The anemia of chronic renal failure: Pathophysiology and the effects of recombinant erythropoietin

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Clinical improvement was dramatic; he was able to play handball and to meet all the physical demands of running his country store. This included working a full day without becoming exhausted, and now being able to unload the heavy boxes of supplies delivered to his store. After one year of rHuEpo therapy (75 units/kg, 3 times/week, intravenously), the hematocrit was 36%; mean corpuscular volume, 96 fl; white blood cell count, 2800/mm³; and platelet count, 82,000/mm³. Serum iron was 165 μg/dl; total iron binding capacity, 183 μg/dl; transferrin saturation, 90%; and serum ferritin, 400 μg/liter. The skin remained deeply pigmented, the liver was only one fingerbreadth below the right costal margin, and the spleen was two to three fingerbreadths below the left costal margin. A plain chest film disclosed that the transverse cardiomegaly also develops as a result of the anemia [40]. Neurobehavioral changes improve as well [38]. Several central-nervous-system abnormalities can be detected chronic renal disease is based on the following characteristics: the red cells are normochromic and normocytic; the circulating red cells are often irregular in shape (the “burr cell” [34]); the erythropoietin: granulocyte ratio in the bone marrow is slightly decreased or normal [3]; renal insufficiency is present (as defined by a serum creatinine above 2–3 mg/dl); and serum erythropoietin levels, measured by radioimmunoassay, are generally within the normal range [35–37]. Obviously, other causes of hypoproliferative anemia, such as early-mild iron deficiency and inflammation, must be excluded.

The anemia of chronic renal failure results in more disabling symptoms than was previously appreciated [38]. Approximately 25% of U.S. dialysis patients receive episodic to regular red-cell transfusions to reduce symptomatic tissue hypoxia. The manifestations of the anemia of chronic renal failure are probably no different than those associated with other severe, chronic anemias; however, because individuals with anemias of other causes do not remain anemic, or do not remain under observation as long as the typical dialysis patient does, most nephrologists believe that the symptoms of anemia consist only of fatigue, increasing angina, shortness of breath, or other obvious signs of organ hypoxia. Having the ability to improve the anemia acutely with rHuEpo has afforded us an opportunity to assess more reliably those tissue or organ systems that are adversely affected by the hypoxemia of anemia. Generalized coldness or a Raynaud’s-like condition is present and reverses with correction of the anemia [27]. Several central-nervous-system-related disorders improve with correction of the anemia: anorexia, insomnia, depression, and sexual disinterest and dysfunction [38]. Neurobehavioral changes improve as well [39]. Cardiomegaly also develops as a result of the anemia [40]. Figures 2 and 3 show a significant decrease in the size of the
heart in the patient under discussion 7 months after the anemia was corrected with rHuEpo therapy. Cardiomegaly has diminished in many other rHuEpo-treated patients after near correction of anemia, as demonstrated by serial chest x-rays [38].

Pathophysiology

Traditional thinking has ascribed the anemia of chronic renal failure to four mechanisms: (1) Epo deficiency [32, 41]; (2) shortened red cell survival [42—44]; (3) retained inhibitors or toxic metabolites that inhibit erythropoiesis [8—11]; and (4) blood loss resulting from the qualitative platelet defect present in uremia [45]. Superimposed on these possible mechanisms are other causes of anemia peculiar to the dialysis patient that might aggravate the underlying hypoproliferative anemia, as I will discuss.

Epo deficiency. Epo deficiency is unquestionably a major mechanism of this anemia. Ninety percent of Epo normally is made in the kidney, and only 10% is produced in the liver [46]. When renal disease develops, maximum Epo secretion presumably is blunted, even when Epo production is stimulated by hypoxia caused by anemia or other forms of impaired oxygen delivery [47]. Erythropoietin stimulates terminal differentiation of committed erythroid progenitors in the marrow, increases cellular hemoglobin synthesis, and causes marrow reticulocytes to shift into the circulation prematurely. The normal response to anemia is an orderly sequence of Epo production that leads to increased marrow erythropoiesis. Renal disease usually disrupts this orderly sequence and results in a submaximal Epo response to an anemic stimulus. When Epo levels are measured by the classic biologic assay, which depends on the erythroid response of an ex-hypoxic rat to injected samples of anemic sera, the levels often are not detectable, because this assay fails to measure normal or subnormal levels; this limitation sometimes can be overcome by using concentrated plasma [48]. With the advent of the newer radioimmunoassay method, which is based on purified urinary Epo [22, 49], more precise measurements of serum Epo levels are possible and indicate that levels in patients with chronic renal failure are within the normal range of 13 to 21 mU/ml (for patients with a normal hematocrit) [35, 37]. It is noteworthy, however, that individuals with normal renal function and similar degrees of anemia have serum Epo levels 10 to 100 times these "normal" values [37]. Even anephric patients have Epo levels that are below normal or in the lower range of normal [36]. Therefore, relative Epo deficiency is clearly present.

Bone marrow inhibition. For more than 30 years, investigators have postulated that inhibitors of erythropoiesis play a significant causal role in this anemia. If present, such inhibitors could blunt or even block the effect of Epo. Four lines of evidence suggest the presence of erythropoietic inhibitors in patients with chronic renal disease. (1) In-vitro erythropoiesis is impaired when uremic serum is incubated with murine marrow cells in the presence of growth factors, including Epo [9]; (2) levels of bioactive Epo in the plasma of some anemic hemodialysis patients are elevated [48]; (3) infusion of Epo-rich plasma from a patient with aplastic anemia into several patients with advanced renal failure and anemia failed to elicit a reticulocytosis [50]; and (4) a higher proportion of patients treated with continuous ambulatory peritoneal dialysis (CAPD) achieve normal hematocrit levels than do hemodialysis patients [51]. Let us examine each of these experimental and clinical observations.

The addition of uremic human serum to murine marrow cells in vitro reduces the Epo-induced proliferation of erythroid progenitor cells (CFU-E: colony forming unit—erythroid) [9]. Three substances have been incriminated as possible inhibiting solutes: parathyroid hormone (PTH) [52], spermine [53], and ribonuclease [54]. The problem with these in-vitro studies, in my view, is that they lack the controls required to support the
selectivity and specificity of such inhibitors. The crude extract of the parathyroid gland is inhibitory to both BFU-E (burst forming unit—erythroid), an earlier progenitor cell line than CFU-E, and to granulocyte progenitor cells (CFU-GM), and to in-vitro heme synthesis, but not to CFU-E [52]. However, purified PTH—either the active N-terminal fragment (amino acids 1-34), or the intact molecule (amino acids 1-84)—when added to marrow cells in culture in the presence of Epo, fails to inhibit in-vitro erythropoiesis [55]. Spermine, although it inhibits CFU-E, also inhibits CFU-GM. This finding suggests that its inhibitory effect is not specific [56]. Also, blood levels of spermine are not elevated in dialysis patients [57]. Ribonuclease-induced CFU-E inhibition occurs only when pharmacologic amounts of ribonuclease are added to the culture medium [54]. When mouse, rat, or dog erythroid marrow cells are used in culture, the uremic inhibition of CFU-E is nonspecific: that is, in-vitro granulopoiesis and megakaryocytopoiesis both are inhibited [58], yet blood concentrations of leukocytes and platelets in patients with chronic renal failure usually are normal. Of more significance, perhaps, is that when an entirely autologous in-vitro culture system is employed, we observed no inhibition of erythroid progenitor cells with uremic sera in the presence of Epo [59].

