

THE INTENSITY OF HEMODIALYSIS AND THE RESPONSE TO ERYTHROPOIETIN IN PATIENTS WITH END-STAGE RENAL DISEASE

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Abstract *Background.* Anemia (characterized by a hematocrit of 30 percent or lower) persists in 40 to 60 percent of patients treated for end-stage renal disease with maintenance hemodialysis, despite concomitant erythropoietin (epoetin) therapy. We tested the hypothesis that inadequate dialysis is a key reason for the insufficient response to erythropoietin in patients with end-stage renal disease who are receiving hemodialysis.

Methods. We prospectively studied 135 randomly selected patients undergoing hemodialysis who had been receiving intravenous erythropoietin for at least four months. The adequacy of dialysis was assessed by measuring the percent reduction in the blood urea nitrogen concentration and the serum albumin concentration. The hematocrit was measured weekly for four weeks, transferrin saturation was measured, and coexisting illnesses were documented.

To determine the effect of an increased level of dialysis on the hematocrit, the thrice-weekly schedule of dialysis was increased to raise the mean urea-reduction value from 60.7 to 72.0 percent for six weeks in 20 consecutive patients whose base-line urea-reduction value was less than 65 percent. The change in the hematocrit in these patients was compared with that observed in the next 20 patients who had an equivalent base-line urea-reduction value but whose level of dialysis was not altered.

Results. The mean (\pm SD) hematocrit of the entire group was 29.2 ± 4 percent, and the mean thrice-weekly

dose of erythropoietin was 59 ± 29 U per kilogram of body weight. The mean serum albumin concentration was 3.8 ± 0.4 g per deciliter, the mean urea-reduction value was 62 ± 4.8 percent, and the mean transferrin saturation was 20 ± 9 percent. Multiple regression analysis revealed direct correlations between the hematocrit and the serum albumin concentration ($P = 0.009$) and between the hematocrit and the urea-reduction value ($P = 0.012$) after adjustment for other factors. A logistic-regression analysis indicated that an 11 percent increase in the urea-reduction value doubled the odds that a patient would have a hematocrit above 30 percent.

After six weeks of increased intensity of dialysis in 20 patients with base-line urea-reduction values of less than 65 percent, the mean (\pm SE) hematocrit rose from 28.4 ± 0.78 percent to 32.3 ± 0.71 percent ($P = 0.002$); there was no significant change in a control group of 20 patients with equivalent base-line urea-reduction values in whom the dialysis level was not altered (28.2 ± 0.84 percent to 26.3 ± 0.85 percent; $P = 0.175$).

Conclusions. In patients with end-stage renal disease, inadequate hemodialysis is associated with a suboptimal response to erythropoietin therapy. Increasing the intensity of dialysis in patients with anemia who are receiving inadequate dialysis results in a significant increase in the hematocrit. (N Engl J Med 1996;334:420-5.)

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THE main pathogenetic factor causing anemia in end-stage renal disease is the diminished synthesis of erythropoietin in diseased kidneys.¹ Before the availability of recombinant erythropoietin (epoetin),² the mainstays of anemia therapy in end-stage renal disease were blood transfusions¹ and largely ineffective androgen injections.³

The original clinical trials of erythropoietin in patients with end-stage renal disease, as well as many subsequent studies, documented an excellent response in patients with anemia (with the hematocrit increasing to 34 percent or above) in "study settings."^{2,4} However, in recent studies a high proportion of U.S. patients undergoing hemodialysis who were receiving erythropoietin (40 to 60 percent) had hematocrit values that did not rise above 30 percent, despite therapy with doses of erythropoietin equivalent to those used in the clinical trials.⁵⁻⁹ Furthermore, a persistent need for blood transfusion has been reported in many patients with end-stage renal disease who are being treated with this drug.^{10,11}

Although iron deficiency is an important cause of resistance to erythropoietin,¹² the relative contribution of

inadequate dialysis to this resistance is unknown. This issue is pertinent because inadequate dialysis (defined in the present study as a reduction in the blood urea nitrogen concentration of less than 65 percent after a dialysis session) is common in therapy for uremia in the United States,¹³⁻¹⁵ and uremia can impair erythropoiesis.¹⁶⁻²⁴ Moreover, the effect of the intensity of dialysis on the response to erythropoietin was not described in any reports of the clinical trials of the drug. For these reasons, we investigated whether there was a relation between the adequacy of dialysis and the response to erythropoietin in patients with end-stage renal disease who were receiving maintenance hemodialysis.

