The primary cause of anaemia in chronic renal failure is lack of erythropoietin production from damaged kidneys. Recombinant human erythropoietin (r-HuEPO) is now a widely available, though expensive, treatment for the anaemia of chronic renal failure, and is effective in more than 95% of cases. Complications of r-HuEPO in this context include hypertension in a third of cases, including hypertensive encephalopathy in a few, and thrombosis of shunts or vascular access devices. Fears that r-HuEPO would cause progression of renal failure have not generally been confirmed but hyperkalaemia may be a problem in the initial phase of treatment. r-HuEPO is up to twice as efficient in effect when administered subcutaneously rather than intravenously. Responding patients will normally do so within 1 month of starting r-HuEPO. Failures to respond are usually due to iron deficiency or intermittent infection.

Other diseases associated with anaemia and an inappropriately low serum erythropoietin include prematurity, the anaemia of cancer and rheumatoid arthritis. The baseline serum erythropoietin may provide a guide to response in some of these cases. Although some encouraging results are being published, patients with these disorders should still be treated with r-HuEPO only as participants in clinical trials. Situations where the serum erythropoietin levels are normal or elevated where r-HuEPO has been employed include boosting of haematocrit presurgery as an adjunct to autologous blood donation, treatment of anaemic patients with myelodysplastic syndromes, and improvement of athletic performance.

Keywords: Erythropoietin, Anaemia, Renal failure.
Erythropoietin (EPO) is a glycoprotein hormone secreted into the blood by peritubular interstitial cells (possibly endothelial cells) in the kidney in response to renal hypoxia. It stimulates the growth and maturation of colony forming units–erythroid (CFU-E) and to a lesser extent burst forming units–erythroid (BFU-E) acting in concert with other colony stimulating factors, resulting in an increase in reticulocytes, and hence circulating red cells. The cloning and expression of the EPO gene in Chinese hamster ovary cells in 1985 led to the production of commercial quantities of recombinant human erythropoietin (r-HuEPO).

Two commercial preparations are commonly available. Epoetin alfa (Eprex®) manufactured by Ortho Cilag and Epoetin beta (Recormon®) from Boehringer Mannheim. The r-HuEPO in these preparations contains 165 amino acids and studies using blocking antibodies directed against specific areas of the EPO molecule and the generation of artificial mutant EPO molecules suggest that amino acids 99–110 are critical for the physiological action of EPO. The two commercial preparations are of equivalent clinical effect though differ in their carbohydrate content.

Although the production of cloned recombinant molecules such as EPO can be scaled up indefinitely without particular problem and the price may drop once the initial investment in research and development has been repaid, there may still be an advantage in the development of longer-acting EPO variants. These would allow longer intervals between dosing and produce a more ‘physiological’ effect with persistent high blood levels rather than the ‘peak and trough’ effect of intermittent dosing. Covalent conjugation of EPO with hydrophilic polymers such as polyethylene glycol (pegylation) may prolong its half-life, by making it more resistant to proteolytic conjugation.

**Dose and Duration of Therapy**

Doses in the range of 15–900 units per kilogram have been employed. Thrice weekly administration of r-HuEPO is compatible with convenient outpatient administration. Subcutaneous (s.c.) injection may be self-administered or given by less experienced grades of staff than intravenous (i.v.) injection. Subcutaneous administration has been compared with intravenous administration by Hörler, who analysed a number of studies, finding that s.c. administration of r-HuEPO could allow a dose reduction of 50%. Similarly Thomson converted 11 patients from i.v. to s.c. r-HuEPO administration without altering the dose and found an increase in mean haemoglobin level from 9.3 g/dl before conversion to 10.4 g/dl 3 months after conversion in the nine analysable patients. Both these studies may be criticized in that conversion was from i.v. to s.c. so that the marrow had been given the opportunity to ‘build up steam’ by development of erythropoietic hyperplasia and recruitment of developing erythroid precursors before the switch to the s.c. route of administration. Nevertheless there seems to be a clear advantage for the s.c. route, possibly because of the greater area under the curve of plasma EPO concentrations after s.c. administration. Pain after s.c. injection of the two commercial preparations of r-HuEPO or saline placebo has been assessed using a visual analogue score. The Boehringer Mannheim preparation was significantly less painful than the Cilag preparation and was also less painful than saline placebo. Both preparations contained the same amount of r-HuEPO in the same volume.