What is the significance of occasional increases in serum Epo levels in the anemic dialysis patient? Using bioassay results from concentrated serum, Caro et al concluded that some patients have serum Epo levels 3 to 4 times normal [48]. Because these patients remained anemic, one might conclude that inhibitors suppressed the erythroid response to the modest elevations in Epo. However, concomitant quantitation of erythropoiesis was not analyzed; hence, an isolated elevated serum Epo level is difficult to interpret. As I noted earlier, one must realize that serum Epo levels in a person with a similar degree of anemia but with normal renal function would be 10 to 100 times normal. Investigators who have used the radioimmunoassay based on purified human Epo consistently have failed to document significantly elevated serum Epo levels in anemic patients during the period of progressive renal failure or during treatment with chronic dialysis [36, 60].

Essers and colleagues infused Epo-rich plasma from a patient with aplastic anemia into several patients with renal failure. Erythroid stimulation, as defined by reticulocytosis, occurred only in patients with mild elevations of BUN, not in those with severe azotemia [50]. The number of patients studied was small, and erythroid function was not quantified (that is, with ferrokinetics). To address this concern, my colleague, Dr. John Adamson, and I developed and studied a uremic sheep model, quantifying the erythroid response to Epo-rich plasma derived from phenylhydrazine and phlebotomy-treated normal sheep [61]. The erythroid response to identical amounts of Epo (as measured by the radioimmunoassay) in uremic sheep (some of which required hemodialysis to remain alive) was similar to that in normal sheep; in some instances, a given animal served as its own control [61]. The biologic clearance of Epo was similar in both the normal and uremic conditions [62]. Therefore, using the sheep model, we could document neither in-vivo nor in-vitro inhibition of erythropoiesis by uremic toxins [63].

The final observation that has been used to argue for the existence of uremic suppression of erythropoiesis is that the hematocrit of patients beginning CAPD often rises toward normal [51, 64, 65]. The mechanism for this rise has yet to be defined. Given that peritoneal membranes are “leakier” than are conventional hemodialysis membranes, it is tempting to speculate that higher-molecular-weight uremic erythropoietic inhibitors are being removed by CAPD; if so, this might explain why CAPD patients with higher Epo levels have better erythropoiesis [51] or have improved Epo production [66]. Unfortunately, such mechanisms do not explain why only about one-
half of patients on CAPD have a significant rise in hematocrit and why, of those that do, most are unable to sustain the rise for more than 18 months [67].

**Shortened red-cell survival.** As Figure 4 shows, red-cell hemolysis, although mild, can contribute to the anemia. Red-cell half-life, however, as quantified by $^{51}$chromium labeling, occasionally is normal. Most radioisotopic studies (using $^{51}$chromium [68], $^{32}$P [7], or $^{14}$C cyanate [69]) confirm the presence of mild hemolysis. The cause of the hemolysis is not known. Studies 30 years ago suggested that some intravascular substance(s) retained in patients with advanced renal failure shortened red-cell survival; when red cells from a patient with advanced renal failure are infused into a normal subject, red-cell life span is restored to normal [42]. Neither hemodialysis nor peritoneal dialysis significantly improves red-cell survival [7, 70]. In the presence of normal kidneys, increased Epo secretion would easily compensate for such a mild degree of hemolysis.

**Bleeding.** Significant blood loss occurs in as many as 25% of patients with progressive renal failure and can contribute to their anemia [71]. The major reason for this increased bleeding propensity is the qualitative platelet defect that develops in azotemic patients [45, 72, 73], accounting for blood loss from the gastrointestinal tract, within the skin, and from other sites. Platelet dysfunction prolongs the bleeding time [74] and impairs platelet aggregation in vitro. Several mechanisms can be invoked to explain this platelet dysfunction: decreased platelet factor 3 activity [75], decreased platelet levels of thromboxane $A_2$ [76], an increase in prostacyclin (PGI$_2$) (an inhibitor of platelet aggregation derived from the vascular endothelium) [76], and suboptimal Factor VIII: von Willebrand complex activity [77].

**Traditional treatments.** The usual method of managing this anemia has been to control it by administering androgens if minimal or no side effects occur, and to give transfusions if severe hypoxic symptoms develop. In dialysis patients, 1 mg of folic acid is given orally daily to offset losses of the vitamin into the dialysate and therefore to prevent development of a superimposed megaloblastic process. Iron is administered either orally or as iron dextran intravenously to keep the serum ferritin above 30–50 ng/ml. Acute red-cell injury during dialysis can be prevented by ensuring that the hemodialysis fluid delivery system functions properly and that the water supply is monitored to prevent exposure to chloramine, formaldehyde, high dialysate temperature, and dialysate hypotonicity.

Administration of androgens can improve the anemia either by stimulating the erythroid marrow directly or, more likely, by stimulating renal and/or liver Epo production [18]. Of the commercially available androgens, only two have been especially popular, nandrolone decanoate and fluoxymesterone. In a 6-month crossover study with 3 other androgens, nandrolone decanoate worked the best [20]. Nandrolone decanoate is given weekly, 100–200 mg intramuscularly, for at least 6 months [19]. If the hematocrit does not rise significantly or if transfusion requirements continue, a 6-month trial with oral fluoxymesterone, 10–30 mg/day, might be necessary [17]. Unfortunately, virilization, liver dysfunction, and other side effects have limited the use of these agents [78, 79].

Red-cell transfusions have been the fastest way to raise the hematocrit and therefore reduce or eliminate hypoxic symptoms. However, transfusions are associated with significant risks:

1. Hepatitis B or non-A, non-B hepatitis are the most common infections acquired via transfusion. The former can now be eliminated by proper screening in the blood bank and/or by immunization. The morbidity and mortality associated with hepatitis is well known. Transmission of the HIV infection from transfusions has been documented, and unfortunately it occurred in the patient discussed today. Over the more than 2 years since the appearance of HIV antibodies in this patient, he has had no obvious clinical effects. Although proper screening should eliminate the transmission of HIV by transfusion, a small number of transfused patients probably still will be exposed [80].