METHODS

We studied 145 patients who were randomly selected from a pool of 580 patients with end-stage renal disease who were receiving maintenance hemodialysis at five outpatient hemodialysis facilities in Brooklyn, New York. Patients were studied for four weeks. In order to be included, the patients had to have been treated for end-stage renal disease with maintenance hemodialysis three times a week for at least three months, had to be 20 years of age or older, had to have been treated with erythropoietin for at least three months, had to provide informed consent, and had to have no severe coexisting condition known to cause anemia (e.g., sickle cell disease). The study was approved by the institutional review board of the State University of New York Health Science Center.

The criteria for exclusion were an age below 20 years; refusal by the patient to participate; known blood dyscrasia or hemoglobinopathy; infection with the human immunodeficiency virus; treatment for any infection with drugs known to affect erythropoiesis, including an-

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drogens; pregnancy; and macrocytosis (a mean corpuscular volume of $100 \mu\text{m}^3$ or more). Patients were also excluded if any of the following events had occurred in the 10 weeks preceding enrollment: blood loss (gastrointestinal bleeding or bleeding from the point of vascular access), blood transfusion, hospitalization, infection (fever and leukocytosis), missed dialysis treatment, and early withdrawal from dialysis.

The following information was obtained from each patient: age, sex, race or ethnic group, cause of end-stage renal disease, and duration of disease. The dose of erythropoietin per kilogram of body weight (given three times a week) on entry to the study was documented. The hematocrit was measured weekly for four weeks with a Technicon H₁ hematology analyzer (Technicon, Tarrytown, N.Y.), and a mean was calculated for each patient. At the end of the second week of the study, the blood urea nitrogen concentration was measured both before and after dialysis; transferrin saturation (serum iron concentration \div total iron-binding capacity $\times 100$), serum creatinine, and serum albumin were also measured before dialysis. Chemical determinations were made with the use of an AutoAnalyzer.

In a subgroup of 39 consecutively enrolled patients, endogenous erythropoietin levels were measured before dialysis (Roche Biomedical Laboratories, Raritan, N.J.) to discern any relation among the production of endogenous erythropoietin, the intensity of dialysis, and the hematocrit.

Conventional dialysis was performed with the use of modified cellulose acetate hollow-fiber dialyzers (Althin Medical, Miami Lakes, Fla.) and bicarbonate-based dialysate. No alterations were made in the patients' hemodialysis prescriptions or dietary instructions during the study period. All patients were receiving oral iron supplements, and calcium carbonate was the prescribed phosphate binder.

Intensity of Dialysis

To assess the intensity of dialysis, we calculated the percent reduction in the blood urea nitrogen concentration after dialysis (predialysis blood urea nitrogen concentration $-$ postdialysis blood urea nitrogen concentration \div predialysis blood urea nitrogen concentration $\times 100$). In addition, a correlate of dialysis level, the serum albumin concentration, was also measured.²⁵

Coexisting Conditions

To gauge any effects of coexisting conditions on the response to erythropoietin, the presence of serious medical conditions or disabilities associated with disease in major organ systems was documented with the use of a previously published index of the severity of coexisting conditions.⁸ Each condition was rated from 0 to 3 depending on its severity, as follows: 0, absent; 1, mild or of minor importance to the patient's life; 2, moderate; or 3, severe. A numerical comorbidity index was generated by totaling the ratings for any medical disorders in each patient.

Coexisting conditions were classified in 1 of 12 categories: (1) persistent angina or myocardial infarction; (2) other cardiovascular problems (hypertension, congestive heart failure, or cardiomyopathy); (3) respiratory disease; (4) autonomic neuropathy (gastroparesis, obstipation, diarrhea, cystopathy, or orthostatic hypotension); (5) neurologic problems, cerebrovascular accident, or sequelae of stroke; (6) musculoskeletal disorders, including all varieties of renal bone disease; (7) hepatic insufficiency or enzymatic pancreatic insufficiency; (8) hematologic problems other than anemia; (9) spinal abnormalities, lower back problems, or arthritis; (10) impaired vision (minor [decreased acuity] to severe [blindness]); (11) limb amputation (minor [finger] to severe [leg or foot]); and (12) mental or emotional illness (neurosis, depression, or psychosis).

