INTERNAL MEDICINE

GRAND ROUNDS

MAY 12, 1994

"MANAGING THE ANEMIA OF KIDNEY FAILURE"

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Recombinant human erythropoietin (EPO) was approved for use in the treatment of the anemia of end stage renal disease (ESRD) on June 1, 1989. Prior to the clinical availability of EPO, anemia was a major cause of morbidity in patients with end stage renal disease. The current wide spread use of erythropoietin in dialysis patients has virtually eliminated anemia and its consequences as a major problem for such patients. The following discussion will highlight selected aspects of the current status of the use, side effects, and beneficial effects of this drug. The central role of iron therapy will also be stressed.

Physiology. The kidney is the primary site of erythropoietin (EPO) production in the adult, with the liver making only a minor contribution (1, 2). The reverse seems to be true in fetal life. Erythropoietin is a glycoprotein hormone. It stimulates erythropoiesis in situations where oxygen delivery is reduced by anemia or hypoxemia. Studies using transgenic mice to identify the renal erythropoietin-producing cells suggest that a population of interstitial fibroblasts known as type I interstitial cells are the major source of renal EPO synthesis (3). Interstitial cells positive for EPO mRNA are limited to the deep cortex and outer medulla in the unstimulated kidney. With worsening anemia, however, the number of positive cells increases and are seen increasingly in the superficial cortex (3). The release of EPO is regulated via a feedback mechanism involving tissue oxygenation. The renal oxygen sensor is probably a heme protein (4). In the presence of decreased oxygen deliver, activation of this sensor appears to lead to the synthesis of a protein that binds to the active site on the enhancer region of the EPO gene, leading to increased EPO production (5). The ensuing rise in red cell production will tend to return oxygen-carrying capacity toward normal. The kidney is well suited to be the site of EPO production because it is able to dissociate changes in blood flow alone from those in oxygenation. For example, hypoperfusion diminishes both the glomerular filtration rate and total tubular Na+ reabsorption. Since active sodium transport is responsible for most of renal oxygen consumption, the parallel relationship between oxygen delivery (reduced by hypoperfusion) and oxygen utilization (reduced by decreased sodium reabsorption) is relatively well maintained, preventing an inappropriate increase in EPO synthesis (3).

Erythropoietin is a glycoprotein with four complex carbohydrate chains which constitutes 40 of its molecular weight of 30,000 daltons (6). The carbohydrate sialic acid moieties, while not necessary for the action of EPO on bone marrow progenitor cells, greatly prolong the half-life of the molecule (7,8). Plasma erythropoietin levels increase in a logarithmic manner as the hematocrit falls, rising from normal levels of 10-12 mU/mL to

values in excess of 1000 mU/mL when the hematocrit reaches a value of less than 20%. Figure 1 shows the relationship of

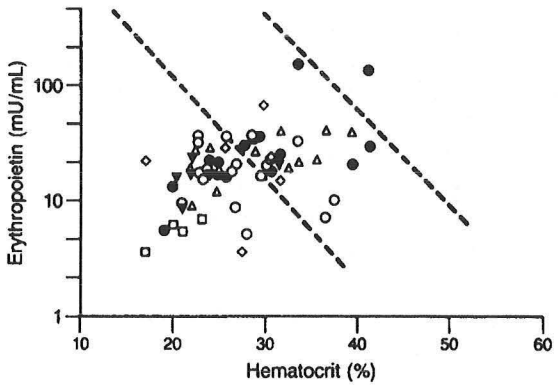


Fig 1. **Relationship of erythropoietin levels to hematocrit in patients on dialysis. Key: closed box, anephric patients; open box, nephric patients. The differing symbols represent original disease type producing ESRD. Note the loss of the normal feedback relationship; rather the relationship is positive and hematocrit level increases with erythropoietin levels. (Adapted with permission.[17])**

erythropoietin levels to hematocrit in patients receiving dialysis therapy (9). The closed symbols represent anephric patient, while the open circles represent nephric patients. Note the lack of the normal inverse relationship; rather, there is now a positive relationship with hematocrit levels rising with increased erythropoietin levels. When patients with ESRD and anemia undergo successful renal transplantation, erythropoietin levels increase markedly, red blood cell production is restored to normal, and erythropoietin levels fall back to the normal range indicating restoration of the normal feedback mechanism (Figure 2) (9).

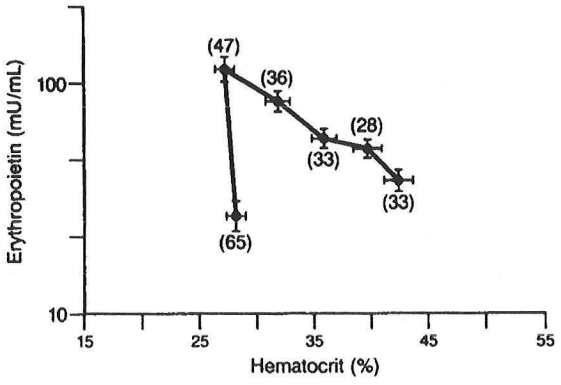


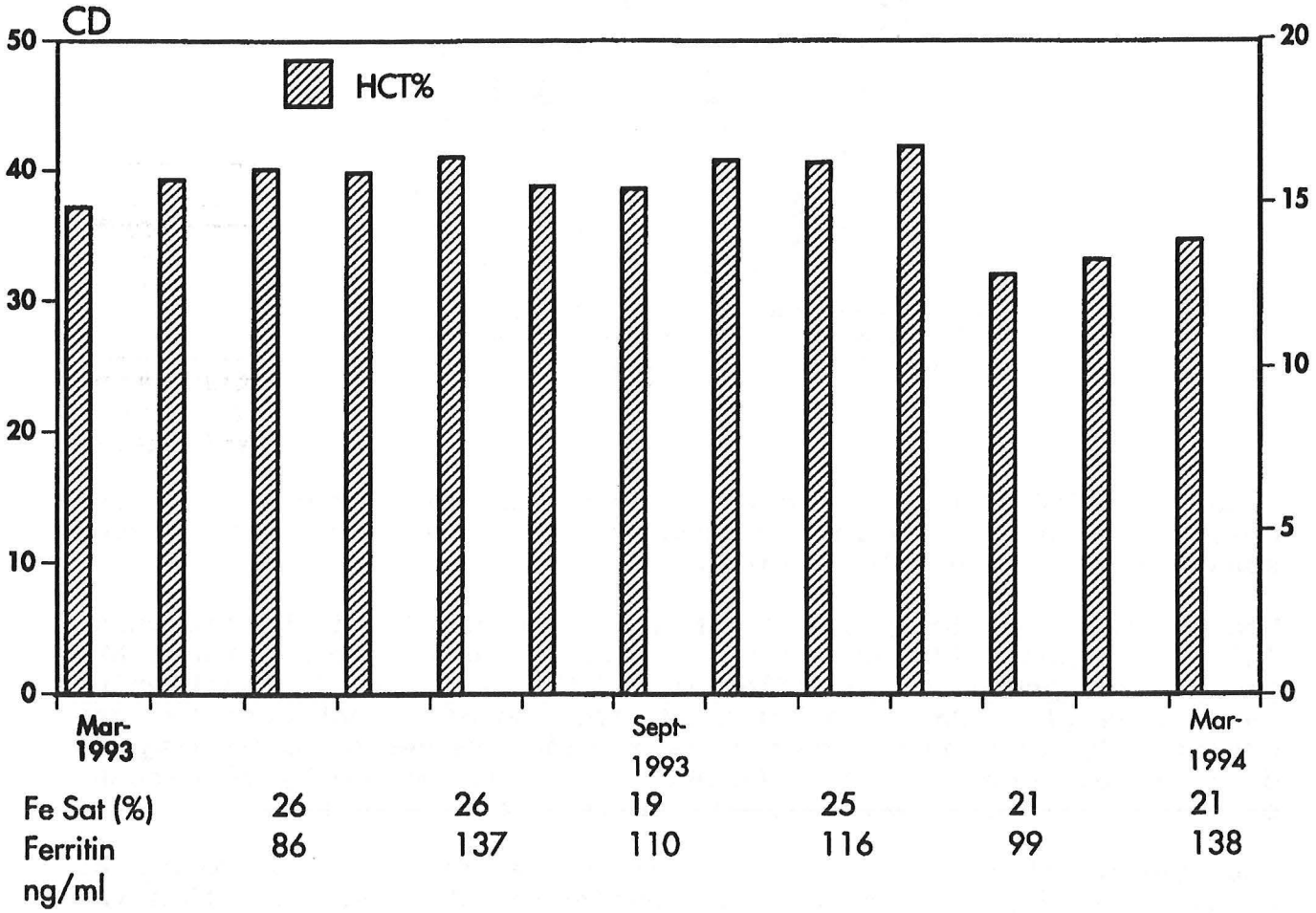
Fig 2. **Correction of anemia following successful transplantation. Plasma erythropoietin levels increase fourfold and then decrease progressively as the hematocrit level increases, indicating operation of the normal feedback loop. Numbers in parentheses represent the number of patients evaluated for erythropoietin level during each period. (Adapted with permission.[17])**