2. Transfusion-induced HL-A antibodies are a major reason why some dialysis patients are unable to receive a kidney transplant.

3. Erythroid marrow suppression can occur if an indiscriminate, repetitive policy of frequent transfusions is allowed, particularly if multiple transfusions are given at one time [15]. This patient’s erythroid function might have been suppressed by such a policy, resulting in a continuing need for transfusions. However, it is difficult not to transfuse a symptomatic, anemic patient who is thereby able to enjoy a more active, productive life.

4. Iron overload can develop easily in the dialysis patient because intravenous iron, either as iron dextran or red-cell transfusions, can exceed the body’s limited ability to eliminate iron through fixed gastrointestinal losses, variable menstrual losses, and procedure-related blood losses [81]. Because the
serum ferritin is in equilibrium with tissue iron stores [82], a value of greater than 300 ng/ml indicates iron excess or iron overload. One unit of blood (that is, 200 ml of red cells) provides 200 mg of iron; thus, iron excess can easily develop from multiple transfusions in the absence of significant blood loss. For every unit of blood transfused, the serum ferritin increases 60 ng/ml [83]. Our patient had more than 300 transfusions in the absence of obvious significant bleeding, so a serum ferritin level of 18,000 ng/ml might have been anticipated, yet a peak value of 5457 ng/ml was noted after about two-thirds of the transfusions had been received. After approximately one year of deferroxamine therapy, his serum ferritin level was 4444 ng/ml: deferroxamine likely was effective in reducing his iron burden [84]. Iron is initially stored in the reticuloendothelial cells of the liver, marrow, and other organs and eventually leads to tissue hemosiderosis, that is, to iron deposition in parenchymal cells. Cellular dysfunction (secondary hemochromatosis) eventually can occur, but the level of iron stores at which cellular dysfunction occurs is not clearly established. Histologic evidence for iron within hepatocytes or myocardial cells does not necessarily indicate tissue dysfunction. The transfusion of 2 to 3 units of red cells per month for 4 years to non-uremic, anemic patients, however, resulted in serum ferritin levels as high as 5000 ng/ml and in evidence of cardiac, liver, and pancreatic dysfunction [85]. Primary hemochromatosis also is associated with this pattern of organ dysfunction. Proximal muscle myopathy has been observed in dialysis patients whose serum ferritin levels exceed 1000 ng/ml [86], but this correlation has not been confirmed [87]; non-cardiac myopathy is an unusual complication of secondary hemochromatosis [85], and it is not observed in primary hemochromatosis. Some authors claim that iron overload occurs with greater frequency in dialysis patients who inherit at least one of the three “hemo- chromatosis alleles,” HL-A-A3, -B7, or -B14 [86]. Heterozygotes for the gene for primary hemochromatosis do not absorb iron excessively, however, and intestinal iron absorption is reduced in iron-overloaded dialysis patients [88]. The patient under discussion here did not have any of these alleles. He did have cardiomegaly that probably was related more to the hypertension and anemia than to the iron overload. He had a normal blood sugar level and no clinical evidence of myopathy. The pancytopenia probably was related to a congested spleen, which in turn might have been related to his history of hepatitis or to transfusion-induced hemosiderosis [89, 90].

Erythropoietin

Erythropoietin is a glycoprotein secreted by the kidney under hypoxic conditions. The intrarenal site of Epo secretion was identified recently. Several investigators, using in-situ hybridization techniques, have identified the endothelial cell of the peritubular capillary in the cortex and outer medulla as the site [91, 92]. The usual stimulus for Epo production is hypoxia, caused either by anemia or other forms of impaired oxygen delivery [47]. For years, intact Epo proved difficult to recover from the kidney, and various hypotheses were advanced to explain this: some thought that a pro-Epo was secreted and then activated to Epo by an alpha globulin in normal plasma [93]; others believed that Epo, like angiotensin, derived from the activation of a liver-generated Epo precursor by an enzyme produced in the kidney [94]. These theories were buried when severely hypoxic rats produced enough Epo to enable the intact molecule to be recovered from kidney extracts [95]. The actual cellular mechanisms involved in the stimulation, manufacture, and release of Epo are not yet known. We have studied the pharmacokinetics of Epo in one anephric hemodialysis patient. The half-life of native Epo (from Epo-rich human plasma) was 6.7 hours, and the half-life of rHuEpo was 7.2 hours. The half-life of rHuEpo in 5 other hemodialysis patients was approximately 6 to 9 hours [96]. The site of Epo degradation is not known. The major Epo receptor sites are the erythroid progenitor cells. An increase in erythroblast intracellular calcium after Epo stimulation could be one of the activating mechanisms [97].

Erythropoietin exists in such small quantities in normal blood or kidney tissue that it has been unrealistic to process it for therapeutic use. The breakthrough in providing Epo for clinical use derived from the isolation of the Epo gene from a human fetal liver genomic library [23, 24, 98]. The cloning strategy used in isolating this gene was based on the amino acid sequence information previously derived from small quantities of the purified urinary protein. Oligonucleotide probes were constructed and the Epo gene was eventually found in this genomic library. The gene, along with other nucleic acid sequences intended to stimulate the expression of Epo, was spliced into a plasmid expression vector. The nuclei of a mammalian cell line, the Chinese hamster ovary (CHO) cell, then were transfected by the Epo-containing plasmid. Use of a mammalian cell line provides for post-translational glycosylation of the protein, which is critical for its in-vivo hormonal activity. The rHuEpo is secreted into the surrounding media and then purified.

The gene, located on the long arm of chromosome 7 [23], is organized into five exons and four intervening sequences, or introns, and exists as a single copy in the human genome [23, 24, 99]. The Epo gene encodes a 193-amino acid polypeptide, the first 27 amino acids of which represent the secretory leader sequence that is cleaved upon secretion from the cell [23, 24, 99]. An additional post-translational modification is the removal of the C-terminal amino acid, resulting in a functional protein containing 165 amino acids and having a molecular weight of 18,400 daltons [23, 24, 99, 100]. The functional protein contains two internal disulfide bonds between cysteines—one pair at positions 7 and 161, and the other at positions 29 and 33—and contains linkages to four carbohydrate chains: three N-linked to asparagine at the 24th, 38th, and 83rd positions, and an O-linkage to serine at the 126th position [101, 102]. The circulating glycosylated hormone has an apparent molecular weight of approximately 36,000 daltons as determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis [101]. The rHuEpo is immunologically and biologically indistinguishable from the native human urinary Epo, and it is structurally very similar [101, 102].