Increased Level of Dialysis

For six weeks, we increased the level of dialysis administered three times per week in 20 consecutive patients with base-line urea-reduction values of less than 65 percent (mean \pm SD, 60.7 ± 4 percent). The hematocrits of these patients, measured weekly, were compared with those of a control group made up of the next 20 patients with base-line urea-reduction values of less than 65 percent (mean, 60 ± 4.4 percent), whose level of dialysis was not changed.

We increased the level of dialysis (from a mean urea-reduction val-

ue of 60.7 percent to one of 72.0 percent) by switching to a bigger dialyzer (from the Althin Medical MCA 160 dialyzer to the F80 dialyzer [Fresenius, Walnut Creek, Calif.]) and increasing the duration of each hemodialysis treatment from 4 hours to 4.5 hours, while ensuring an "arterial" blood flow (from the patient to the dialyzer cartridge) of more than 350 ml per minute. The MCA 160 dialyzer is a modified cellulose acetate dialyzer with a urea clearance rate specified by the manufacturer of 180 ml per minute at a blood flow of 200 ml per minute and a dialysate flow of 500 ml per minute, whereas the F80 is a high-flux polysulfone dialyzer with a specified urea clearance rate of 192 ml per minute under similar rates of blood and dialysate flow. The dose of erythropoietin was held constant during the six weeks of increased dialysis.

Statistical Analysis

To assess the independent association of the hematocrit (the outcome variable) with all the other measured variables, we used a backward stepwise multiple regression analysis with the hematocrit treated as a continuous variable. Independent variables were age, race or ethnic group, sex, cause of end-stage renal disease, duration of disease, duration of dialysis treatment, comorbidity index, urea-reduction value, serum albumin concentration, serum creatinine concentration, transferrin saturation, and dose of erythropoietin.

Also, we categorized patients according to whether the hematocrit was ≤ 30 percent or > 30 percent; we then used a backward stepwise logistic-regression analysis to assess differences between the groups. Because there were two extreme values for the dose of erythropoietin, both of the above analyses were repeated with the use of the natural logarithm of the dose of erythropoietin. Since the results of analyses using the natural logarithm of the erythropoietin dose were similar to those of analyses using the actual dose of erythropoietin, we have pre-

Table 1. Basic Clinical and Laboratory Data on the 135 Study Patients.*

VARIABLE	
Mean age — yr	56.5 \pm 15.5
Sex — M/F	65/70
Race or ethnic group — no. (%) [†]	
Black	94 (70)
White	20 (15)
Hispanic	17 (13)
Asian	4 (3)
Cause of end-stage renal disease — no. (%)	
Diabetes mellitus	49 (36)
Hypertension	45 (33)
Glomerulonephritis	19 (14)
Systemic lupus erythematosus	5 (4)
Autosomal dominant polycystic kidney disease	5 (4)
Obstructive nephropathy	2 (2)
Unknown	10 (7)
Duration of end-stage renal disease — mo	
Mean	40 \pm 45
Range	4–204
Length of dialysis treatment — hr	3.6 \pm 0.4
Dose of erythropoietin — U/kg [‡]	59 \pm 29
Comorbidity index	1.2 \pm 1.6
Reduction in blood urea nitrogen — %	62 \pm 4.8
Hematocrit — %	29.2 \pm 4
Serum albumin — g/dl	3.8 \pm 0.4
Serum creatinine — mg/dl [§]	12.2 \pm 3.3
Transferrin saturation — %	20 \pm 9

*Plus-minus values are means \pm SD.

[†]Percentages do not total 100 because of rounding.

[‡]Given three times per week.

[§]To convert the value for serum creatinine to micromoles per liter, multiply by 88.4.

sented only the models using the actual dose. Stratified regression analyses were also performed, with patients categorized according to transferrin saturation: ≤ 20 percent or >20 percent. Results of the multiple regression analyses include both the regression coefficient and the standardized regression coefficient, whereas the results of the multiple logistic-regression analyses include odds ratios, 95 percent confidence intervals, and P values.²⁶

Multiple analyses of variance for repeated measures were used to compare the hematocrit values at base line with the values at six subsequent weekly intervals. Adjustment was made for bias due to multiple comparisons among the periods by dividing the critical P values by 6, as required by the Bonferroni method of adjustment.²⁷

All P values are two-tailed. Unless otherwise stated, values are means \pm SD. Computations were performed with SPSS software.²⁶

RESULTS

Of the 145 patients enrolled, 10 did not complete the study and were excluded from the statistical analysis. Of these 10 patients, 4 were hospitalized because of clotted vascular access, 2 were withdrawn from the study because of noncompliance after missing one dialysis session, 2 were excluded because they insisted on the early discontinuation of dialysis treatments during the study period, and 2 were withdrawn because of blood loss in a discarded clotted dialyzer.