Serum erythropoietin and anemia in renal cystic diseases. The importance of erythropoietin in the genesis of the anemia of chronic renal failure is highlighted by the failure of some

patients with ESRD due to cystic renal disease to develop anemia.

Case Report

C.D. is a 74 year old male with ESRD secondary to autosomal dominant polycystic kidney disease. He was initiated on dialysis in 1972. He has not required EPO therapy as the hematocrit has remained consistently close to 40%. In Dec. 1993, he underwent a left AK amputation. Following surgery, the hematocrit fell to 32%, presumably an effect of the inflammatory response associated with surgery. The hematocrit has risen slowly in the intervening months.



Anemia frequently fails to develop or is of a milder degree in ESRD patients with hereditary or acquired renal cystic disease. Autosomal dominant polycystic kidney is generally associated with a milder anemia and serum erythropoietin levels are reported to be

higher than in other kidney diseases (10,11). Acquired renal cystic disease, first described in 1977 (12) in association with ESRD and prolonged time on dialysis, may be associated with improvement of anemia (13,14). It is probable that the cysts, directly or indirectly, lead to the production of erythropoietin, since higher serum erythropoietin levels and hemoglobin are generally correlated with a greater number of renal cysts (Fig 3) (11,14). How cysts development might stimulate the

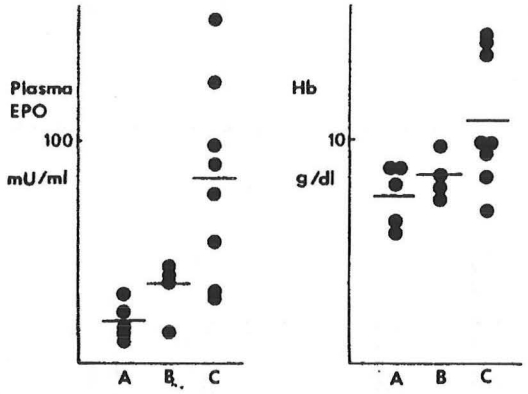


Fig 3. Plasma erythropoietin levels (Epo; mU/ml) and haemoglobin concentration (Hb; g/dl) in patients with no cysts (group A), less than five cysts (group B) or multiple renal cysts (group C).

production of EPO is unknown. Cyst-induced distortion of the cellular architecture in the area of the cortex where the oxygen sensor resides might be involved (14).

Use of EPO in End Stage Renal Disease. The anemia of chronic renal failure is generally due to reduced or virtually absent renal EPO production, presumably a reflection of the reduction in functioning renal mass (1). On the other hand, the use of recombinant EPO has essentially eliminated anemia as a major cause of morbidity in dialysis patients. In the United States, for example, 80 percent of chronically dialyzed patients currently receive EPO.

The anemia of chronic renal failures is generally regarded as multifactorial, but the striking response to EPO indicates that the other factors (e.g. shortened red cell survival and uremic inhibitors of erythropoiesis) must be of lesser importance.
Table 1 shows the major benefits resulting from EPO therapy.

Table 1

Benefits of rHu-EPO Therapy

1. Avoidance of transfusions
   - Risk of blood borne infections
   - HLA sensitization
   - Iron overload
   - Transfusion reactions
2. Enhanced exercise capacity
3. Regression of left ventricular hypertrophy
4. Decrease in ischemic heart disease symptoms
5. Improved tolerance of hemodialysis procedure
6. Improved hemostasis
7. Improved immunologic functioning
8. Relief of pruritus
9. Improved quality of life
10. Enhanced cognitive and electrophysiologic brain function

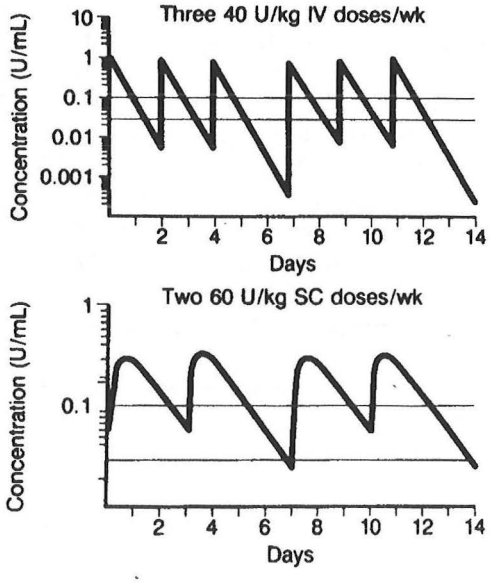
In addition to increasing the red cell mass, EPO has other hematologic benefits, including increasing the platelet count and correcting the abnormality in platelet function, thereby lowering the bleeding time and lessening the risk of uremic bleeding (15,16). By unclear mechanisms, EPO also relieves a variety of other uremic signs and symptoms such as pruritus (17), sexual dysfunction in men, and impaired carbohydrate and cortisol metabolism.