The journey from the isolation of the human Epo gene, to cloning, to animal testing, and to clinical use has been surprisingly fast and remarkably free of serious problems. The gene was found in 1983 [23], the recombinant hormone was tested in mice and dogs by the AMGen Corporation in 1984 and 1985 [101, 102], and the first clinical trial in humans on hemodialysis using AMGen’s rHuEpo began in Seattle in December 1985 [26]. A multicenter, phase-III clinical trial in the United States using AMGen’s rHuEpo has been in progress since November
Recombinant human erythropoietin has been effective in virtually all anemic hemodialysis patients in doses of greater than 50 units/kg, intravenously, three times weekly. Depending on the dose of rHuEpo, the hematocrit rises at a rate of 1.0 percentage points/week (with 50 units/kg, 3x/wk) to 1.8 percentage points/week (with 150 units/kg, 3x/wk). The maintenance dose required to keep the hematocrit stable at 33–38 has been 25–100 units/kg, 3x/wk, in the majority of patients; approximately 35% of patients require more than this amount [29]. When enough rHuEpo is given to stimulate erythropoiesis, iron stores decrease, as evidenced by a fall in serum ferritin. Serum ferritin levels decreased by more than 50% in 5 iron-overloaded patients who received rHuEpo for one year (Fig. 5). Most iron-overloaded patients eventually become iron depleted because: (1) iron intake ceases (no more transfusions), (2) blood loss continues via dialyzer blood loss (which will be greater because there is more hemoglobin per milliliter of blood residual), and (3) the marrow's need for iron increases. Although iron overload can be corrected, it remains to be learned whether functional derangements in iron-congested organs can be reversed. Even though the patient under discussion has had a reduction in iron stores during the past year of rHuEpo therapy, his platelet count has increased only slightly, the spleen is slightly smaller, and leukopenia persists. Theoretically, negative iron balance could be accentuated by periodic phlebotomy and increased rHuEpo dosage, but no evidence currently exists that this patient is at risk from hemosiderosis. The use of rHuEpo in patients with chronic renal failure might provide newer insights into the significance of the various proposed mechanisms causing the anemia. Preliminary evidence in a small number of patients indicates that the mild hemolysis may improve significantly, as quantitated with 51chromium-tagged red cell survival, when the hematocrit has been maintained at nearly normal levels for many months with rHuEpo (Fig. 6). Further studies are required to determine red-cell survival in patients whose anemia has been corrected fully. Nevertheless, the mild shortening of red-cell survival, in our experience, does not influence the amount of rHuEpo required to maintain a stable hematocrit.

The platelet count in patients treated with rHuEpo also has increased significantly, but not to levels above normal [27, 29]. This slight increase in platelet count, however, is not likely to be responsible for the improvement in the uremic platelet defect (a shortening in the bleeding time) that occurs when the hematocrit increases to over 30, either by transfusions [103] or by rHuEpo [104]. Because the degree of uremia is unchanged in these studies, another factor related to anemia might account for at least part of the qualitative platelet defect. The doses of rHuEpo and the schedule of administration used to correct the anemia (that is, intermittent bolus injections) are not necessarily physiologic of course. Nevertheless, if uremic erythropoietic inhibitors exist, they must be of minor importance, given that they can be overcome so easily. Whether uremic erythropoietic inhibitors actually do exist could be determined by quantitative erythroid studies comparing the response of normal and uremic subjects to rHuEpo. Therefore, the anemia of chronic renal failure is primarily, if not entirely, due to erythropoietin deficiency. This anemia should be considered a hormone deficiency resulting from the inability of the diseased kidney to produce adequate amounts of Epo. Other factors can complicate the anemia of chronic renal failure. These are primarily the result of other aspects of chronic renal failure or its treatment. These factors also can interfere with the effectiveness of rHuEpo therapy. Iron deficiency is most common and has been reviewed elsewhere [105]. The guidelines for determining relative iron deficiency, however, must be modified in patients undergoing rHuEpo therapy. Prior to rHuEpo therapy, the erythroid mar-
row can respond only at a subnormal rate, at best with a twofold increase [106]. In patients not dependent on transfusions, iron stores were maintained relatively easily with oral iron; the demand for iron by the erythroid cells was low. Under these circumstances, iron stores are best quantified with the serum ferritin level and not the serum iron or percentage of saturation of transferrin [105] (as long as infection or severe inflammation is not present). With rHuEpo stimulation, however, the erythroid marrow responds more than two- to threefold, as determined by ferrokinetic studies [26, 107], so that a state of relative iron deficiency can develop. This state is defined as a transferrin saturation below 20%, a normal serum ferritin level, and a temporary decrease in rHuEpo-induced reticulocytosis [26, 38]. It is postulated that the erythroid marrow avidly removes iron from the two binding sites on circulating transferrin at a rate exceeding the ability of the reticuloendothelial cell to release iron to transferrin.

Hyperparathyroidism, especially osteitis fibrosa, can interfere with erythropoiesis, as evidenced by the improvement in anemia in some dialysis patients after subtotal parathyroidectomy [108], and by the blunted effectiveness of rHuEpo in patients with severe hyperparathyroidism [109]. The quantitative importance of the latter effect awaits further study. It is a rare fibrosis, as judged by bone biopsy, and not elevated PTH levels per se, that correlates best as a predictor of erythropoiesis after subtotal parathyroidectomy [108]. This finding suggests that marrow fibrosis limits erythroid marrow expansion from Epo.

Aluminum excess produces a non-iron-deficient microcytosis [110, 111], which can aggravate the anemia. Treatment of the aluminum excess with weekly injections of deferoxamine results in an increase in red-cell volume within 3 months and in eventual improvement in the anemia [32]. What role aluminum excess plays in the absence of microcytosis awaits further study. Using a deferoxamine stimulation test, Casati et al [28] and Van Wyck and colleagues [112] demonstrated that aluminum excess results in a modest blunting of the erythropoiesis-stimulating effects of rHuEpo. But the aluminum excess does not interfere with the efficacy of rHuEpo at doses of 150 and 300 U/kg, 3x/wk. Because hemodialysis patients with non-iron-deficiency microcytosis have been excluded from studies with rHuEpo to date, it is not clear what practical influence, if any, aluminum excess has on rHuEpo effectiveness.

Hypersplenism can aggravate the hemolysis and should be suspected in any patient with a palpable spleen, leukopenia, thrombocytopenia, and increasing transfusion requirements. Splenectomy usually is beneficial for patients in whom 51chromium-labeled red-cell studies disclose a markedly shortened red-cell survival and in whom there is a 2:1 or greater sequestration of red cells in the spleen as compared with the liver [113]. The causes of hypersplenism are probably multifactorial and include chronic hepatitis [89], transfusion-induced hemosiderosis [90], marrow fibrosis from severe hyperparathyroidism [114], silicone exposure [115], and other causes of acute hemolysis [116]. Although the patient under discussion had marked splenomegaly, isotope-sequestration studies failed to demonstrate significant red-cell entrapment, and red-cell survival was not markedly shortened.

