Paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria is a rare, acquired haemytic anaemia in which the circulating red blood cells are abnormally sensitive to lysis by activated serum complement. As the name implies, excessive destruction of red cells takes place mainly during the night so that haemoglobinuria is seen only or principally in the early morning. The platelets and granulocytes in paroxysmal nocturnal haemoglobinuria are also abnormally sensitive to complement, and thrombocytopenia or granulocytopenia or both are often seen during the disease.

Paroxysmal nocturnal haemoglobinuria may be diagnosed simply and reliably by the acidified serum lysis (Ham’s) test; haemosiderinuria is a valuable sign of chronic intravascular haemolysis since iron-containing granules will be present in the urinary sediment even if there is no haemoglobinuria at the time. Haemolysis in paroxysmal nocturnal haemoglobinuria is due to a defect in the erythrocyte membrane. Nevertheless, not all circulating erythrocytes are equally sensitive to activated complement since a considerable population of abnormal cells usually coexist with moderately or normally sensitive red cells.

The proportions of normal and abnormal cells in a given patient can best be measured by analysing the curves obtained from complement lysis sensitivity tests. Thus the severity of haemolysis will depend on both the relative proportions of normal and abnormal cells and the degree of the abnormality. Platelets and granulocytes also interact abnormally with complement, and, as with the red cells, only some of the granulocytes are defective. These reactions may partly be responsible for the venous thromboses which occur in patients with paroxysmal nocturnal haemoglobinuria as well as for the chemotactic defect in the granulocytes incubated with activated complement. Recently Tumen et al have shown that erythroid and myeloid precursor cells also have an increased sensitivity to complement.

Paroxysmal nocturnal haemoglobinuria is a chronic disease, and, if threats such as haemytic crises and thromboses can be avoided, patients may live for many years. Venous thrombosis is a frequent problem in patients with paroxysmal nocturnal haemoglobinuria and can cause headache and abdominal pain. Progressive diffuse hepatic venous thrombosis is one of the most serious complications and a common cause of death. Indeed, abdominal pain in patients with paroxysmal nocturnal haemoglobinuria should be considered secondary to intra-abdominal thrombosis, particularly hepatic venous thrombosis, unless proved otherwise.

Recently Clarke et al have presented evidence of widespread renal lesions in paroxysmal nocturnal haemoglobinuria, which they attributed to repeated microvascular thrombosis, and no fewer than seven of the 104 patients reviewed by Polli et al died from renal failure. Vascular accidents in the brain caused the deaths of three of the eight patients reviewed by Clarke et al and 12 of the 104 reviewed by Polli et al. Neutropenia in paroxysmal nocturnal haemoglobinuria results in increased susceptibility to infection, which may be exacerbated by other factors such as saturation of the reticuloendothelial system as a result of haemolysis or abnormal granulocyte function.

There is good evidence that the abnormal cells in paroxysmal nocturnal haemoglobinuria arise from a defective haemopoietic stem cell, and that normal and abnormal cells coexist in the patient’s bone marrow. The clonal origin of the abnormal red cells in a patient with paroxysmal nocturnal haemo-

2 Central Midwives Board. Approved training syllabus, September 1980.
globinuria who was also heterozygous for the two variants of glucose-6-phosphate dehydrogenase (G6PD) was confirmed by finding that the red cells showing the paroxysmal nocturnal haemoglobinuria defect had a single-enzyme phenotype while the normal red cells had a double-enzyme phenotype. 10 Another patient presented with paroxysmal nocturnal haemoglobinuria and erythroblastopenia and only the neoplastic clone had the paroxysmal nocturnal haemoglobinuria abnormality. 11 The abnormality in granulocytes is also thought to be clonal. 12 13 The paroxysmal nocturnal haemoglobinuria clone may arise in a normal marrow or in one which is already abnormal. The abnormal clone may not persist but may gradually disappear with time and, rarely, patients with paroxysmal nocturnal haemoglobinuria develop aplastic anaemia. Indeed, the similarities between paroxysmal nocturnal haemoglobinuria and aplastic anaemia have been emphasised by Dacie and Lewis 15 and the myelodysplastic syndromes, including paroxysmal nocturnal haemoglobinuria and aplastic anaemia, share the tendency to transform to acute leukaemia.

Paroxysmal nocturnal haemoglobinuria is usually treated symptomatically. Nevertheless, the only definitive treatments for stem-cell disorders such as paroxysmal nocturnal haemoglobinuria are to alter or replace the abnormal stem-cell population. Stem-cell proliferation has not yet been altered beneficially but normal stem cells can be provided by bone marrow transplantation. A patient with paroxysmal nocturnal haemoglobinuria complicated by refractory marrow failure has been treated successfully by infusion of normal bone marrow. 16 Since the donor was an identical twin, the patient did not require immunosuppression before receiving the cells but, despite the lack of treatment directed against the abnormal clone, the abnormal cells were displaced by the normal bone marrow. Transplantation of allogeneic bone marrow has also been successful in the treatment of paroxysmal nocturnal haemoglobinuria. 17 18 Nevertheless, at present the hazards of allogeneic bone marrow grafting stand in the way of justifying transplantation as the treatment of choice for patients with paroxysmal nocturnal haemoglobinuria, who may live for years with conventional supportive treatment.


Research in the NHS

The difficulties encountered by NHS doctors in doing clinical research were the subject of a half-day seminar in Oxford last month, organised by the research committee of the Oxfordshire AHA(T). The origins of the seminar lay in the growing awareness among doctors in the Oxfordshire area of the difficulty of carrying out good research, and indeed much of the meeting was taken up with a catalogue of problems. Predictably, many of these concerned the inadequacy of resources, particularly time, laboratory space, and the skills of ancillary workers. Speakers also drew attention to NHS doctors’ uncertainties about their participation in research, the discouraging attitudes of some senior managers and authority members, and the difficulties that doctors might face in seeking help or collaboration from their local university. While no one suggested that health authorities should assume total responsibility for providing doctors with the resources needed for their research, several speakers argued that a more helpful and encouraging attitude by the authorities would not come amiss.

At a deeper level of analysis the seminar considered the hallmark of good research and the preconditions for its attainment. Some speakers, particularly those with outstanding records of research achievement themselves, argued that if high standards were to be maintained research workers must be trained properly through early exposure to the rigorous demands of the scientific method and must be insulated from all the non-scientific influences that detracted from a serious and dedicated commitment to a research career. Several factors were identified that militated against the training of good researchers in the NHS, including the rigid structures of specialist training that inhibited the development of an inquisitive mind, the sheer pressures of clinical work that often relegated research to the status of a spare-time activity, and the attractions of early promotion to a consultant post.

Other speakers rejected this approach as excessively purist, suggesting instead that research was an integral part of self-education and should thus be pursued by all doctors. There was a place, they claimed, for the careful collection and analysis of simple data as well as the theoretical and methodological complexities of advanced research, and the former needed encouraging and funding as much as the latter. The locally organised research scheme operated by the health authorities was regarded as a valuable way of promoting research, not only in providing funds (some £4m in the current financial year) but also in exposing research ideas and proposals to the critical appraisal of colleagues. Interestingly, however, the needs and experiences of general practitioners were not raised at all in the