Dosing. The starting dose of EPO for most patients with adequate iron stores and without underlying active inflammation is 50 to 100 units/kg (U/kg) given intravenously or subcutaneously three times weekly; an acceptable response should occur within three months. There is however, a wide interpatient variability as the dose of EPO required to reach a target hematocrit of 32 to 38 percent with the lower level being chosen if there is a significant rise in blood pressure) ranges from 50 to 300 U/kg. A starting dose of 100 U/kg given intravenously has been recommended (1). Ninety percent of patients will respond to this dose as compared to 70 percent with 50 U/kg. The logic of starting high and then titrating down is that a month of therapy may be wasted on the nonresponders if the lower dose is used initially. A larger starting dose has also been recommended in transfusion-dependent patients. Data from the National Phase III Multicenter EPO Study indicates that 65 percent of such patients require 100 U/kg given intravenously three times weekly to maintain an hematocrit between 32 to 38 percent (18). However, these guidelines are less useful in view of the current enthusiasm for subcutaneous EPO administration. Intravenous therapy may require 50 percent more EPO than the subcutaneous route. In addition, titrating up from a smaller initial dose allows the hematocrit to rise more smoothly and more economically than the titrate down approach. From early studies, the average

dose of EPO required to maintain a hematocrit above 30% was determined to be 60 U/kg. About 60-70% of patients can be expected to respond at this dosage level. About 20-25% of patients are very sensitive and will respond to doses lower than 35 U/kg three times weekly. 10 to 15% of patients are resistant and require doses of 150 U/kg or greater three times weekly to achieve the same hematocrit (19).

Erythropoietin: Subcutaneous administration. The initial trials and early clinical applications of erythropoietin (EPO) used the intravenous route, but a number of factors now favor the subcutaneous route. The pharmacokinetics of EPO are quite different depending on the route of administration. The dose adjusted maximum concentration when EPO is given intravenously is 10 fold greater than when it is given subcutaneously (8). Moreover, bioavailability of subcutaneously administered EPO is only 31% of the intravenous dose, yet clinical studies indicate that subcutaneous EPO is effective at a considerably lower dose and at a considerable savings. Thus, the erythropoietic response is independent of the peak concentration, but is dependent on the duration of time that the serum erythropoietin level is maintained above a critical level (19). The critical concentration varies widely among patients accounting for the variability in individual dosing requirements. Since red cell production will be satisfactorily maintained by keeping EPO levels between 30-200 mU/mL, this can be most economically achieved by using subcutaneous EPO. The very high peaks obtained with intravenous dosing are unnecessary to initiate erythropoiesis in the bone marrow, and the very low levels which occur between doses will permit erythropoietin dependent cells to die. Absorption from subcutaneous sites is slow, lasting for up to 4 days (19). Thus, the slow absorption from subcutaneous dosing 2-3 times weekly results in erythropoietin levels in the target range for the entire week. In contrast to this more physiologic stimulation of the erythron, intravenous pulse administration of EPO may allow for periods where the erythron is not stimulated. Figure 4 shows

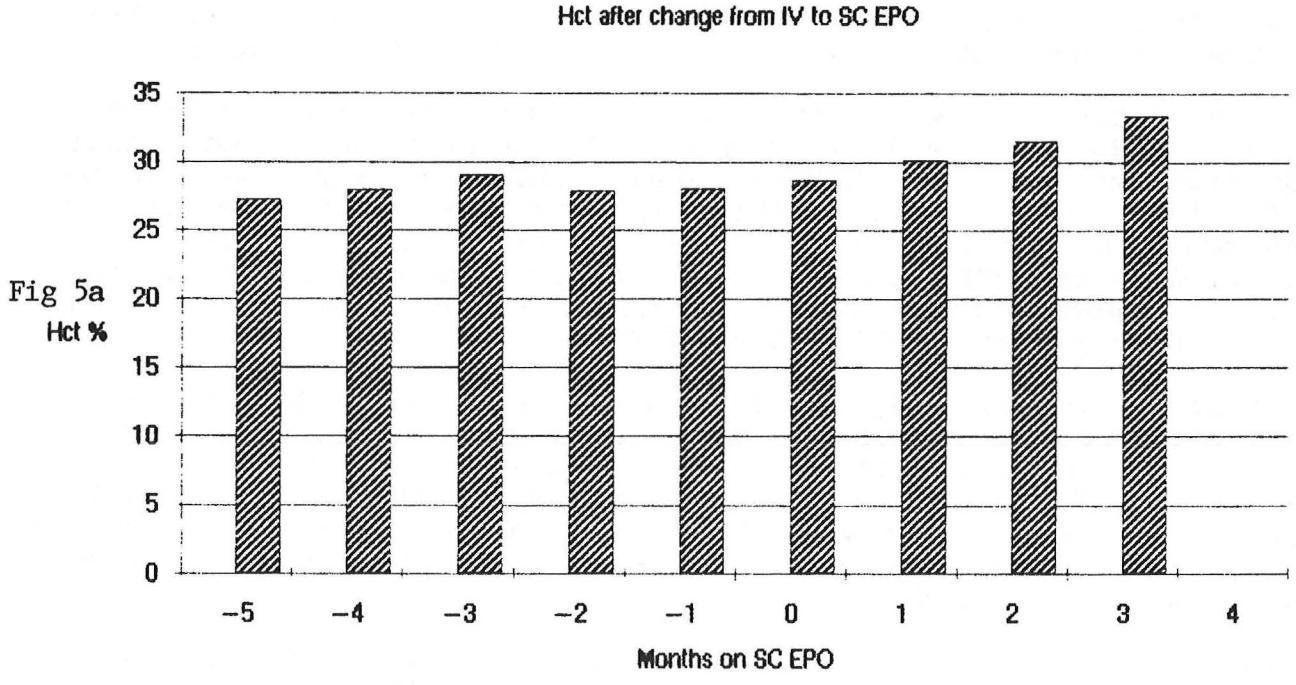
Fig. 4



concentration-time simulations for IV EPO given as three 40 U/kg per week and SC EPO given as two 60 U/kg doses per week (19). The target erythropoietin zone between the horizontal lines represents the erythropoietin levels found in normal individuals with mild anemia (hematocrit 30%). Note that intravenous dosing results in much higher peak levels than subcutaneous dosing, but concentrations regularly drop below 30 mU/ml for a significant period of time. Subcutaneous dosing, however, results in concentrations in the target range for nearly the entire week.