Folate deficiency, acute or chronic hemolytic conditions, acute or chronic blood loss, and creation of the anephric state all can aggravate the anemia of chronic renal failure. Because patients’ appetites sometimes increase when anemia is corrected, adequate oral intake of folate-containing foods will probably easily compensate for the folate lost via dialyzer diffusion [117]. Because uremic anephric patients respond as well to rHuEpo as do uremic patients whose kidneys are in place [26], the criteria for nephrectomy could change in the future. Severe hemolysis or severe blood loss obviously can overcome the erythroid marrow’s ability to compensate acutely, even with rHuEpo therapy, and both these mechanisms should be considered in any patient in whom a stable hematocrit suddenly drops, whether or not rHuEpo is being given. The only patient treated with rHuEpo who continued to require transfusions in the U.S. multicenter clinical trial had chronic, active gastrointestinal bleeding [29].

Generally, injections of rHuEpo have been well tolerated. Flu-like or other transitory symptoms occasionally occur after the injection. To date, no antibodies to rHuEpo have been detected in the serum of more than 500 patients receiving rHuEpo three times weekly for up to 2 years [38].

An increase in the red-cell mass to normal or nearly normal levels can create hemodynamic and other consequences for the patient with renal failure. Hypertension is aggravated in 30% to 50% of patients during the period that the hematocrit is rising [25, 29, 38] and requires careful medical control. Hemodynamic studies indicate that peripheral vascular resistance increases with a rising red-cell mass, whether induced by transfusion [118] or rHuEpo [119]; this change might explain the rise in blood pressure. Of our 68 patients who responded to rHuEpo, 6 experienced grand mal seizures; in 3, the seizures occurred during the first 3 months of rHuEpo therapy when the hematocrit was rising and were associated with a sudden rise in blood pressure (132/84 to 198/112 mm Hg in one patient). Two of these 3 patients, plus the other 3, continue to receive rHuEpo and have maintained a hematocrit level of 35 without any recurrence in seizures. Winears et al also reported that a seizure occurred in one of their 10 patients [25]. Hypertension and seizures are relatively common in patients with chronic renal failure, whether or not they are being treated with dialysis. I suspect that for some patients, particularly those who have had severe anemia for a long time, the sudden hemodynamic changes caused by a relatively rapid rise in red-cell mass can contribute to the worsening hypertension and to the lowered seizure threshold. Dialyzer clearance for creatinine is significantly less at normal hematocrit levels than at hematocrits of less than 22 [120]. However, no increase in predialysis creatinine or BUN levels were reported in the U.S. multicenter clinical trial with rHuEpo [29]. Appetites improve, and our dietitians at the Northwest Kidney Center have documented increases in potassium, sodium, and protein intake. Hyperkalemia can become a problem in some patients [26, 28]. Therefore, in selected patients more dialysis, Kayexalate, or dietary counseling may be required. An increase in vascular access clotting has been reported [28], but this was not a significant problem in the U.S. multicenter clinical trial [29].

Implications for the future

Management of the anemia of chronic renal failure and treatment of the patient with chronic renal failure will change as a result of rHuEpo therapy [38]. Recombinant human Epo can
prevent the anemia and its complications if patients with progressive renal failure can be identified and treated when their hematocrit falls below 30. For dialysis patients, transfusions should no longer be required except when sudden, acute bleeding occurs. Theoretically, autologous transfusions could be provided for planned, major surgery. Androgen therapy will no longer be necessary. Complications from transfusions most likely will be eliminated and iron overload will no longer develop. Instead, maintaining adequate iron stores for optimal erythropoiesis will be the major challenge, because all hemodialysis patients will require supplemental iron to compensate for their fixed dialyzer blood losses. Many patients have gastrointestinal intolerance to oral iron, and at least 11% develop anaphylactic reactions to iron dextran [121]; iron deficiency therefore could become a major problem in the management of the hemodialysis patient and either will reduce the effectiveness of rHuEpo and/or will increase the need for and cost of rHuEpo therapy.

The future management of the patient with chronic renal failure will be modified by the fact that rHuEpo-treated patients will be healthier before beginning dialysis, and hopefully they will not lose their employment because of fatigue. Some patients will continue to feel healthy despite very low endogenous creatinine clearance values, and criteria for initiating dialysis could change. Indeed, it might be difficult to convince some patients that they need dialysis.

The impact of rHuEpo on the health of patients with chronic renal failure should be substantial. Undoubtedly as more experience is gained in the treatment of the anemia with rHuEpo, the pathophysiology of the anemia and the consequences of the anemia in renal failure should be better elucidated.

Questions and answers

DR. JAMES BOURDEAU (Division of Nephrology, Michael Reese Hospital/University of Chicago, Chicago, Illinois): When recombinant human erythropoietin becomes available for clinical use, how much will it cost?

DR. ESCHBACH: I hope that the U.S. Food and Drug Administration will approve rHuEpo for clinical use in dialysis patients by late 1988 or early 1989. AMGen, who produces the rHuEpo used in the multicenter U.S. clinical trial, has yet to reveal what the cost will be. My hope is that rHuEpo will be accessible to all who can benefit from it. The End-Stage Renal Disease Program of Medicare probably will pay for it, but how it is paid for and how those without supplemental insurance will pay for it is not clear to me. If the Health Care Financing Administration (HCFA) includes the cost of rHuEpo in the dialysis composite rate, I doubt that dialysis centers would be able to provide adequate amounts of rHuEpo and still receive adequate reimbursement for their dialysis costs. Hopefully, the HCFA will reimburse centers for the cost of rHuEpo, as it now does for blood transfusions and intravenous iron dextran. The intent of the original legislation that created the End-Stage Renal Disease program was to provide Medicare funds to rehabilitate patients who have chronic renal failure. Because rHuEpo should significantly enhance patient rehabilitation, it will be important that the End-Stage Renal Disease Program help to ensure that access to rHuEpo not be an issue.

DR. FREDRIC COE (Director, Joint University of Chicago/Michael Reese Hospital Program in Nephrology): Is hypertension from rHuEpo different than the routine volume-expansion hypertension that is said to account for the vast majority of hypertension in dialyzed patients?