The physiological effect of EPO continues for some days after administration, in keeping with the in vitro observation that immediate neutralization of EPO effect with anti-erythropoietin antibodies after stimulation of erythropoiesis with r-HuEPO does not stop further erythroid maturation. Maintenance doses of erythropoietin used by Esbach & Adamson in the successful correction of the anaemia of haemodialysis patients were generally in the range 75–100 U/kg three times weekly though some patients required less than 50 units three times weekly to maintain the haematocrit over 35%. In a large multicentre European study of transfusion-dependent haemodialysis patients only one of 132 patients failed to achieve a target haemoglobin of 10 g/dl on a total weekly dose of 200–225 U/kg given i.v. twice or three times a week. A low starting dose (50 U/kg i.v. three times weekly) was recommended in order to allow the circulation to adapt to changes in haematocrit and viscosity.

Most patients respond within 3–4 weeks of initiating r-HuEPO, and there is no point in continuing treatment beyond this time without dose escalation. Table 1 summarizes the policy

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Bloomsbury policy on r-HuEPO use in renal failure</th>
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<tbody>
<tr>
<td><strong>Starting dose</strong></td>
<td>75 U/kg, self administered three times weekly s.c.</td>
</tr>
<tr>
<td>Target haemoglobin</td>
<td>8.5–10.0, maximum 10.5 g/dl</td>
</tr>
<tr>
<td>Blood pressure and blood count fortnightly</td>
<td></td>
</tr>
<tr>
<td>When target Hb level achieved cut dose every 2 months to establish maintenance dose</td>
<td></td>
</tr>
<tr>
<td>All patients on ferrous fumarate (equivalent to 200 mg iron/day)</td>
<td></td>
</tr>
<tr>
<td>If ferritin falls below 100 μg/l give i.v. iron dextran</td>
<td></td>
</tr>
<tr>
<td>All patients with functioning fistulae or aspirin 75 mg/day</td>
<td></td>
</tr>
<tr>
<td>Increase heparin dose if clotting of lines or dialysers occurs</td>
<td></td>
</tr>
<tr>
<td>For vascular access operation keep Hb&lt;10.0 g/l and give preoperative hydration</td>
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for r-HuEPO administration to patients with chronic renal failure in my own health district. Monitoring of iron status during therapy with r-HuEPO is obligatory as suboptimal responses are frequently due to developing iron deficiency. Such monitoring is usually performed by measurement of serum ferritin. Like other acute phase proteins, however, ferritin may be falsely elevated in the presence of inflammatory disease.

The use of the H*1 blood counter with its ability to estimate the proportion of hypochromic red cells which increase when iron deficiency develops, provides an inexpensive and immediate method of monitoring iron status. An example of data from red cell analysis in a patient with iron deficiency is shown in Fig. 1. In a study of 46 patients on dialysis in four separate units in the UK Macdougall et al. found that the proportion of hypochromic red cells increased during the first
3 months of r-HuEPO treatment. All patients were taking oral iron supplements. In 15 patients the percentage of hypochromic red cells exceeded 20%. All these 15 patients had transferrin saturations less than 20%. Five of 14 patients with >10% hypochromic cells after 3 months treatment were given intramuscular (i.m.) iron, and in all cases the percentage of hypochromic red cells fell to within the normal range in 6–14 weeks. If these findings are confirmed in a larger series then measuring the proportion of hypochromic cells may be the optimum method of detecting the onset of iron deficiency in patients taking r-HuEPO.

Nuclear magnetic resonance imaging may also be used to provide a non-invasive assessment of body iron status though it has as yet only been described in patients with iron overload treated with phlebotomy and erythropoietin.12

Bleeding, intercurrent infection, operation, aluminium toxicity and thalassaemia trait also impair the erythropoietic response to r-HuEPO therapy.

**Erythropoietin in Chronic Renal Failure**

Lack of erythropoietin production from damaged kidneys is the major cause of anaemia in chronic renal failure. Its replacement by r-HuEPO is therefore an attractive option. Numerous clinical studies have demonstrated that the anaemia can be substantially improved in more than 95% of patients. Esbach & Adamson9 have reported on a multicentre trial of 247 haemodialysis patients treated with r-HuEPO who increased their haematocrit by an average of 10%. r-HuEPO therapy also improves exercise capacity in proportion to the improvement in haemoglobin level.14 Figure 2 summarizes the improvements in haematocrit level found on various doses of r-HuEPO in three studies using i.v. dosing three times weekly. A clear dose-dependent response is seen.

The benefits of r-HuEPO are not confined to the physical symptoms of anaemia in renal failure. Temple et al.15 applied a battery of cognitive function tests to nine patients undergoing haemodialysis before and after r-HuEPO, comparing them with nine patients undergoing haemodialysis who did not receive r-HuEPO. The r-HuEPO group achieved a significant improvement in IQ score on the Wechsler Revised Adult Intelligence Scale of 8.7 points, compared with the control group improvement of 2.5 points. They concluded that anaemia makes a reversible contribution to uraemic cognitive dysfunction. The effect of r-HuEPO treatment on cognitive function in healthy volunteers does not appear to have been investigated.