EPO given subcutaneously three times a week will maintain the hematocrit at the same level and at a lower dose than intravenous EPO (20). As an example, twice weekly subcutaneous EPO has been shown to be as effective as the same dose given three times a week by the intravenous route (21); this represents a 33 percent reduction in dose and cost. These findings of a 25 to 50 percent EPO dose reduction have been confirmed by others (19,22,23). As a result of these demonstrated cost savings, we switched all of our hemodialysis patients from intravenous to subcutaneous EPO (two or three times per week) over a period of one month. In 22 patients who had sufficient data to analyze, the mean hematocrit rose by 7 percent in the first three months, while the cost of EPO fell by 25 percent (Figures 5a and 5b). Only one patient asked to

Fig 5a



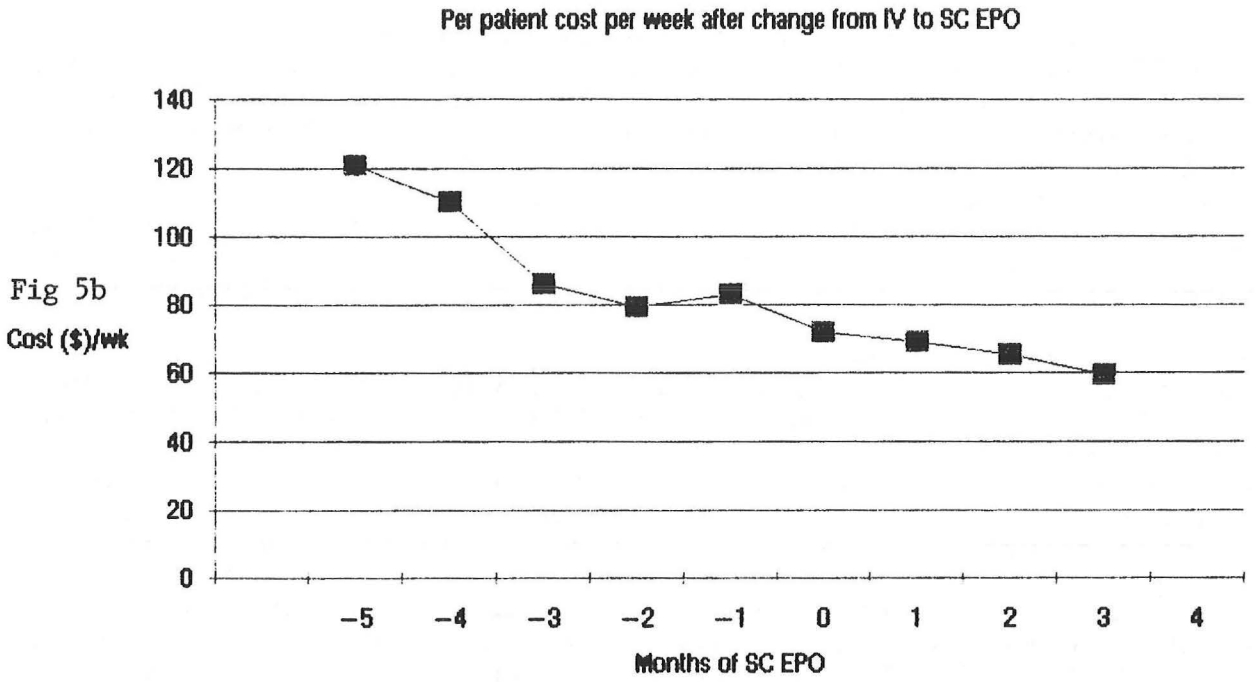


Fig 5b

return to intravenous therapy. The adverse effects of subcutaneous EPO are generally similar to those for intravenous EPO, except that the subcutaneous route is less likely to cause hypertension. However, some patients complain of pain at the site of injection, possibly induced by the citrate used as a stabilizer (22). This problem can be minimized by using a concentrated formulation.

When subcutaneous EPO is given daily, it is more effective and the total weekly dose is less than with twice or three times weekly administration (24). However, once weekly therapy also may be effective. In predialysis patients, for example, subcutaneous EPO can maintain the hematocrit at 35 to 40 percent with a single weekly dose of 4000 U/kg (25). A similar once weekly regimen has been used successfully in small groups of hemodialysis patients, with a cost saving of 67 percent (26).

Chronic Peritoneal Dialysis. Most patients treated with continuous ambulatory or cycling peritoneal dialysis receive subcutaneous EPO, since it is more conveniently self-administered at home. Maintenance EPO doses in these patients range from 4,270 to 8,890 U/wk (27). Once weekly EPO administration, at an average dose of 88 U/kg, is as effective as twice weekly dosing to achieve a target hemoglobin of 10 g/dL.

Lowering dose requirements. The cost of EPO is high, even when compared to the cost of managing the complications of the alternatives, i.e. blood transfusions and androgen therapy (28). This high cost has stimulated a search for ways to lower the dose

(Table 2). The best current method is subcutaneous

Table 2

Lowering Dose Requirements

1. EPO cost is high; $5300 yearly
2. Subcutaneous route decreases dose 10-50%
3. Androgen therapy, weekly
4. Polysulfone dialyzers

administration (19). Androgen therapy with 100 mg of nandrolone decanoate intramuscularly once a week may be beneficial by increasing bone marrow sensitivity to EPO (29); however, the activity of androgens is relatively modest and side effects are likely to limit their general use (30). Using a high flux, polysulfone dialyzer is another modality that may improve the response to EPO (31).

EPO resistance. Some patients are relatively resistant to EPO and require doses greater than 100 U/kg (Table 3). The most common cause is iron

Table 3

Causes of Resistance to Erythropoietin Therapy.

Iron deficiency	Inflammation/infection
Aluminum Toxicity	Osteitis Fibrosa
Underdialysis	Hemolysis
Blood loss	Hemoglobinopathy
Miscellaneous	

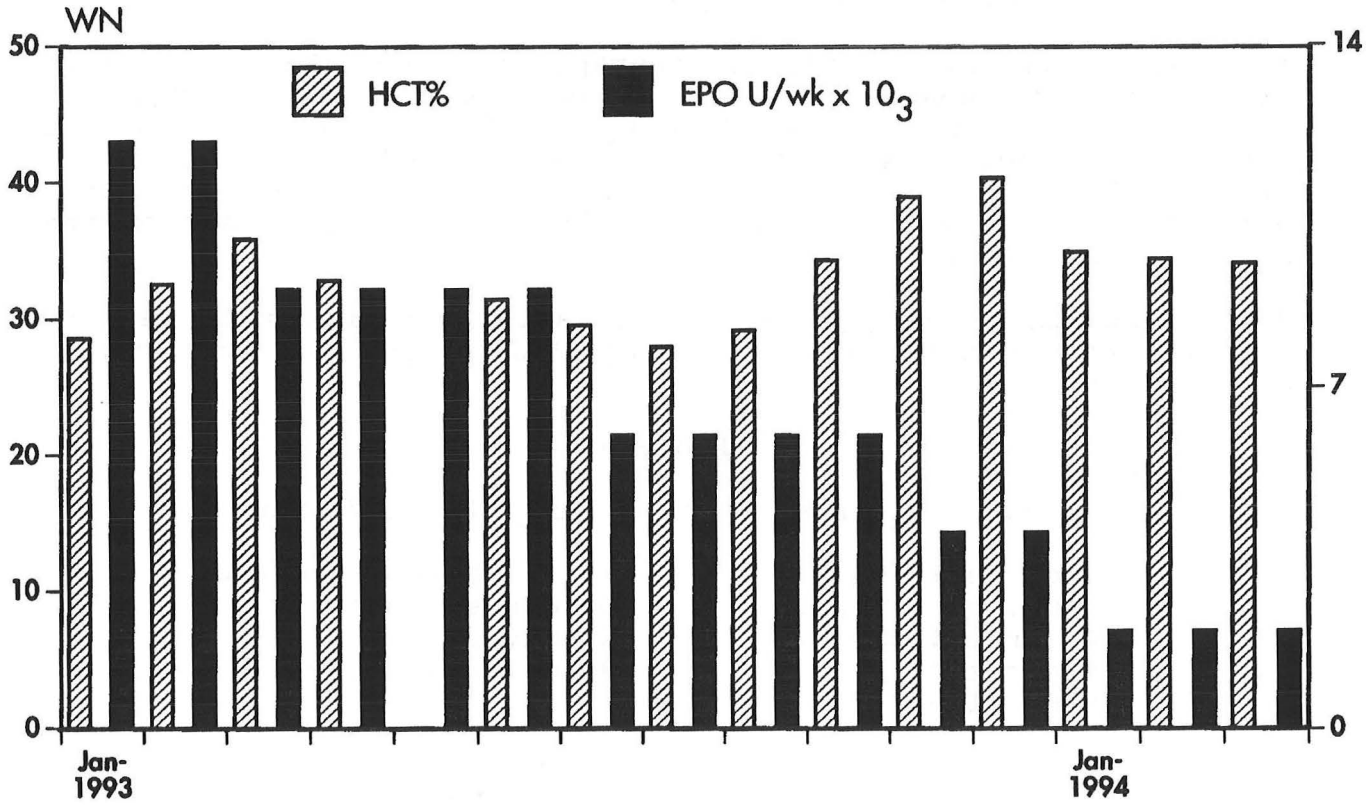
deficiency induced in part by the rapid increase in erythropoiesis. Bone marrow fibrosis due to secondary hyperparathyroidism may contribute and should be suspected when EPO resistance occurs in iron replete patients (32). Chronic inflammation, occult malignancy, and unsuspected hematologic disorders (such as folate deficiency) also must be considered.

