How Should We Manage Myelofibrosis?

G. D. PEGRUM, MD, FRCP, FRC Path, *Professor of Haematology*, M. FOADI, MD, *Senior Lecturer*, M. BOOTS, MB, MRC Path, *Lecturer*, M. CLARKE, MB, *Lecturer*,
Haematology Department, Charing Cross Hospital Medical School, London

Primary idiopathic myelofibrosis, often referred to in the USA as agnogenic myeloid metaplasia, is a condition that usually presents as a pancytopenia or leucoerythroblastic blood picture[1,2]. This is almost always associated with marked splenomegaly and a dry marrow tap. Biopsy of the marrow shows evidence of increased reticulin. There are often numbers of teardrop poikilocytes in the peripheral blood and occasionally there is a leukaemoid blood picture, which usually occurs in patients evolving from polycythaemia rubra vera. Sometimes these conditions co-exist in a hybrid state with features of both conditions[3]. Thrombocythaemia is not uncommon and the patients may first be seen with evidence of thrombosis. Gout is occasionally a presenting feature, with a raised serum uric acid. Massive splenomegaly can sometimes be associated with portal hypertension[4,5]. There is evidence indicating that the marrow fibrosis in this condition is secondary to the development of an abnormal cell clone[6,7]. It is important to exclude secondary causes, especially metastatic tumours, and isotope studies should be done to demonstrate myeloid metaplasia. There is now considerable evidence of immunological dysfunction in myelofibrosis[8-10], and we have demonstrated the presence of immune complexes in all our patients[11]. This has led us to reconsider the management of this condition.

Traditionally, patients have received supportive therapy with blood transfusions. More active measures such as anabolic steroids[12-15], busulphan[14,16-18], splenic irradiation[19] and splenectomy[20,21] have all been used with varied success. After five years or less, patients usually develop increasingly severe anaemia and massive splenomegaly. At this stage splenectomy is often contemplated and has been shown to be beneficial[22] especially when portal hypertension is present[23]. However, the results are frequently disastrous, with precipitation of a blastic crisis[24], and many think that splenectomy has little to offer. Following our observations, we have chosen to take a more active approach to the management of this condition and used repeated courses of chlorambucil and prednisone[25]. Our view is that patients need to be treated early in their illness, and the spleen should not be allowed to extend beyond 10 cm below the left costal margin as measured in the midclavicular line. Reduction of spleen size may be slow initially, but it is important to continue with treatment even in the presence of pancytopenia. We prefer to use chlorambucil and prednisone, but other measures may be effective if introduced early and with perseverance. We have used two or four weekly courses on a continuous basis for more than three years without problems. Some patients whose clinical and haematological parameters remain satisfactory may be given less frequent courses of treatment.

Although we have only been using this management for four years, 21 patients who had been suffering from the disease for several years have been kept well, with good haemoglobin levels and minimal splenomegaly. We have endeavoured to keep the spleen size as small as possible but it seldom becomes impalpable and usually remains easily felt up to 5 cm below the left costal margin. During our studies two patients have developed increasing numbers of primitive cells, and one of them has died; the work of Goldman[26] suggests that it might be possible after ablative measures to reconstitute with peripheral blood stem cells obtained before treatment. Three other patients died of unrelated diseases. In our series portal hypertension has not occurred, no doubt due to keeping splenomegaly under control. Splenectomy does not appear to be necessary and we have not used this form of therapy for more than three years. The immediate morbidity and mortality, together with the poor long-term prospects[21], seem to contra-indicate this procedure, despite recent papers advocating splenectomy[27]. Peripheral arterial disease often complicates the condition in elderly males and this is certainly improved in patients treated in the manner we have described. Patients with the hybrid form of myelofibrosis often become markedly polycythaemic. The initial red cell mass may be normal or slightly increased. Treatment shrinks the spleen, reducing the degree of pooling, and accounting for an increase in haemoglobin and red cell mass. In these subjects we have continued to reduce the spleen size, venesecting when necessary to keep the PCV below 45 per cent. In some instances we have clear isotopic evidence of improved marrow function, but morphological evidence is more difficult to obtain, as can be expected from the variable nature of the marrow biopsy findings. There are now methods to measure the amount of reticulin[28], but these seem to be unrelated to haemoglobin levels, which are of clinical importance. Although it is difficult to judge the effect of therapy with an uncommon chronic condition such as primary myelofibrosis, the evidence we have indicates that these more active measures should be taken to improve both the morbidity and mortality.

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Dr Samuel Dodd Clippingdale

Dr Clippingdale was not directly connected with the Royal College of Physicians of London, but deserves to be remembered as an industrious and interesting medical historian. He was born in 1853, the son of a general practitioner in the East End of London. He trained in medicine at Aberdeen University and The London Hospital, and qualified MRCS in 1875. In the following year he obtained the Aberdeen MB, and in 1879 proceeded to the MD. In 1880 he became FRCS. He practised in Kensington, and was Surgeon to the Kensington Dispensary and Children's Hospital, and Police Surgeon for Kensington. Prominent in local medical affairs, he became President of the West London Medico-Chirurgical Society. His interests were wide. He was also Vice-President of the Section of Balneology and Climatology of the Royal Society of Medicine.

His work in medical history was largely on the biographical and personal sides, so he studied wills, pedigrees, heraldry, inscriptions on tombstones, and the registers of cemeteries. He was specially attracted to Kensal Green Cemetery, where a number of interesting medical men are buried. He was described as showing charm, sympathy, and old-fashioned courtesy. He also revealed a pleasing sense of the romantic and dramatic. He and Mr Victor Plarr, Librarian of the Royal College of Surgeons of England, obtained permission from Lord Ilchester to visit Holland House in the late afternoon of 17th June 1919, and sat reverently in the room in which Joseph Addison had died exactly 200 years before.

Dr Clippingdale wrote on climatology, heraldry, quackery, and rivers. His papers about medical men include:

'A Medical Roll of Honour—Physicians and Surgeons who remained in London during the Great Plague.' *British Medical Journal*, 1909, Feb 6th, p. 351.

Medical Parliamentary Roll (1558-1909). London, 1910.

'Medical Baronets, 1645-1911.' *British Medical Journal*, 1912, May 25th.

'The Crest of Thomas Greenhill, Surgeon. An Heraldic Tribute to Human Fecundity.' *West London Medical Journal*, 1914, **19**, 286.

'Medical Court Roll, Physicians and Surgeons and some Apothecaries, who have attended the Sovereigns of England from William I to George V, with a medical note on Harold.' MS, 2 vols.

He also wrote in *The London Hospital Gazette* a long series of biographies of former members of the staff of The London Hospital.

Of these works the Medical Court Roll is the most outstanding, and a remarkable compilation. It is a massive holograph manuscript in two volumes, now in the library of the Royal College of Surgeons of England. There is a photostat copy in the library of the Royal College of Physicians of London. The Roll covers the medical attendants not only of the monarchs, but also of members of their families over a period of 850 years, and includes much miscellaneous information on related topics. For this work alone medical historians remember Dr Clippingdale with gratitude. He died in 1925 in The London Hospital. There are obituaries in the *British Medical Journal* and Plarr's *Lives of the Fellows of the Royal College of Surgeons of England*, but not in *The Lancet*.

A. M. Cooke