Immune function in patients on r-HuEPO has been studied in several ways. Veyts et al.16 measured granulocyte respiratory burst activity in 22 haemodialysis patients on r-HuEPO. They found depressed phagocytic glycolytic activity of haemodialysis patients was normalized during
correction of anaemia by r-HuEPO treatment, and such improvement was more marked with prolongation of treatment. Patients undergoing haemodialysis have decreased secretion of IgA and IgG from cultured peripheral blood lymphocytes compared with healthy controls.\textsuperscript{17} This decreased secretion improves on r-HuEPO treatment. \textit{In vitro} studies suggest that this is due to a direct stimulant effect of EPO on B-lymphocytes.

r-HuEPO is bound to some dialysis membranes such as the copolymer of polyacrylonitrile and methallyl sulphonate\textsuperscript{18} and dialysis patients taking r-HuEPO should be given their injection after dialysis rather than before.

Hypertension is the commonest side-effect of r-HuEPO treatment. r-HuEPO treatment increases whole blood viscosity in proportion to haematocrit.\textsuperscript{19} Esbach & Adamson\textsuperscript{9} found that 31\% of their patients treated with r-HuEPO became hypertensive or required increase in drug treatment for hypertension. Van de Borne \textit{et al.}\textsuperscript{20} performed continuous ambulatory blood pressure monitoring on 13 patients treated with r-HuEPO. Although they achieved only a modest mean increase in haematocrit (7.5\%) they found that r-HuEPO increased the percentage of hypertensive (systolic > 140, diastolic > 90 mmHg) blood pressure measurements from 33\% to 52\%. The presumed mechanism for the hypertension is an increase in peripheral vascular resistance due to an increase in whole blood viscosity without reflex vasodilatation.

Stone \textit{et al.}\textsuperscript{21} reported on the r-HuEPO treatment of 12 patients with renal failure not severe enough to require dialysis. Eleven of these patients responded with an increase in haematocrit of at least 6\%, and the twelfth did not respond because of a lethal infection. Measurement of red cell mass confirmed that the increase in haematocrit was not due to a decrease in plasma volume. Two patients had worsening of their renal failure sufficient to require dialysis, raising the possibility that increase in haematocrit may cause a deterioration in renal function. Recent trials have not confirmed the impression of worsening renal function or hyperkalaemia with r-HuEPO (e.g. Clyne & Jogestrand\textsuperscript{14}) and studies on eight pre-dialysis patients who had anaemia corrected by r-HuEPO therapy showed no change in baseline glomerular filtration rate, renal blood flow and filtration fraction.\textsuperscript{22}

Pruritus can be a troublesome symptom in uraemia, not always responding to treatment of the renal failure. De Marchi \textit{et al.}\textsuperscript{29} investigated the effect of r-HuEPO (36 U/kg three times weekly) treatment in a double blind crossover fashion on pruritus in 20 patients with renal failure of whom 10 had severe pruritus. Eight of the ten patients with pruritus had a marked reduction in symptoms associated with a reduction in plasma histamine levels which were raised in patients with pruritus. The conclusion is that r-HuEPO lowers histamine levels in patients with renal failure. r-HuEPO improves the uraemic defect in platelet adhesion and aggregation independent of an effect on the haematocrit.\textsuperscript{23} Increase in haematocrit improves platelet access to endothelium which may also improve uraemic bleeding manifestations.

**Erythropoietin in Continuous Ambulatory Peritoneal Dialysis (CAPD)**

Quality of life in terms of energy, social life, relationships at home and leisure pursuits has been assessed in 22 CAPD patients with anaemia before and after r-HuEPO treatment using the Nottingham Health Profile.\textsuperscript{24} All parameters measured significant and sustained improvement. Improvement in well-being appears to be related to improvement in anaemia. Watschinger \textit{et al.}\textsuperscript{25} studied the pituitary function of chronic renal failure patients and found a variety of abnormalities including high FSH, and blunted pituitary responses to thyrotropin releasing hormone compared with normal. However, r-HuEPO treatment did not change the majority of hormones measured suggesting that improvement in well-being was not due to hormonal changes.

Dialysis efficiency\textsuperscript{26,27} has been investigated in a total of 43 patients on continuous ambulatory peritoneal dialysis, 17 of whom were treated with r-HuEPO. No significant relationship was found between the level of circulating haemoglobin and the peritoneal transfer efficiency of small solutes and water.