Iron Balance During Dialysis and Following Erythropoietin. Adequate iron stores are essential for achieving maximum benefit from erythropoietin (EPO). Decreased iron stores or decreased availability of iron is the most common reason for resistance to the effect of EPO (33).

Case Report

W.N. is a 77 year black male with end-stage renal disease resulting from hypertension. He began hemodialysis April 22, 1987. He underwent parathyroidectomy for severe secondary hyperparathyroidism in 1989, but surgery was incomplete.

Immunoreactive serum PTH levels remain high, and he still requires intensive medical therapy with intravenous 1,25 (OH)2D and oral phosphate binders. His anemia has been responsive to EPO. In early 1993, the dose of EPO was 12,000 units weekly. Fe Sat (%) was less than 20% with a low normal ferritin level of 88 ng/ml. Repeated treatments with intravenous iron dextran have increased Fe Sat to 28%, ferritin to greater than 500 ng/ml. The hematocrit can now be maintained at 35% with an EPO dose of 2,000 units weekly.



Fe IV (g)			1 gm		1 gm		0.5 gm
Fe Sat (%)	16	17	34	8	18	28	28
Ferritin ng/ml	118	88	135	271	261	520	534

The nontransfused dialysis patient is in a state of continuous iron loss from gastrointestinal bleeding, blood drawing, and most important, the dialysis treatment itself. Hemodialysis patients lose an average of 2 grams of iron per year (34). Thus, iron deficiency will develop in all patients receiving EPO unless supplemental iron therapy is given orally or intravenously. Serial evaluation is necessary for early detection of this complication. Plasma iron and ferritin levels, and the percent transferrin saturation (plasma iron divided by total iron binding capacity[TIBC=plasma transferrin *1.4]) should be measured at baseline and then monitored bimonthly. A reduction in plasma

ferritin can be expected during the first few months after the initiation of EPO as iron is mobilized from iron stores and used for red cell production. Iron deficiency is present when the transferrin saturation falls below 20 percent and the plasma ferritin concentration is less than 100 ng/mL. It is important to appreciate that ferritin is also an acute phase reactant; thus, a falling plasma iron and transferrin saturation coupled with a rising plasma ferritin is more likely to indicate the presence of inflammation (see below). If pre-EPO iron indices indicate iron deficiency, then initiation of EPO should be delayed until the effect of iron replacement on erythropoiesis can be ascertained. Repletion of iron stores alone will raise the hematocrit to the target level in a significant proportion of patients. Furthermore, EPO administration in the presence of iron deficiency will be ineffective and is economically unsound.

Iron Therapy. All dialysis patients should receive supplemental iron, except for those with excessive iron stores (plasma ferritin concentration >500 ng/mL). Intestinal iron absorption is intrinsically normal in renal failure, but may be reduced by food and antacids. Thus, oral iron should be given between meals, if tolerated. Giving one of the doses at bedtime may be a simple and effective expedient. The goal of oral iron therapy during EPO administration is to maintain transferrin saturation greater than 20 percent and the plasma ferritin concentration above 100 ng/mL and preferably above 200 ng/mL. In many patients, transferrin saturation and plasma ferritin continue to fall despite oral iron therapy, indicating the need for parenteral iron. Intravenous iron dextran is usually given in doses of 50 to 100 mg with each dialysis treatment for a total of 10 to 20 injection. A total of 2 grams or more per year may be required, depending on the amount of dialytic and gastrointestinal blood loss. EPO is capable of stimulating erythropoiesis so vigorously that the demand for iron can exceed the ability of the bone marrow to release stored iron, i.e. a state of functional iron deficiency. Clinically this state of functional iron deficiency can be detected by documenting a normal serum ferritin concentration and a bone marrow that stains positively for iron (35). It is likely in these circumstances that iron saturation will be low, i.e. less than 20%. Thus, during EPO therapy, monitoring iron saturation is a more reliable way to detect the presence of functional iron deficiency than is following serum ferritin levels. Moreover, it is probable that a serum ferritin higher than the usual normal range is necessary to rule out an iron deficient state in patients with ESRD (36).

Inflammatory and Infectious Causes of EPO Resistance. Following iron deficiency, inflammation and infection are the most common causes of EPO resistance (Table 4). There are two

Table 4

Inflammatory and Infectious Conditions in ESRD

Inflammations	Infections
Malignancy	Pneumonia
Surgery	URI
Arthritis	UTI
Pericarditis	Access infection

predominant mechanisms of anemia with these conditions (Table 5). In the presence of inflammation or infection, iron is

Table 5

Mechanisms of Inflammation-induced Anemia

1. Reticuloendothelial blockade
2. Suppressed erythropoiesis by activated macrophages

cleared more rapidly from the plasma by the reticuloendothelial system thus reducing the amount of iron available for transferrin to deliver to developing erythrocyte progenitors. Further, activated macrophages decrease iron release and increase the rate of ferritin synthesis and iron storage. The second mechanisms involves activated macrophage production of the cytokines interleukin-1 and tumor necrosis factor (TNF) which inhibit the proliferation of erythroid progenitor cells. The pattern of laboratory abnormalities outlined in Table 6 is consistent with

