.[4] The disease has been reported from many countries, but almost all the patients have been Caucasians. Both sexes are affected and the inheritance is autosomal recessive. Most of the patients have been diagnosed during childhood, but some were not recognized till adulthood. Mild to moderate anaemia and jaundice are characteristic clinical findings, and there appears to be relatively little disability. Less than a quarter of the reported patients were sufficiently anaemic to need repeated transfusions. The spleen is usually moderately to greatly enlarged and the liver often slightly enlarged, with heavy iron deposits. Some patients had gall stones or hepatic cirrhosis, a few were mentally retarded, and one had bilateral cataracts.

The white cell and platelet counts and the absolute reticulocyte counts are usually normal. The red cells are mostly normochromic and show anisocytosis, but some are irregularly contracted or hypochromic and microcytic. In stained blood films tear-drop poikilocytes and basophilic stippling are often seen as well as an occasional erythroblast. The osmotic fragility of red cells may be slightly abnormal, but most cases show normal autohaemolysis.

The bone marrow is the most striking feature of HEMPAS. It is very hypercellular, with erythroblasts accounting for 50-90% of the nucleated cells (they normally comprise fewer than 30%). The morphological abnormalities are mostly in the intermediate and late normoblasts, 10-35% of which are binucleated, and about 10% contain from three to seven nuclei. Multilobed nuclei and nuclear fragmentation have also been noted, and there may be mild megaloblastic changes. Iron-laden macrophages, some containing phagocytosed red cells and erythroblasts, are conspicuous and are evidence of intramedullary destruction of developing and mature red cells—the morphological expression of the ineffective erythropoiesis.

Electron-microscopy of erythroblasts has shown an abnormality in the form of an extra linear structure parallel to the inside of the cell membrane. It seems possible that this abnormality may be responsible for the defective cell division, which in turn gives rise to multinucleated erythroblasts, and for the characteristic serological reactions.

The plasma level of unconjugated bilirubin is raised and the serum iron and transferrin saturation are abnormally high. The haptoglobin level is often low, and the plasma lipids, including cholesterol, are reduced. Plasma iron clearance is accelerated, iron turnover much increased, but iron incorporation into red cells much reduced. Red cell survival is moderately shortened, and the survival curve shows a single population of red cells. Though the anaemia and hyperbilirubinaemia are chiefly due to intramedullary destruction of erythroblasts, shortening of the life span of circulating red cells contributes to it in varying degree.

HEMPAS red cells are agglutinated and lysed by an IgM antibody present in many normal acidified sera but not in the patient's serum. This finding is characteristic and diagnostic of HEMPAS, distinguishing it from the other types of congenital dyserythropoietic anaemias. The mechanism of lysis differs from that in paroxysmal nocturnal haemoglobinuria in which the red cells lyse in fresh normal serum, including the patient's serum, because they are very sensitive to lysis by complement. HEMPAS red cells are strongly agglutinated by anti-i (like the red cells of newborn infants) and are also lysed by anti-i and anti-I, but these reactions are less specific.

[1] Lewis, S. M., and Verwilghen, R. L., *British Journal of Haematology*, 1972, **23**, 1.
[2] Lewis, S. M., Nelson, D. A., and Pitcher, C. S., *British Journal of Haematology*, 1972, **23**, 113.
[3] Heimpel, H., and Wendt, F., *Helvetica Medica Acta*, 1968, **34**, 103.
[4] Verwilghen, R. L., Lewis, S. M., Dacie, J. V., Crookston, J. H., and Crookston, M. C., *Quarterly Journal of Medicine*, 1973, **42**, 257.

Meeting in Guernsey

This autumn the B.M.A. will hold the second of its Annual Postgraduate Meetings in Guernsey. The first, at Inverness last year, was such a success that plans were immediately laid for further meetings of their kind, and a cordial welcome awaits visitors to Guernsey on 28-29 September. The programme is published in the *Supplement* this week. As well as having a distinctive local flavour it offers some first-rate postgraduate teaching.