**Erythropoietin in Patients with Failing Renal Transplants**

Jindal \textit{et al.}\textsuperscript{28} treated nine patients with anaemia and failing renal transplants who were taking immunosuppressive agents with r-HuEPO. All patients responded, requiring an average maintenance dose of 120 ± 32 U/kg/week to obtain a haemoglobin of 10 g/dl. Immunosuppression in this context does not appear to suppress the marrow erythropoietic response to r-HuEPO. Reluctance to remove a failed kidney which is causing hypertension is sometimes partially due to worry that anaemia will be exacerbated due to the removal of endogenous EPO secretion. r-HuEPO may be used to prevent this anaemia.

The effectiveness of r-HuEPO in renal failure is such that failure of treatment should prompt a
Table 2

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Number of patients treated/placebo</th>
<th>Dose used</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmerson et al.76</td>
<td>16/8</td>
<td>50 to 150 U/kg (Mean 92)</td>
<td>47% required transfusion, compared with 88% in placebo group</td>
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<tr>
<td></td>
<td></td>
<td>s.c. x 2/week</td>
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<tr>
<td></td>
<td></td>
<td>100 U/kg</td>
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<tr>
<td></td>
<td></td>
<td>s.c. x 3/week</td>
<td>0% required transfusion, compared with 23% in control group. Mean Hb treated group after 3 weeks 11.8, compared with 10.0 control group Significant increase in reticulocyte count only</td>
</tr>
<tr>
<td>Halvorsen et al.77</td>
<td>14/13</td>
<td>100 U/kg</td>
<td>6/7 needed no transfusion. Mean haematocrit increased from 0.263 to 0.296. Thrombocytosis and neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i.v. x 3/week</td>
<td>Increased platelet and reticulocyte count, did not decrease transfusion requirements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 to 300 U/kg</td>
<td>1/4 rhEPO babies required transfusion compared with 3/4 of placebo group. Mean r-HuEPO group Hct after 8 weeks 31.4% compared with 25.2% in placebos</td>
</tr>
<tr>
<td>Phibbs et al.32</td>
<td>4</td>
<td>100 U/kg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>i.v. x 1/week</td>
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<tr>
<td></td>
<td></td>
<td>200 U/kg</td>
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</tr>
<tr>
<td>Halperin et al.78</td>
<td>7</td>
<td>100 U/kg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>s.c. x 5 week</td>
<td></td>
</tr>
<tr>
<td>Shannon et al.33</td>
<td>20</td>
<td>200 U/kg</td>
<td></td>
</tr>
<tr>
<td>Shannon et al.34</td>
<td>4/4</td>
<td>i.v. x 1/week</td>
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<td></td>
<td></td>
<td>100 U/kg</td>
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<tr>
<td></td>
<td></td>
<td>s.c. x 5 week</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>200 U/kg after 2-3 weeks</td>
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search for causes, particularly iron deficiency or intercurrent infection.

In the UK the average annual cost of r-HuEPO maintenance is approximately £2500 per patient. In a cost benefit analysis of r-HuEPO treatment this must be weighed against the cost of red cell concentrates, admissions for transfusion and disposables. In one of the few comprehensive studies of expenditure on r-HuEPO the true cost to the NHS of one year’s treatment was estimated as £1200 per patient.30 This is the effective cost of the reduction in morbidity associated with r-HuEPO treatment in renal failure. A study in Australia found a net cost-benefit to the whole community when the savings of returning to work (paying tax), stopping social security payments and transfer to home dialysis were taken into account.31

Erythropoietin in the Anaemia of Prematurity

The anaemia of prematurity is an exaggeration of the progressive physiological decrease in haemoglobin levels seen in the first 2 months after birth. It is associated with a reticulocytopenia, erythroid hypoplasia and an inappropriately low EPO level. Contributory factors are the decreased red cell lifespan and repeated blood sampling.

Phibbs et al.32 attempted to treat the anaemia of prematurity with 100 U/kg i.v. r-HuEPO twice weekly. Whilst they increased the reticulocyte count in r-HuEPO babies, compared with a placebo-treated group, no other benefit was found. In another placebo-controlled trial in 20 infants 200 U/kg/wk, i.v., transiently increased reticulocyte and platelet counts, but did not reduce transfusion requirements.33 A further study by the same authors34 used 100 U/kg daily for 5 days out of 7, increasing to 200 U/kg/day if target reticulocyte responses were not achieved after 2–3 weeks. Only one of four r-HuEPO treated babies required transfusion, compared with three of four placebo-treated control babies. At the end of 8 weeks treatment the mean haematocrit of r-HuEPO treated babies was 31.4% compared with 25.2% in the placebo group. Table 2 summarizes some of the studies of r-HuEPO in the anaemia of prematurity.