Table 6

Diagnosis of Inflammatory Anemia

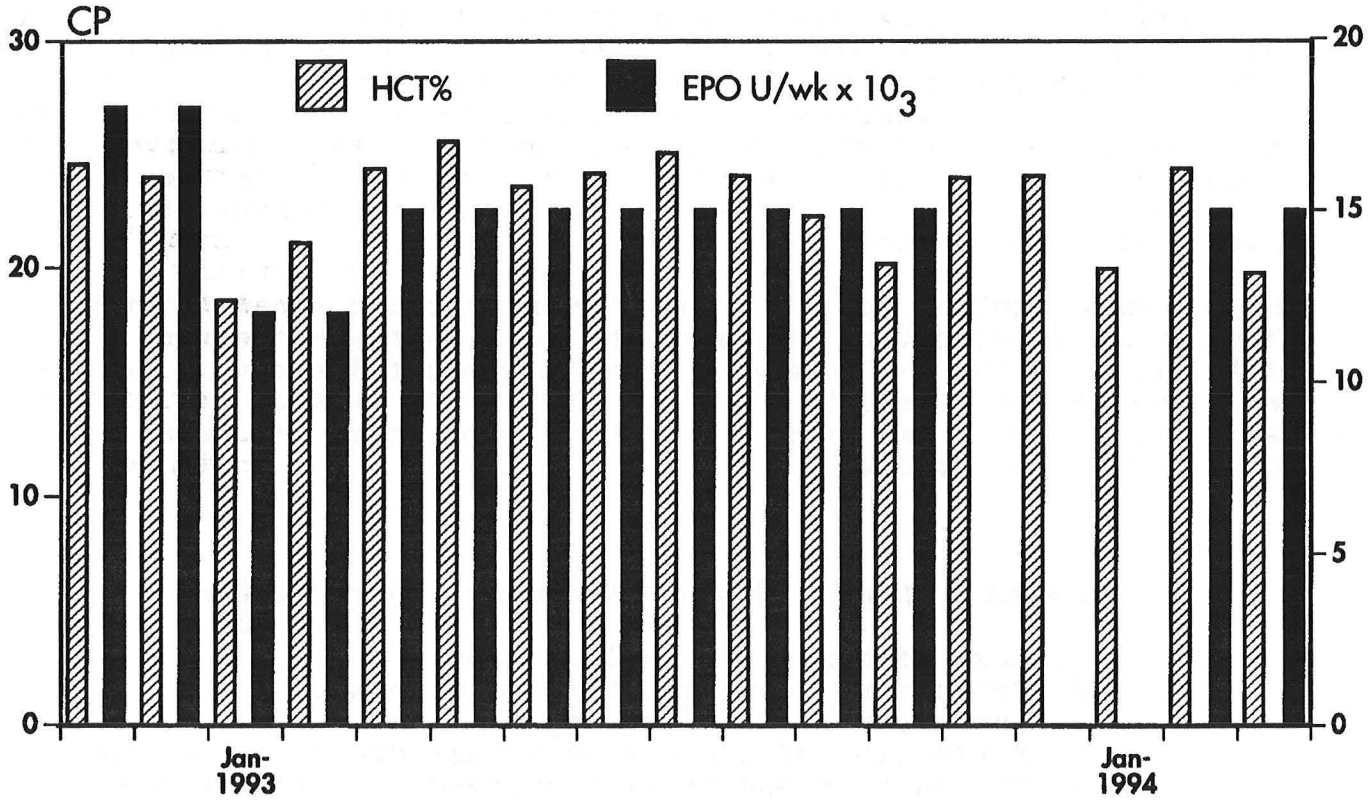
1. Normochromic, normocytic anemia
2. Absence of iron deficiency, Al^{+++} overload, and high PTH
3. Low serum Fe, low TIBC, low transferrin sat
4. High ferritin

the anemia seen in inflammatory disorders. Treatment of this type of anemia is directed at diagnosing and treating the underlying disorder.

Case Report

C.P. is a 79 year old male with renal failure due to analgesic nephropathy. He initiated dialysis in Nov. 1989. He underwent nephrectomy for renal cell carcinoma in Jan. 1990.

In Feb 1993, a chronic non-healing draining perirectal abscess of several years duration was biopsied and found to be a mucinous adenocarcinoma, probably of colon origin. Primary surgical treatment was not felt to be indicated and a diverting colostomy was established followed by chemotherapy and several months of radiation therapy. A chronic draining fistulous tract is still present. He has an elevated PSA, but no diagnostic or therapeutic intervention is planned. Despite doses of EPO of 18,000 units weekly, the hematocrit can only be maintained above 20% using regular blood transfusions. Iron saturation remains high and serum ferritin levels have risen progressively. Except for chronic hypotension, his dialysis treatments are uneventful and his quality of life appears reasonably good.



RBC's (Units)	2	2	3		2	2	2	1
Fe Sat (%)	(25)	(22)	(46)	(46)	(80)	(66)		
Ferritin ng/ml	(491)	(499)	(635)	(597)	(688)	(1506)		

Occasionally, the reticuloendothelial blockade can be overcome by substantially increasing the dose of EPO. However, this approach is usually not successful and may not be cost effective. For some patients with chronic inflammatory conditions, periodic transfusions may be the only reasonable solution.

Side Effects of EPO Therapy. A variety of side effects accompany

the use of EPO (Table 7).

Table 7

Side Effects of rHu-EPO Therapy

Hypertension	Headache
Seizures	Decrease in dialysis efficiency
Dialyzer clotting	Vascular access clotting
Flu-like reaction	

The most common side effects, aside from hypertension and its related problems, are headache which occurs in 15 percent of cases and an influenza-like syndrome affecting 5 percent (37,38). The influenza-like syndrome is of unknown etiology, but is responsive to anti-inflammatory drugs and does not seem to occur with subcutaneous EPO administration (39). Correction of anemia with EPO is also associated with enhanced vascular access clotting (37), necessitating an increase in heparin dose of approximately 25 percent in most patient (40). Although EPO also improves the hemostatic defect caused by uremia and raises the platelet count (15,16), there is no evidence that these changes cause a hypercoagulable state.

Hypertension following erythropoietin in chronic renal failure. Twenty to 50 percent of patients who receive erythropoietin (EPO) intravenously for the anemia of chronic renal failure will develop an elevation in diastolic pressure of 10 mm Hg or more (41,42,43). A number of potential factors could be involved in the development of hypertension (Table 8).

Table 8

Potential Causes of rHu-EPO-induced Hypertension

1. Loss of hypoxic vasodilatation
2. Failure to downregulate cardiac output
3. Increased blood viscosity
4. Activation of pressor hormones/adrenergic system
5. Decrease in endothelial-derived relaxing factor
6. Increase in endothelin
7. Increase in vascular smooth muscle cytosolic calcium
8. Direct vasoconstrictor effect of rHu-EPO
9. Genetic predisposition