The mean age of the remaining 135 patients was 56.5 ± 15.5 years (Table 1). The group consisted of 65 men and 70 women, of whom 94 were black (70 percent), 20 were white (15 percent), 17 were Hispanic (13 percent), and 4 were Asian (3 percent). The causes of their end-stage renal disease are listed in Table 1. The mean duration of end-stage renal disease before the study was 40 ± 45 months (range, 4 to 204), and the mean length of each prescribed dialysis treatment was 3.6 ± 0.4 hours (range, 3 to 4.5). Eight of the 135 patients (6 percent) had had positive stool tests for occult blood within the preceding 10 weeks. None of these eight patients had ever had overt gastrointestinal bleeding or melena. No subject received a blood transfusion during the study.

The mean hematocrit of the group was 29.2 ± 4 percent, the mean urea-reduction value was 62 ± 4.8 percent, and the mean serum albumin concentration was 3.8 ± 0.4 g per deciliter (Table 1). Erythropoietin was ad-

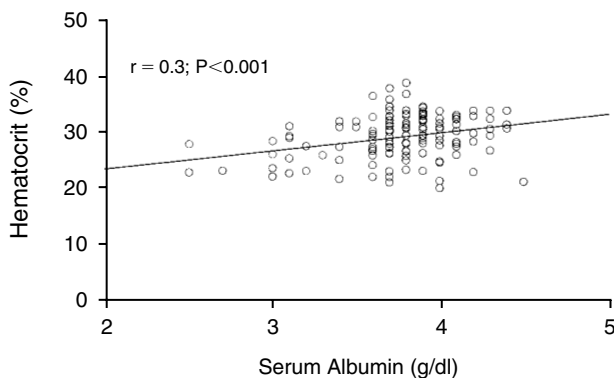


Figure 1. Relation between the Hematocrit and the Serum Albumin Concentration.

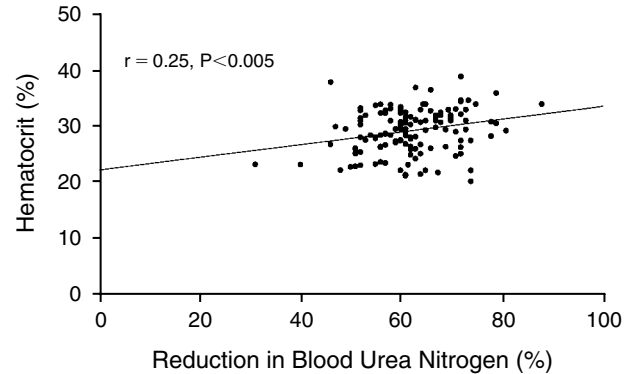


Figure 2. Relation between the Hematocrit and the Urea-Reduction Value.

ministered intravenously to each patient three times a week after dialysis in a dose of 59 ± 29 U per kilogram of body weight (range, 13 to 200). The target hematocrit for all dialysis facilities was 35 percent. Sixty-two of the 135 patients (46 percent) had hematocrits above 30 percent, but only 4 of 135 (3 percent) reached the target hematocrit of 35 percent or higher. All study subjects had been receiving erythropoietin for at least four months. The mean comorbidity index was 1.2 ± 1.6 , the mean transferrin saturation was 20 ± 9 percent, and the mean serum creatinine concentration was 12.2 ± 3.3 mg per deciliter (1080 ± 290 μ mol per liter).

The relations between the hematocrit and the serum albumin concentration and between the hematocrit and the urea-reduction value are shown in Figures 1 and 2, respectively. The urea-reduction value correlated with the serum albumin concentration ($r = 0.24$, $P = 0.006$).

Multiple regression analysis revealed that the serum albumin concentration and the urea-reduction value had direct univariate associations with the hematocrit after adjustment for other factors ($P = 0.009$ and $P = 0.012$, respectively) (Table 2). There was an inverse relation between the hematocrit and the dose of erythropoietin ($P = 0.006$). The serum albumin concentration, the urea-reduction value, and the dose of erythropoietin explained 18 percent of the variation in the hematocrit. The transferrin saturation ($P = 0.089$) did not have a statistically significant relation with the hematocrit (Table 2). Separate analyses of subgroups of subjects stratified according to transferrin saturation (75 with levels of 20 percent or below and 60 with levels above 20 percent) gave results similar to those of the analysis for the whole group (Table 3).