A transient hypoplastic neutropenia has been reported in neonates, but not adults, treated with r-HuEPO. Recently the mechanism of this cytopenia has been elucidated by in vitro culture work.35 By culturing adult and fetal stem cells with granulocyte colony stimulating factor (G-CSF) after pre-incubation with r-HuEPO they showed that fewer neutrophils were produced from fetal stem cells than adult stem cells. Adding r-HuEPO to cultures already stimulated with G-CSF did not impair neutrophil production in fetal or adult cultures. Production of macrophages from fetal and adult stem cells in macrophage colony stimulating factor (M-CSF) stimulated cultures was not affected by pre-incubation with r-HuEPO, in keeping with the clinical observation that monocytopenia was not found in r-HuEPO-treated neonates. Thrombocytosis has been noted by some investigators treating the anaemia of prematurity.
Erythropoietin in the Anaemia of Rheumatoid Arthritis (RA)

This disorder is a paradigm for the anaemia of chronic disease which affects many patients with longstanding inflammatory conditions, and is the commonest anaemia among hospitalized medical patients. This anaemia is characterized by a normochromic, normocytic blood picture which may occasionally be mildly microcytic and hypochromic, simulating iron deficiency. The serum iron and total iron binding capacity are low but the serum ferritin is normal or high. Iron stores are usually normal, but a proportion of patients will have absent iron stores in the bone marrow but a normal serum ferritin. A block in haemoglobin-derived iron reutilization has been proposed, and erythropoietin levels are often inappropriately low for the level of haemoglobin. Fortunately most patients are asymptomatic of their anaemia, and haemoglobins in the range of 9–12 g/dl are often well tolerated. For symptomatic patients however, blood transfusion provides only temporary relief, and runs the risk of stimulating red cell alloantibody production, making the selection of blood units to cover future joint replacement operations more difficult.

Patients with inflammatory disorders have increased secretion of Interleukin 1 (IL-1) produced by mononuclear cells, which has been demonstrated to suppress erythropoiesis in vitro. This suppression can be reversed by increasing doses of r-HuEPO, suggesting that trials of r-HuEPO would be worthwhile in anaemia of chronic disease.

Means et al. treated two rheumatoid patients with 100 U/kg three times weekly i.v. and found no significant response until the dose was increased to 150 U/kg, normal haematocrit values being reached after 4 months of treatment. Thus response to exogenous EPO is blunted in patients with RA in comparison with patients with renal failure. Unfortunately neither patient improved clinically in terms of functional activity during r-HuEPO treatment.

Pincus et al. treated 17 patients for 8 weeks with r-HuEPO or placebo and found a 6% increase in haematocrit in 4 of 13 r-HuEPO treated patients. All 11 patients who continued the study for a further 24 weeks reached a normal haematocrit level and 10/11 showed an increase in haematocrit of 6% or more. They required a dose between 12.5 and 250 U/kg i.v. three times weekly. This and other studies showed no improvement in activity scores during r-HuEPO treatment.

Erythropoietin in Myelodysplastic Syndrome

This heterogeneous group of pre-leukaemic clonal marrow disorders are characterized by mixed cytopenias. They are increasingly diagnosed in an ageing population and often treated by supportive measures. Anaemia, with requirement for recurrent transfusion, is a common feature of the myelodysplastic syndromes (MDS). Most anaemic patients with MDS have elevated serum EPO concentrations. Ganser & Hoelzer (1992) have summarized the published information on r-HuEPO in MDS. Of 121 patients treated with similar doses of r-HuEPO a fifth of patients had an increase in haemoglobin and a reduction in transfusion requirements. Some patients do appear to have an increase in platelet counts or a reduction in platelet transfusion requirements. It is known that megakaryocytes have receptors for EPO and r-HuEPO increases the platelet count in laboratory animals. There are some suggestions of a reduction in platelet transfusions in myeloma patients treated with erythropoietin in recent trials. However, it should be recalled that a low haematocrit is associated with an increased bleeding tendency and increasing the haematocrit by correction of anaemia by r-HuEPO may therefore improve bleeding manifestations.

The relatively low rate of responders in MDS compared with renal failure patients makes selection of patients for treatment in this group of diseases important. Will increase in dose of r-HuEPO increase the number of responders? Large doses of r-HuEPO have been employed by Casadeval et al. in the treatment of 14 transfusion-dependent myelodysplastic patients. They employed 100,000 units (approximately 10 times the conventional dose) by i.v. injection twice weekly. After treatment they found no significant change in haemoglobin, reticulocyte counts or transfusion requirements. However, in a study by Rose et al. of 41 MDS patients the response to r-HuEPO was to some extent predicted by the endogenous EPO levels. Responders had a median level of 46 U/l and non-responders 200 U/l. Adamson et al. measured transferrin receptor protein levels before and after r-HuEPO in an effort to determine which of 20 MDS patients would respond to r-HuEPO. Half their patients responded to r-HuEPO by a 50% decrease in transfusion requirement or increase in haematocrit of 6%. They could find no useful predictor of response. Clearly larger trials of r-HuEPO in MDS are needed to identify responding patients.