Blood pressure is less likely to rise after subcutaneous administration (44), possibly because this route of administration does not elevate plasma endothelin levels (45). Several factors are thought to contribute to this hypertensive response, including a high dose of EPO, a rapid increase in hematocrit, a large absolute elevation in hematocrit, and a prior personal or family history of hypertension (41,42,46); however, a consistent

relationship with any one of these parameters is difficult to demonstrate. The possible contribution of increased plasma endothelin levels after intravenous EPO administration is uncertain (45). The rise in blood pressure appears to be due to rapid reversal of anemia-induced peripheral vasodilatation with a less then complete reversal of the anemia-induced rise in cardiac output. Why this occurs is unclear, but impaired myocardial compliance resulting from the cardiac hypertrophy commonly seen in uremia may be an important factor. Mayer et al (47) studied hemodynamic parameters in 18 hemodialysis patients pre- and post-treatment with EPO. Post treatment cardiac output decreased significantly, while diastolic blood pressure and peripheral resistance increased significantly. In elderly patients treated with EPO, a high cardiac output gradually falls over a period of one year and is accompanied by a 25 percent reduction in left ventricular mass (48). Other factors may also contribute to the rise in blood pressure. One is the 23 percent increase in whole blood viscosity induced by EPO (49). For predialysis patients treated with EPO, the development of hypertension is associated with a failure of plasma volume to contract in a manner proportionate to the expansion of the red cell mass (50). This is unlikely to be an important mechanism in the dialyzed patient where plasma volume regulation is controlled by the ultrafiltration process. On the other hand, there is at present no evidence that EPO has a direct effect on vascular endothelium to cause vasoconstriction or even to have an indirect effect, such as increasing calcium uptake or stimulating the release of circulating vasoconstrictors (41). At the other end of the spectrum, some chronically hypotensive dialysis patients show an improvement in blood pressure following EPO therapy (Fig 6)(47). However, this does not appear to be associated with a lessening of hemodynamic instability during dialysis (51).

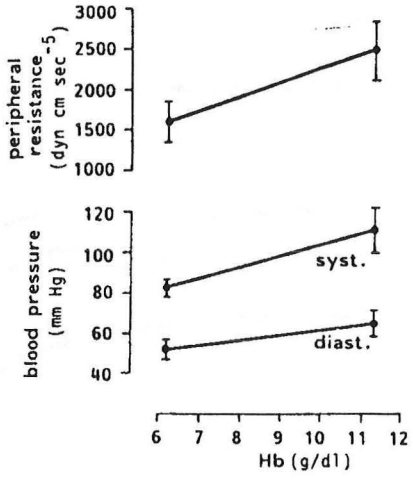


Fig 6. **Hemodynamic parameters in four hypotensive hemodialysis patients before and after partial correction of anemia by r-HuEPO.**

Hypertensive Encephalopathy. Hypertensive encephalopathy sometimes

accompanied by seizures may occur when EPO causes a rapid rise in blood pressure (52). Hyperperfusion of the cerebral circulation due to a breakdown of cerebral autoregulation may be important in these cases (46). It is not possible to predict in advance who will develop this complication; as a result, prodromal symptoms (such as persistent headache or visual disturbances) must be looked for, particularly in previously normotensive individuals in the early weeks and months after the institution of EPO therapy.

Treatment. Therapy of EPO-induced hypertension begins with prevention. The risk of hypertension can be ameliorated by aiming for an hematocrit of 30 to 35 percent, a level that is sufficient to relieve symptoms without producing a significant elevation of blood pressure (42). Patients who still become hypertensive can be treated with fluid removal (via dialysis or, if the patient has only chronic renal failure, diuretics) and the administration of antihypertensive agents. Beta-adrenergic blockers and vasodilators should be considered as agents of first choice, although calcium channel blockers and angiotensin converting enzyme inhibitors also may be effective. The dose of EPO should be reduced or discontinued for several weeks in severe cases or when other therapeutic measures are ineffective.

Adequacy of Dialysis. EPO therapy modestly reduces the adequacy of dialysis, since an increasing hematocrit means that each mL of blood contains more red cells and less plasma (53). As an example, Buur et al (39) examined a group of 14 dialysis patients and demonstrated that the dialyzer clearance of creatinine, phosphorus, and potassium fell by 10 to 17 percent, leading to elevations in the plasma concentrations of these substances. These changes could be reversed by a 10 to 15 percent increase in the dialysis prescription. In addition to the increase in the dialysis prescription, the dose of heparin and the dose of phosphate binders also needed upward adjustment. Figure 7 shows the theoretical

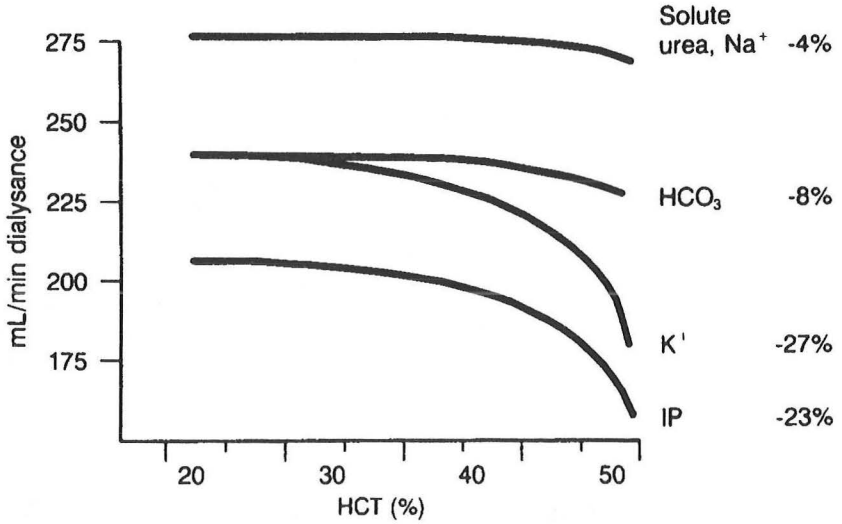


Fig 7. **Theoretical effect of hematocrit on dialyzance of urea, bicarbonate, phosphate, and potassium. (Adapted with permission from FA Gotch, unpublished.)**

effect of hematocrit on dialysance of urea, bicarbonate, phosphate and potassium (54). Within the clinically relevant hematocrit range of 28-40% percent, the magnitude of the reduction in dialysance is not so great that a modest adjustment in the dialysis prescription cannot overcome the effects. Currently, the midweek, predialysis serum urea nitrogen and the Kt/V (the dialyzer clearance of urea x time on dialysis/ body urea space) are used to assess the adequacy of the dialysis treatment. However, urea is so permeable across biologic and artificial membranes, stability of its plasma concentration and of the Kt/V cannot be used as evidence that EPO has no adverse effect on dialysis adequacy. Plasma levels of phosphate, creatinine, and potassium are more likely to be useful as markers of dialysis adequacy. However, correction of anemia with EPO may lead to increased levels of urea, potassium, and phosphate independent of an effect on dialysance and the explanation may be that enhanced appetite has increased the rate of solute generation.

Regression of Left Ventricular Hypertrophy. Cardiovascular disorders are a major cause of morbidity and mortality in ESRD patients (Table 9). A number of conditions

Table 9

Cardiac Findings in Chronic Hemodialysis

1. Dilatation of the left ventricle
2. Increased cardiac output
3. Impaired myocardial contractility
4. Left ventricular hypertrophy

common to dialysis patients increase cardiac work (Table 10). These conditions are variably affected by the dialysis procedure, but hypertension and anemia appear to be the most important in causing cardiac overload.