DR. ESCHBACH: Yes, I believe it is different. Twenty years ago, Neff and colleagues studied cardiac output and peripheral vascular resistance in 6 anemic hemodialysis patients before and after correcting the anemia with red cell transfusions [118]. Peripheral vascular resistance was low when the hematocrit was 20, so they postulated that anemia led to vasodilation. When the hematocrit was increased to 40 by increasing red-cell mass with red-cell transfusions, while controlling plasma volume with dialysis, peripheral vascular resistance increased significantly and hypertension was accentuated, even though cardiac output was decreased from baseline elevated levels. On the other hand, extracellular volume overload is common in the dialysis patient and is known to contribute to hypertension. Maintaining a euvolemic state with adequate dialysis ultrafiltration often, but not always, maintains a normal blood pressure. Most patients treated with rHuEpo who have become more hypertensive when their hematocrit rises above 30 have not developed extracellular volume overload, although it always must be ruled out. In our patients, serial chest x-rays have failed to document pulmonary congestion, and heart sizes even can diminish. Radioactive chromium red-cell-mass studies indicate that plasma volume decreases as the hematocrit rises, without an increase in whole-blood volume. Hypertension has developed in anephric patients whose anemia is corrected with rHuEpo [26]; therefore renal renin production probably is not a factor in the genesis of this hypertension. Approximately 80% of patients with progressive renal failure develop hypertension. We thought that hypertension often was controlled by dialysis because of better sodium control through ultrafiltration. I believe that mechanism is important, but I wonder whether the anemia-induced vasodilation also contributes to a lowering of blood pressure. If it does, then correcting the anemia should reverse the process. Some of the rHuEpo-treated patients who became hypertensive eventually became normotensive when they adjusted to the non-anemic state.

DR. BOURDEAU: Has blood viscosity been measured prior to and following administration of rHuEpo? Is it possible that the increasing hypertension is related to an increase in blood viscosity?

DR. ESCHBACH: Blood viscosity increases in anemic hemodialysis patients as the hematocrit rises from rHuEpo therapy [122]. The increase is not any greater than what would be observed in an anemic individual with normal renal function whose hematocrit returns to normal as a result of iron or other hematinlc therapy, however. Increasing blood viscosity per se is not the cause of the increasing arterial pressures observed during acute correction of anemia with rHuEpo.

DR. GARY TOBACK (Section of Nephrology, Mitchell Hospital, University of Chicago): I want to ask about the pathophysiology of anemias in patients with chronic inflammatory diseases. You provided data indicating that the response of the marrow to a fixed dose of recombinant erythropoietin was reduced in patients with inflammatory disease. What abnormality occurs in the marrow that leads to this reduced responsiveness to erythropoietin?

DR. ESCHBACH: The decreased responsiveness of the erythroid marrow to rHuEpo in the presence of an infection or
inflammatory state (such as after surgery) is not a direct marrow abnormality. Rather, the defect is a block at the reticuloendothelial cell that prevents the release of iron to circulating transferrin, thus limiting the amount of iron available for hemoglobin synthesis. We do not have enough experience to know whether excessive rHuEpo can overcome this inflammatory block. A recent study did suggest that rHuEpo could correct the mild anemia in patients with rheumatoid arthritis [123], but the response was slower than that observed with comparable doses used in hemodialysis patients. Whether the anemia occurring with other inflammatory states can be corrected with rHuEpo, and at what dose, remains to be determined.

DR. TOBACK: As you mentioned, a considerable body of evidence suggests that the serum of patients with end-stage renal disease contains inhibitors of erythropoiesis. Your presentation indicated that provision of recombinant erythropoietin can overcome this inhibition, and you surmised that the inhibitors were not the major determinant of the anemia. I would like to suggest an alternative hypothesis concerning these findings. Could it be that in anemic patients, who have or don't have renal failure, hypoxia is perceived by a specific set of cells that release one or more inhibitors that act on CFU-E cells to block erythroid development? Exogenous erythropoietin acting on the same target cells could overcome this inhibitory effect, stimulate erythropoiesis, increase red-cell mass, ameliorate cellular hypoxia, and thereby shut off production of the inhibitor. In this hypothesis, a circulating inhibitor still could mediate the anemia, and its effect could be overcome by erythropoietin, as you observed. Although the inhibitors would have to be identified to test this hypothesis, I would be interested in your thoughts.

DR. ESCHBACH: To my knowledge, production of neither murine nor canine erythroid marrow cells is inhibited when anemic sera from subjects without renal failure is added to these cultured erythroid cells in the presence of erythropoietin. In the intact organism without renal disease, anemia or hypoxia leads to an appropriate erythropoietin response with subsequent erythroid stimulation. Segal and colleagues failed to detect any inhibition of autologous CFU-E cell growth when anemic, predialysis serum was incubated in the presence of erythropoietin [59]. On teleologic grounds, I do not understand why hypoxia per se would result in the release of inhibitors to CFU-E growth. There is no evidence that hypoxia results in the release of CFU-E inhibitors.

DR. JORDAN J. COHEN (Dean of Medicine, State University of New York at Stony Brook, Stony Brook, New York): There is, of course, another way that a putative inhibitor might play a role in the anemia of chronic renal disease. Given the poor correlation between the degree of renal insufficiency and the degree to which the hematocrit falls in this patient population, could something be inhibiting the release of erythropoietin by the kidney rather than be inhibiting the effect of the hormone on the bone marrow? Why should a patient with relatively mild renal insufficiency, who has only a moderate reduction in renal size, develop anemia if major inhibitors of the bone marrow are not present and if erythropoietin production is normally determined by renal mass?

DR. ESCHBACH: I know of no evidence that renal mass correlates with the ability of the kidney to produce erythropoietin. Rather, the responsiveness of the renal cell (presumably the peritubular capillary endothelial cell [91, 92]) to hypoxia is regulated at the cellular level by factors that we do not yet understand. These cells are adjacent to the proximal tubule. Does tubular function relate to Epo secretion? If so, how? The term “inhibitor” has been used to connote a product of tissue metabolism not excreted by the kidney. If you are referring to an inhibitor in a broader sense, then there might be substances or cellular mechanisms that interfere with the usual hypoxic stimulus to these cells. On the other hand, we have no information about how these cells sense the existence of hypoxia, so there also might be mechanisms that accentuate the cells’ Epo response to hypoxia. Hopefully, scientists soon will be able to answer these questions.

DR. CARL POCHEDLY (Department of Pediatrics, Michael Reese Hospital): What are the long-term adverse side effects of erythropoietin? Has it been used extensively in children?