In vitro, myeloblasts possess receptors for granulocyte colony stimulating factor (G-CSF)
and G-CSF promotes the proliferation of reticulum cells.40 Worries that an increased rate of leukemic transformation would be found in patients with MDS treated with growth factors have not so far been substantiated.49 Cytogenetic analysis of 24 patients with MDS, of whom half had chromosome abnormalities, before and after erythropoietin treatment showed no evidence of an increase in numbers of chromosome abnormalities or ratio of cytogenetically normal to abnormal cells.42,50

Besides the endogenous serum EPO level other factors appear to be important in determining response in MDS, such as the number of BFU-E/CFU-E available to be stimulated—these are in any case often decreased in MDS.51

Erythropoietin in the Anaemia of Malignant Disease

This anaemia is multifactorial in origin. Contributing causes include anaemia of chronic disease, poor nutrition, marrow infiltration and effects of chemotherapy/radiotherapy. Erythropoietin levels are lower in anaemic cancer patients than in patients with iron deficiency with equivalent haemoglobin levels, suggesting the possibility of response to r-HuEPO.

James et al.52 studied 21 patients with anaemia and ovarian carcinoma receiving platinum-based chemotherapy. (Besides its effect on marrow function such chemotherapy may also decrease erythropoietin response by impairing renal function.) Treatment with 300 U/kg s.c. thrice weekly achieved a notable reduction in blood transfusion requirements and an increase in mean haemoglobin level compared with the control group.

Abels53 found that 150 U/kg three times weekly increased haematocrit levels and decreased transfusion requirements in his series of cancer patients undergoing chemotherapy.

It is possible that administration of r-HuEPO before chemotherapy may decrease the erythroid marrow suppression caused by chemotherapy, minimizing the requirement for transfusion.

Erythropoietin in Multiple Myeloma

Anaemia is a frequent presenting feature of multiple myeloma. Effective chemotherapy results in a reduction in plasma cell infiltration of bone marrow, and restoration of haemoglobin to normal levels. Patients receiving chemotherapy will have additional bone marrow suppression and patients who have not responded to treatment will remain anaemic. A high gamma globulin level may result in an increased plasma volume with haemodilution.

Ludwig et al.54 treated 13 anaemic patients with myeloma for an average of 30 weeks with escalating doses of r-HuEPO from 150 to 250 U/kg s.c. three times weekly. Eleven out of 13 responded with an increase in haemoglobin of at least 2 g/dl. These patients had normal renal function. No significant change in paraprotein levels was noted implying that treatment of the myeloma was not the cause of improvement. The publication of these data led to a brief flurry of correspondence from centres using androgens to treat the anaemia of myeloma, claiming equal efficacy at far less expense.

Multiple myeloma is associated with secretion of a paraprotein into the plasma, and a small proportion of cases will be associated with plasma hyperviscosity syndrome. An inappropriately low EPO level is sometimes found in multiple myeloma. Reinhart et al.55 have recently provided evidence that the anaemia in these cases may be the result of a mechanism to compensate for the high plasma viscosity. He studied 16 patients with myeloma/Waldenström's disease and found an inverse relationship between plasma viscosity and EPO levels in response to anaemia in these patients. Additionally, exchange transfusion experiments in rats were performed in order to change plasma viscosity independent of haematocrit. Raising plasma viscosity with gamma globulin prevented both plasma EPO and renal EPO mRNA responses to anaemia. The increased plasma viscosity of myeloma patients may reduce renal EPO production in response to anaemia. Caution should be exercised when administering r-HuEPO or blood transfusion to patients with myeloma and elevated plasma viscosity levels lest increased whole blood viscosity reduces tissue oxygenation despite increase in haematocrit.

Erythropoietin Before Surgery and Autologous Transfusion

Administration of r-HuEPO before surgery may be used to induce erythroid hyperplasia in the bone marrow so that when blood loss occurs during surgery the postoperative recovery in haemoglobin levels is accelerated—the bone marrow is already producing red cells. A higher haematocrit level at the start of surgery means that more red cells can be lost at surgery with less chance of anaemia postoperatively. In combination with autologous blood donation r-HuEPO can increase red cell production, allowing more blood to be donated, decreasing the exposure to homologous blood.
r-HuEPO has been investigated as an adjunct to preoperative autologous blood donation in Japan. Before elective orthopaedic surgery patients were randomly allocated doses of r-HuEPO between 3000 and 9000 U i.v. twice weekly from the time of the first blood donation. A total of 1.2 litres was collected from the patients in three weekly donations of 400 ml. The volume of red cells in the donations increased with the dose of r-HuEPO administered, and was more than that harvested from controls not treated with r-HuEPO. Serum EPO concentrations were measured in r-HuEPO and control patients. Patients receiving pretreatment with r-HuEPO had peak serum EPO levels at day 7 after surgery, and those not treated with r-HuEPO peaked on day 1 after surgery. r-HuEPO thus suppresses the natural EPO response to venesection, and thus should probably be continued into the postoperative period if maximum red cell production is to be achieved.