The results of logistic-regression analyses with a hematocrit above 30 percent as the outcome variable are shown in Table 4. The logistic model showed that an 11 percent increase in the urea-reduction value doubled the odds that a patient would have a hematocrit above 30 percent (the exponential of 11 times the logistic-regression coefficient of 0.063).

The mean level of endogenous erythropoietin in the 39 subjects in whom it was measured was 11.7 ± 10.6

Table 2. Results of a Multiple Regression Analysis with the Hematocrit as the Outcome Variable.*

VARIABLE†	REGRESSION		STANDARDIZED	
	COEFFICIENT	SE	REGRESSION COEFFICIENT	P VALUE
Serum albumin concentration	2.41	0.908	0.220	0.009
Percent reduction in blood urea nitrogen	0.101	0.039	0.216	0.012
Dose of erythropoietin	-0.069	0.025	0.226	0.006
Transferrin saturation	0.059	0.035	0.138	0.089

* $r^2=0.194$. SE denotes standard error.

†Other variables that were examined but that did not have statistically significant associations with the hematocrit included age ($P=0.37$), sex ($P=0.51$), race or ethnic group ($P=0.97$), cause of end-stage renal disease ($P=0.73$), duration of end-stage renal disease ($P=0.39$), length of dialysis treatment ($P=0.74$), and comorbidity index ($P=0.25$).

mU per milliliter. The correlation of the level of endogenous erythropoietin with the urea-reduction value did not reach statistical significance ($r=0.26$, $P=0.11$), and the correlation with the hematocrit was close to zero ($r=-0.06$, $P=0.68$).

Effect of Increased Dialysis

In the 20 patients with a base-line urea-reduction value below 65 percent whose dialysis level was increased for six weeks, the mean (\pm SE) hematocrit rose from 28.4 ± 0.78 percent to 32.3 ± 0.71 percent ($P=0.002$) (Fig. 3). The dialysis level in these patients was increased from a mean urea-reduction value of 60.7 percent to one of 72.0 percent. The mean thrice-weekly dose of erythropoietin in these patients was 51 ± 19 U per kilogram, as compared with 48.7 ± 26 U per kilogram in the control group ($P=0.133$).

With an increase in the urea-reduction value from 60.7 percent to 72.0 percent, the logistic-regression model predicted an increase in the proportion of patients with a hematocrit above 30 percent from 43 to 60 percent. The observed increase in the proportion of patients with a hematocrit above 30 percent was from 40 percent at base line to 70 percent after the sixth week in the group of 20 patients with increased dialysis. In the control group of patients with equivalent base-line urea-reduction values whose dialysis level was not altered, there was no significant change in the hematocrit; the mean (\pm SE) value at base line was 28.2 ± 0.84 percent, and the mean at the end of week 6 was 26.3 ± 0.85 percent ($P=0.175$) (Fig. 3).

DISCUSSION

Our key findings are that inadequate dialysis (indicated by a urea-reduction value of less than 65 percent) is associated with a poor response to erythropoietin (i.e., a low hematocrit) in patients with end-stage renal disease who are receiving hemodialysis, and that increasing the level of dialysis in patients who are receiving inadequate dialysis results in an increase in the hematocrit.

Although therapy with erythropoietin can alleviate

anemia in patients with uremia, in a high proportion of patients treated with erythropoietin (40 to 60 percent) the hematocrit does not rise above 30 percent.⁵⁻⁹ According to a statement by the National Kidney Foundation¹⁴ and the report of a consensus conference of the National Institutes of Health on morbidity and mortality in patients undergoing dialysis,¹⁵ many patients with end-stage renal disease in the United States who are undergoing dialysis receive a suboptimal level of dialysis. Inadequate dialysis (indicated by a urea-reduction value of less than 65 percent) has been indicted as the principal reason for the 24 percent annual mortality rate among U.S. patients receiving dialysis, as compared with 10 to 15 percent of such patients in Europe and Japan.¹³⁻¹⁵

In patients with end-stage renal disease who are being treated with hemodialysis, inadequate dialysis may result from an insufficient duration of dialysis, use of a dialyzer that is too small, low blood flow due to faulty vascular access or recirculation of blood, missed dialysis sessions or early withdrawal from scheduled dialysis, and dietary indiscretions that provide excess solute for removal during dialysis. Reimbursement from Medicare for dialytic therapy has remained at a constant level, while labor costs have escalated. This imbalance may contribute to inadequate levels of dialysis by encouraging reductions in the duration of hemodialysis treatments for economic reasons.