DR. ESCHBACH: Recombinant human erythropoietin has been given three times weekly for more than 2 years to 18 patients in Seattle who originally were enrolled in the phase-I clinical trial. Routine blood and serum analysis, clotting parameters, chest x-rays, electrocardiograms, and clinical observation and examination have revealed no direct side effects from the recombinant hormone. No antibodies to rHuEpo have been detected in the serum of these patients. The only adverse events appear to be related to correction of the anemia, especially a rising blood pressure in some patients. Seizures rarely occur. These effects occur mainly during the first 3 to 4 months, when the hematocrit is rising relatively rapidly. It remains to be determined whether these adverse effects will occur less frequently if the anemia is corrected over a longer period. It is interesting, though, that seizures have not recurred in patients continuing to receive rHuEpo. Patients do not seem to be refractory to rHuEpo after they initially respond. To answer your second question, the United States clinical trials with rHuEpo have not involved children. But the response of a 7-year-old, transfusion-dependent, iron-overloaded hemodialysis patient from Marburg, West Germany, to rHuEpo was similar to that reported in adults [124].

DR. SERAFINO GARELLA (Associate Chairman of Medicine, Michael Reese Hospital): One of the strongest pieces of evidence suggesting that inhibitors to erythropoiesis exist in patients with renal failure is that the erythropoietin level in some of these patients is, if not normal for the degree of anemia, at least close to normal. Because patients with renal failure demonstrate a shortened red-cell survival as well as decreased production rates, would they not require higher levels of erythropoietin to maintain a given hematocrit? If the answer is positive, then finding “normal” levels of erythropoietin in patients with the anemia of renal disease would be evidence in favor of the existence of inhibitors.

DR. ESCHBACH: If uremic inhibitors acted against the production of renal erythropoietin, it might be one explanation for your hypothesis. However, inadequate production of erythropoietin by the diseased kidney, regardless of the underlying disease, also can account for the findings of “normal” levels of serum erythropoietin in patients with chronic renal failure and anemia.

DR. KAI LAU (Director, Renal Division, Michael Reese Hospital): To use the apparently sluggish response of patients with renal disease to exogenous erythropoietin as evidence for
the presence of bone-marrow inhibitors, one would need to know the dose-response curve of normal subjects. Do we have such data?

Dr. Eschbach: Not at this time. We cannot rule out the presence of erythropoietic inhibitors in renal failure until we study the effect of rHuEpo in normal subjects and compare the erythropoietic response with the response to similar doses of rHuEpo given to hemodialysis patients.

Dr. David Bushinsky (Section of Nephrology, Mitchell Hospital, University of Chicago): Have you used phlebotomy in conjunction with increased amounts of erythropoietin to accelerate the rate of iron loss to relieve some of the complications of iron overload?

Dr. Eschbach: Your suggestion is valid and has been tried [124]. The question is whether iron overload needs to be corrected more rapidly than using rHuEpo without concomitant phlebotomy. The relationship between the serum ferritin level and organ dysfunction secondary to iron overload has not been established. Patients with serum ferritin levels greater than 5000 µg/ml (in the absence of active inflammation) are at increased risk of developing organ dysfunction from iron [85]. Our experience suggests that serum ferritin levels fall 50% within one year of the administration of effective doses of rHuEpo coupled with the usual dialyzer blood losses and without concomitant phlebotomy. Therefore I believe that only occasionally will patients require supplemental phlebotomy to manage the iron overload.

Dr. Bushinsky: Knowing the pool size of erythropoietin and its degradation rate, one could calculate the production rate in normal individuals and compare it with the amount of exogenous erythropoietin needed to achieve the same serum level. You could answer many of the questions relating to possible inhibition of erythropoiesis in uremia by determining whether exogenous administration equals endogenous production. Has this approach been attempted?

Dr. Eschbach: No. Exogenous erythropoietin in the form of rHuEpo has been given only as bolus injections intravenously or subcutaneously 3 times weekly. This regimen does not achieve steady-state conditions.

Dr. Cohen: Do we know what level of erythropoietin is achieved in the circulation of your patients? They are clearly not in a steady state, given the episodic doses of rHuEpo they receive, but can one estimate the average circulating level of erythropoietin and compare it with what one sees in nonuremic patients who are anemic for other reasons?

Dr. Eschbach: The serum levels of rHuEpo depend on the dose and the route of administration. In one patient given 15 U/kg intravenously, the serum level increased from a baseline value of 17 mU/ml to 260 mU/ml one hour later and declined to 52 mU/ml by 24 hours. In another patient, given 150 U/kg intravenously, the serum level increased from a baseline of 22 mU/ml to 2300 mU/ml one hour later and declined to 322 mU/ml by 24 hours. Larger doses will result in even higher circulating levels of rHuEpo. When 150 U/kg was injected subcutaneously into another patient, the serum erythropoietin level increased slowly from a baseline value of 19 mU/ml to 192 mU/ml by 24 hours [96]. These values are not steady state and therefore are impossible to compare with levels of serum erythropoietin randomly measured from nonuremic patients with anemia.

Pharmacokinetic studies with rHuEpo have yet to be performed in normal individuals.

Dr. Stuart Sprague (Renal Fellow, Joint University of Chicago/Michael Reese Hospital Program in Nephrology): It appears that one can adjust the dose of rHuEpo to achieve whatever hematocrit is desired in an individual patient. Regarding the side effects associated with rHuEpo therapy, such as high blood pressure, seizures, and the need for more dialysis, what information is available regarding the optimal hematocrit in these patients? Is a hematocrit of 35% or 35% as good as 40% in improving a patient’s functional status?

Dr. Eschbach: The adverse effects of hypertension and seizures appear to be a function of the rate at which the hematocrit rises during the acute treatment period. Patient performance probably depends on the final hematocrit level, but exercise-tolerance studies are required to determine what hematocrit level is optimal. It is not known whether a higher hematocrit level will be associated with a higher incidence of hypertension, or whether hypertension will be more difficult to control. Preliminary data suggest that the incidence of seizures is more a function of the rapid rise in hematocrit (and blood pressure) during the acute treatment period, and is not a function of the hematocrit itself. We have no data suggesting that patients with hematocrits maintained at 40% will require more dialysis than will patients with hematocrits of 30%.

Dr. Satish Kumar (Renal Fellow, Joint University of Chicago/Michael Reese Hospital Program in Nephrology): Are the erythropoietin-producing endothelial cells morphologically distinguishable from other endothelial cells?

Dr. Eschbach: These cells have been located in the anemic mouse kidney by silver grains adhering to their surfaces using an in-situ hybridization technique with a 35S-labeled mouse Epo genomic probe. Approximately 20% to 50% of the cortical interstitial endothelial cells do not adhere to the probe [125], and I don’t believe that routine histology can distinguish between those cells that do and do not react with the probe.

Dr. Cohen: If you had an unlimited supply of rHuEpo, and cost was not a factor, when in the course of the development of progressive renal failure would you recommend that it be given initially?