Surgery is associated with a well recognized risk of thrombosis in the postoperative period, due to immobility, increased platelet count, and other factors. If a predicted operative blood loss does not occur (i.e. the operation went well) a relatively high haematocrit due to preoperative r-HuEPO treatment may contribute to thrombotic risk in the postoperative period. Similarly if the operation was cancelled or postponed. The full application of prophylactic measures such as pressure stockings or low dose heparin may be necessary in such cases, and even venesection may be required in cases with a higher haematocrit than normal.

r-HuEPO may provide a useful adjunct to preoperative treatment of Jehovah’s witness patients or others who reject homologous or autologous blood transfusion. Surgeons in our own district have performed a hip replacement on a Jehovah’s witness patient with a preoperative haemoglobin of 9 g/dl, increasing it by r-HuEPO administration to 12.5 g/dl at the time of operation.

Erythropoietin to Improve Athletic Performance

In the 1968 Mexico City Olympic games held at 2000 metres above sea-level significant numbers of gold medals were awarded to athletes from Kenya, Tunisia and Ethiopia who had the advantage of training at altitude, a practice which results in a compensatory erythrocytosis and polycythaemia. Artificially induced erythrocytosis by homologous or autologous transfusion has been used in an effort to improve athletic performance ('blood doping'). r-HuEPO avoids the infective risks of homologous blood or a period of poor athletic performance after autologous blood donation in the lead-up to major competition. Although transfusion or r-HuEPO treatment is banned by the International Olympic Committee, such practices are almost impossible to detect. Training at altitude is not banned and Eastern block countries train athletes under reduced atmospheric pressure in hypobaric tanks. An increased red cell mass is found in long distance runners and Schwandt et al. found an increased EPO concentration 3 hours and particularly 30 hours after a marathon run. Possibly the chronic hypoxia associated with this activity stimulates renal EPO production.

Increasing the haemoglobin content of blood raises its oxygen carrying capacity and r-HuEPO has been shown to increase aerobic power and exercise endurance. The increase in circulating haemoglobin improves the pH buffering as haemoglobin buffers lactic acid produced by anaerobic muscle work such as short sprints. Temperature homeostasis is also improved, possibly because increased red cell mass allows more circulation through the skin capillary bed. Such circulation would normally be diverted to muscle.

The above are a minority of the factors involved in athletic performance and any increase in haematocrit will increase blood viscosity and potentially reduce blood flow. The major risk of r-HuEPO use in athletics is thrombosis due to the high haematocrit induced by r-HuEPO associated with dehydration due to sweating, and adequate fluid intake is critical.

Other Uses for r-HuEPO

Successful r-HuEPO treatment is associated with mobilization of iron into haemoglobin. Anaemia associated with iron overload is thus a more attractive option for r-HuEPO treatment than anaemia with normal or reduced iron stores. In iron overload states administration of r-HuEPO accelerates the rate at which venesection can be performed or reduces the drop in haemoglobin level induced by venesection.

In acquired immunodeficiency syndrome (HIV) treatment with zidovudine commonly causes anaemia by bone marrow suppression. r-HuEPO treatment reduces the number of transfusions required by those patients with starting EPO levels less than 500 U/l. In the USA the FDA has approved the use of r-HuEPO for this purpose.

In allogenic bone marrow transplantation (BMT) there is an inappropriately low serum EPO for the level of circulating haemoglobin compared with healthy controls and patients with iron
deficiency anaemia. Administration of r-HuEPO to ABO compatible allograft recipients from day 1 to day 30 decreased the time to reach a stable haematocrit from 123 to 58 days after the BMT. There was also a halving in the red cell transfusion requirement in the month after transplantation. It should be remembered that an average transplant requires 100 units of platelet concentrate and 10 units of red cells so reducing the number of red cell concentrates transfused will only slightly reduce the risks of virus transmission. No decreased requirement for platelet support has yet been demonstrated in BMT recipients treated with r-HuEPO.