Table 10

Factors Increasing Cardiac Work

1. Arteriovenous shunt
2. Hypertension
3. Volume overload
4. Dialysis procedure
5. Anemia

Cardiac hypertrophy is a very common finding (55). Left ventricular hypertrophy progresses with time on dialysis (56). The anemia of chronic renal failure correlates with left ventricular hypertrophy (57). In a prospective study of 15 hemodialysis patients followed for one year after institution of intravenous EPO (initial dose of 150 U/kg/week adjusted to achieve

an hematocrit of 30-35%), a 33% reduction in left ventricular mass index was achieved (58) (Table 11). The reduction in LVMI occurred in both hypertensive patients receiving antihypertensive drugs,

Table 11

Regression of Ventricular Hypertrophy After One Year of EPO

	pre	post	p-value
IVST (cm)	1.42±0.33	1.07±0.13	<.01
LVPWT (cm)	1.28±0.21	1.01±0.11	<.01
LVMI (g/m^2)	211±48	139±50	<.05
CI ($l/min/m^2$)	5.5±1.5	4.0±0.9	<.001
Hematocrit (%)	19.7±2.4	32.3±3.5 (ref. 58)	<.001

as well as in normotensive subjects, but the magnitude of regression was greater in normotensive subjects. The 21% reduction in cardiac index with partial correction of the anemia is consistent with other reports. Similar findings have been reported from other centers suggesting that anemia may be a more important determinant of left ventricular hypertrophy than hypertension in this population (48,59,60). Although correction of anemia reduces left ventricular mass, this beneficial effect may be negated by worsening of blood pressure control (61).

EPO and Ischemic Heart Disease. The ESRD patient with anemia and significant coronary artery disease is particularly susceptible to angina at low work loads. Partial correction of such anemia with EPO (hematocrit from 25% to 35%) in selected patients reduces exercise-induced myocardial ischemia (62). Figure 8 demonstrates the pre and post EPO ST depression occurring during treadmill stress testing in 7 patients who had coronary artery disease by angiography, a baseline hematocrit of <27%, a reproducible ECG positive treadmill test, and no disturbance of repolarization of the ECG at rest. The failure to control hypertension resulting from correction of the anemia may negate these beneficial effects.

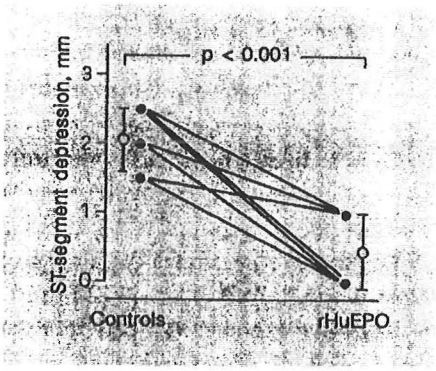


Fig 8. ST depression during treadmill stress testing. rHuEPO = Erythropoietin. ST segments were evaluated at the same performance level (maximum in the stress test at a hematocrit of 25%).

EPO and transfusions. Prior to the advent of EPO, 10-25% of hemodialysis patients required transfusions. The appropriate use of EPO has decreased the number of transfusion-dependent patients by two-thirds (63). Because of frequent transfusions, iron overload was also a common occurrence in the past. As outlined above, EPO has made iron deficiency a far more common problem. However, the occasional patient who is EPO resistance and requires regular transfusions can still develop iron overload (ferritin greater than 1000 ng/ml). EPO administration coupled with phlebotomy is useful to treat EPO responsive patients with severe iron overload (ferritin >3000 mcg/ml, increased density of organs on CT scanning, myopathy, cirrhosis, cardiomyopathy, and pancreatic insufficiency) (64).

Improved Quality of Life. Several studies suggest that a marked reduction in patient symptoms and an improved sense of well-being follow correction of anemia with EPO (Table 12) (65). However, partial correction of anemia has little effect on the

Table 12

Changes in Quality of Life After Correction of Anemia

	Baseline (%)	Post-EPO (%)
Tire easily, no energy	84	58*
Weak, lacks strength	77	53*
Faint, dizziness	23	12*
Nervous, tense, anxious	53	37*
Depressed	40	38
Karnofsky 1 or 2 (normal/able to carry on normal activity)	27	48*
Employed (full/part-time)	22	23
Too ill to work	31	28

Adapted (ref 65)

number of patient who are employed. Because of other co-morbid conditions, it has been difficult to substantiate widespread improvement in the quality of life. However, when large numbers of patients are studied, improvement in a number of parameters have been found (66). In the phase III clinical trial of EPO, questionnaires were completed by 300 subjects regarding subjective and objective quality of life indicators. After 10.3 months of EPO therapy, significant improvement in a number of disease symptoms were reported (Figure 9) (67,68). Also, functional ability based on Karnofsky scores improved over this same 10.3 month time period (Figure 10).

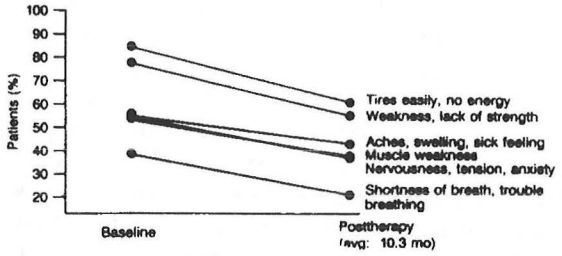


Fig 9. **Symptom relief and epoetin therapy. McNemar Test between baseline and second follow-up: $P = 0.001$. (Adapted from *JAMA*, 1990; 263:825-830. Copyright 1990, American Medical Association.[18])**

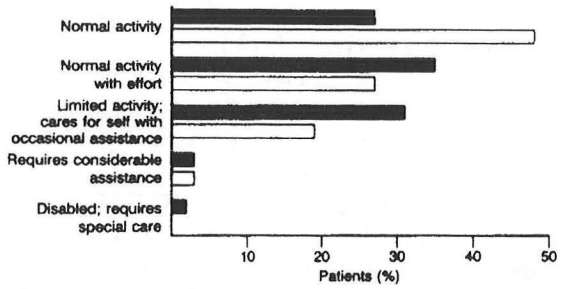


Fig 10. **Functional ability based on Karnofsky scores in patients on hemodialysis receiving epoetin therapy. ■, Baseline; □, posttherapy (mean, 10.3 months). (Adapted from *JAMA*, 1990; 263:825-830. Copyright 1990, American Medical Association.[18])**

EPO and Exercise Capacity. Exercise capacity in patients with ESRD, as measured by $VO_{2\ max}$, is less than 50% of that in normal individuals (69,70). Progressive work exercise training on a cycle ergometer following correction of anemia with EPO (hematocrit 21.2 to 35%) improved this measurement by 17% over baseline (71). Another study by the same group also documented mild improvement in strength and endurance (72). These somewhat modest improvements suggest that anemia is only one of many factors which reduces exercise capacity in ESRD patients. Other potential factors not affected by correction of anemia or exercise training include peripheral neuropathy, uremic bone disease, disuse atrophy, and uremic myopathy.

EPO in chronic renal failure. EPO effectively corrects the anemia in patients with renal insufficiency who do not yet require dialysis (73,74). Unfortunately, the improvement in exercise capacity of responsive individuals is only modest; as a result, widespread use of EPO in this population cannot be recommended unless there is a specific indication (such as anemia-dependent angina or easy fatiguability). Although raising the hematocrit may raise the systemic and perhaps the intraglomerular pressures, no adverse effect on the progression of renal disease has been demonstrated in these patients as long as the blood pressure is well controlled (75).

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