Dr. Eschbach: I’d recommend that it be administered when the hematocrit decreases to below 30%. I base this opinion on the subjective responses of anemic patients with progressive renal failure who have been treated with rHuEpo. Future detailed objective studies utilizing exercise-tolerance testing might modify that recommendation.

Dr. Paul Sacks (Renal Fellow, Joint University of Chicago/Michael Reese Hospital Program in Nephrology): In your discussion, you touched on the increased incidence of dialyzer clotting as one of the adverse complications of rHuEpo therapy. Others have included an increased incidence of arteriovenous fistula clotting with this form of therapy [25]. Using your patients as their own controls, what is the excess incidence of vascular-access clotting that can be attributed to rHuEpo therapy? Is there a direct correlation between this complication and the increase in hematocrit?

Dr. Eschbach: The results of the multicenter trial with rHuEpo failed to document an increased incidence in vascular-access clotting when the target hematocrit of 35% was obtained and maintained [29]. Because most hemodialysis patients have
either a Gore-Tex or bovine arteriovenous graft, both of which tend to clot once or twice yearly (in contrast with an autogenous fistula), and because graft clotting is quite episodic, it is difficult to know whether a rising hematocrit that may be associated with improved hemostasis [103, 104] results in increased graft clotting. We have analyzed the data from our patients. Of 68 patients treated with rHuEpo for 12 to 27 months, clotting occurred 3 or more times in the vascular accesses of only 8 patients. Clotting occurred only in Gore-Tex or bovine grafts, and it was not necessarily related to an acute rise in the hematocrit.

DR. SATISH KATHPALIA (Attending Nephrologist, Michael Reese Hospital): You mentioned that rHuEpo has been used to treat bleeding in uremic patients. How does this therapy correct bleeding?

DR. ESCHBACH: A prolonged bleeding time is the major manifestation of platelet dysfunction in uremia. Casari showed that the bleeding time decreases toward normal in anemic hemodialysis patients when the hematocrit increases to over 30% with rHuEpo therapy [104]. This observation suggests that anemia might affect platelet function. One theory is that anemia increases the shear stress on the endothelial cell and results in an increase of prostaglandin I₂ production, which in turn leads to increased vascular friability and bleeding. Correcting the anemia thus would indirectly decrease PGI₂ activity.

DR. MARK RICHTER (Section of Nephrology, Mitchell Hospital, University of Chicago): As you have pointed out, patients with chronic renal failure treated with rHuEpo feel better, and many of the symptoms we have attributed to uremia in fact might be related to anemia. Long-term studies will determine whether this translates into improved morbidity and mortality rates in our patients. Our dialysis-prescribing habits are in large part based on the results of the National Cooperative Dialysis Study [126]. In that study, patients had a mean hematocrit of 20.0% to 27.1%. Do we need to rethink our entire concept of the adequacy of dialysis now that our patients will have higher baseline hemoglobin levels? Isn't it possible that patients with higher hemoglobin levels might do quite well with less dialysis?

DR. ESCHBACH: Theoretically I believe you are correct; patients with nearly normal hemoglobin levels could tolerate higher serum creatinine and urea nitrogen levels. But many patients tend to eat more after rHuEpo therapy and thus have a tendency to have higher serum potassium levels [28] and to consume more sodium-containing foods [38]. These patients might require more, not less, dialysis. Until carefully controlled studies indicate that dialysis patients with nearly normal hematocrit levels can do as well with less dialysis, I would caution against shortening dialysis times, except possibly with high-flux membranes. More experience is required for us to know how patients with nearly normal hematocrits tolerate high-flux dialysis.

DR. POCHEDLY: There are two uses of rHuEpo that you didn't mention. These are its use in sickle-cell disease and also its use by athletes to increase their stamina. What do you think about the use of rHuEpo in these situations?

DR. ESCHBACH: The clinical trials using rHuEpo have not included anemic patients with sickle-cell disease; therefore, there has been no experience in their treatment. In patients with sickle-cell disease, rHuEpo stimulates fetal hemoglobin production [127] and probably improves the anemia. It is unknown at this time whether such an improvement would result in an increase in sickling and hemolytic crises.

Blood "doping," that is, erythrocyte reinfusion, increases exercise tolerance [128], and I understand the technique is employed by some athletes to increase their stamina. I suspect that rHuEpo also will be used surreptitiously in place of blood doping. Unless baseline hematocrit levels were known on all athletes, it would be difficult to monitor the misuse of rHuEpo in athletes, because the reticulocyte count would return to normal within 7 days after intravenous rHuEpo injections are withheld. Because some athletes will think, "If a little is good, more should be better," some could attain a very high hematocrit, which could be associated with an increased frequency of vascular complications.

DR. NICOLAOS E. MADIAS (Chief, Division of Nephrology, New England Medical Center, Boston): Improvements, in the sense of general well-being and exercise tolerance, are anticipated following rHuEpo treatment. Have such changes been documented using quantitative methods?

DR. ESCHBACH: A quality-of-life questionnaire has been completed by patients before rHuEpo therapy, immediately after the target hematocrit was attained, and 3 to 6 months later. Although the details of this questionnaire have not been published, preliminary data available at the December 1987 meeting of the American Society of Nephrology indicated significant improvement in various facets of quality of life when the anemia is corrected [29]. Three groups have studied exercise tolerance by using a bicycle ergometer to assess oxygen utilization [129-131]. In general, oxygen utilization increases as the anemia improves, but not necessarily to normal. It is unclear whether correction of the anemia with rHuEpo will completely normalize oxygen utilization in the patient on chronic hemodialysis.

DR. JOHN T. HARRINGTON (Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts): What will be the financial cost to the patient, and ultimately to society, if a substantial percentage of patients with end-stage renal disease begin to receive rHuEpo routinely?

DR. ESCHBACH: At this time, I do not know what the cost of rHuEpo therapy will be. It is hoped that the kidney-Medicare program eventually will pay for rHuEpo, so the cost ultimately will be society's. I suspect that approximately 75% of dialysis patients will benefit from rHuEpo therapy. It will be expensive, but its relative cost will be less because of the savings that result from correcting the anemia. For instance, the direct costs of blood transfusions and androgens (used to stimulate erythropoiesis) will be eliminated. The indirect costs of transfusions and androgens also will be eliminated: complications from hepatitis B infection; non-A, non-B hepatitis and other transfusion-related infections; iron overload; HL-A sensitization preventing a kidney transplant (which is more cost effective than dialysis); and side effects from androgens. Patients will be healthier and, I suspect, will require fewer costly stays in the hospital. I anticipate that eventually more patients will be rehabilitated, employed, and thus will contribute to society and pay taxes.

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References

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