Following the observation that increased levels of fetal haemoglobin (HbF) such as seen in hereditary persistence of HbF have a protective effect against sickling crises, efforts have been made to increase the HbF level in patients with sickle cell anaemia by pharmacological means. High doses of r-HuEPO increase the fetal haemoglobin level, however Goldberg et al. found no benefit in three patients treated with r-HuEPO, either on its own, or in combination with hydroxyurea. Hydroxyurea alone was effective. Higher r-HuEPO doses, perhaps combined with venesection would still appear worth investigating.

**Selection of Patients for Erythropoietin Treatment**

Endogenous serum erythropoietin levels are generally related to response in anaemic patients though a wide variability exists. As might be expected patients with a low erythropoietin level respond better to exogenously administered r-HuEPO than those with a high level. As a generalization, patients with a serum EPO level below 100 mU/ml may often benefit, those with levels over 300 mU/ml respond less frequently.

**Unwanted Effects of Erythropoietin**

Minor flu-like symptoms, headaches and arthralgia are relatively common after starting treatment with r-HuEPO, but are rarely severe enough to postpone treatment. The finding that some human growth factors stimulate tumour cell growth has led to caution in the application of these factors in clinical practice. For example, myeloblasts possess receptors for granulocyte colony stimulating factor (G-CSF) and G-CSF promotes the proliferation of reticulum cells. r-HuEPO induces proliferation of leukaemic blast cells in vitro, though only in the presence of other growth factors. Studies at the M. D. Anderson Center UCL suggest that administration of GM-CSF during induction chemotherapy for acute myeloid leukaemia is associated with a lower remission rate and reduced survival. However, examination of bone marrow morphology in patients on r-HuEPO suggests that in general the effects of erythropoietin on haemopoiesis are remarkably confined to intermediate and late erythroid progenitors.

So far as non-haemopoietic tumours are concerned, Mundt et al. have tested the proliferation-inducing effect of EPO on various human cell lines including melanoma, hepatoma, carcinoma of breast, carcinoma of kidney and adenocarcinoma of lung and found no stimulatory effect. Similarly Berdel et al. tested r-HuEPO and a variety of other cytokines for the stimulation of clonal growth by a variety of human cell lines and found r-HuEPO to neither stimulate nor inhibit cell growth. Whilst a stimulatory effect of r-HuEPO on malignant cells cannot be entirely excluded, such an effect seems unlikely.

The effect of r-HuEPO on blood pressure in patients with renal failure has already been discussed. Interestingly, hypertension has not been a frequent problem in patients without renal failure treated with r-HuEPO. Graafland et al. report two renal transplant patients who developed anaemia during treatment with enalapril, which responded to stopping enalapril. They suggest that increased renal blood flow associated with the ACE inhibitor reduced renal erythropoietin secretion, resulting in anaemia.

Thrombosis of vascular access devices may be similarly attributed to stagnation due to reduced blood flow, possibly associated with increased platelet aggregation. However, Macdougall et al. measured fistula blood flow in 10 patients and found that it did not alter in a year of r-HuEPO treatment despite an increase in haematocrit and whole blood viscosity. The most significant changes in a variety of coagulation tests and factors measured were a decrease in the natural anticoagulants protein C and protein S after 4 months of treatment. Bleeding time improved with increase in haematocrit. Al Momen et al. reported two haemodialysis patients with significant clotting in the vascular access and extracorporeal circuits. They found high levels of tissue-type plasminogen activator inhibitor (PAI) with deficiency in tissue-type plasminogen activator resulting in impaired fibrinolysis. Low doses of oral danazol were used to normalize fibrinolytic activity. James reports one of 21 patients treated with r-HuEPO whose treatment was stopped after 17 doses as it was thought that a
deep venous thrombosis may have been related to therapy. However, this patient was suffering from ovarian cancer, a disease known to increase the risk of thrombosis. Very large series of patients will be required to determine the possible increased risk of thrombotic events in r-HuEPO treated patients.

**Homologous Blood Transfusion—The Alternative to r-HuEPO**

The indications for r-HuEPO, and the enthusiasm with which it is used, will depend on the real and perceived risks of homologous blood transfusion. The world AIDS epidemic stimulated fear in the public mind of transfusion-transmitted viral disease. Although the introduction of donor selection with exclusion of high-risk groups and HIV and hepatitis C antibody testing of donations has made blood transfusion a safer option, risks of infection are still present. Antibody reactions against white cell and platelet antigens in homologous blood are a frequent cause of pyrexial transfusion reactions and cross-matching does not always prevent haemolytic reactions due to atypical red cell antibodies in the recipient. In addition homologous blood is immunosuppressant and repeated transfusions may lead to iron overload. Increasing use of r-HuEPO will reduce patient requirements for homologous blood transfusion. The anaemia of chronic renal failure is a clear indication for r-HuEPO; other indications will be clarified by the hundreds of ongoing clinical trials currently in progress.

**References**