Although studies in both animals and humans document impaired erythropoiesis in the presence of uremia,¹⁶⁻²⁴ the existence of uremic inhibitors of erythropoiesis in humans remains speculative. Evidence of the existence of such inhibitors includes the blunting of in vitro growth of murine or canine erythroid colonies by uremic serum but not by normal serum¹⁶⁻¹⁸; the stimulation of reticulocytosis in people with normal renal function but not in people with severe renal failure by the infusion of plasma rich in erythropoietin from a patient with aplastic anemia²¹; the persistence of ane-

Table 3. Results of a Multiple Regression Analysis with the Hematocrit as the Outcome Variable and with Patients Stratified According to Transferrin Saturation.

VARIABLE	REGRESSION COEFFICIENT	SE*	P VALUE
Transferrin saturation $\leq 20\%$ (n = 75)			
Serum albumin concentration	2.98	1.190	0.015
Percent reduction in blood urea nitrogen	0.094	0.542	0.088
Dose of erythropoietin	-0.066	0.032	0.044
Transferrin saturation $> 20\%$ (n = 60)			
Serum albumin concentration	1.34	1.551	0.392
Percent reduction in blood urea nitrogen	0.123	0.060	0.044
Dose of erythropoietin	-0.825	0.042	0.056

*SE denotes standard error.

emia despite high serum levels of erythropoietin (30 to 100 mU per milliliter) in some patients with chronic uremia, suggesting that their erythroid cells are unable to respond to erythropoietin²⁰⁻²²; increases in the hematocrit without concomitant increases in levels of endogenous erythropoietin, caused by the initiation of hemodialysis therapy²³ or a switch from maintenance hemodialysis to continuous ambulatory peritoneal dialysis²⁴ in some patients with chronic renal failure, suggesting the extraction by dialysis of an inhibitor of erythropoiesis; and a lower hematocrit in patients treated with erythropoietin and receiving dialysis who missed one or more dialysis treatments over a 10-week period than in their counterparts who received all scheduled dialysis treatments.²⁸ Before recombinant erythropoietin became available, patients who received dialysis three times a week had higher hematocrits than those who underwent the procedure twice a week.³

Eschbach et al.,²⁹ however, using ferrokinetics as an index of erythropoiesis, found no significant difference between uremic and nonuremic subjects treated with erythropoietin who were receiving dialysis. We did not measure ferrokinetics in our subjects and are unable to explain why our findings differ from those of Eschbach et al. Measures of the adequacy of dialysis were not reported for the 24 uremic patients receiving dialysis whom they studied, however.²⁹ It is possible that patients with uremia who receive adequate dialysis may respond to erythropoietin as well as do subjects with normal renal function. It is unlikely that an insufficient dose of erythropoietin is the chief factor explaining the persistence of hematocrit values at or below 30 percent in many patients treated with erythropoietin who receive hemodialysis, since the doses of erythropoietin used in most clinical settings are equivalent to doses used in clinical trials of the drug.

Deficiencies in folate and vitamin B₁₂ can impair the response to therapy with erythropoietin.¹ We did not measure the levels of these substances in our subjects and cannot rule out an effect of a deficiency of either folate or vitamin B₁₂ on our findings. In addition, resistance to therapy with erythropoietin has been described in some patients with end-stage renal disease who have bone marrow fibrosis caused by secondary hyperpara-

Table 4. Results of Multiple Logistic-Regression Analysis with a Hematocrit above 30 Percent as the Outcome Variable.

VARIABLE*	ODDS RATIO	95% CONFIDENCE INTERVAL		P VALUE
Serum albumin concentration	5.895	1.68	20.72	0.006
Percent reduction in blood urea nitrogen	1.065	1.01	1.12	0.011
Dose of erythropoietin	0.971	0.94	1.00	0.053

*Other variables that were examined but that did not have statistically significant associations with a hematocrit above 30 percent included transferrin saturation (P=0.3), age (P=0.14), race or ethnic group (P=0.63), sex (P=0.63), cause of end-stage renal disease (P=0.64), duration of end-stage renal disease (P=0.4), length of dialysis treatment (P=0.87), and comorbidity index (P=0.13).

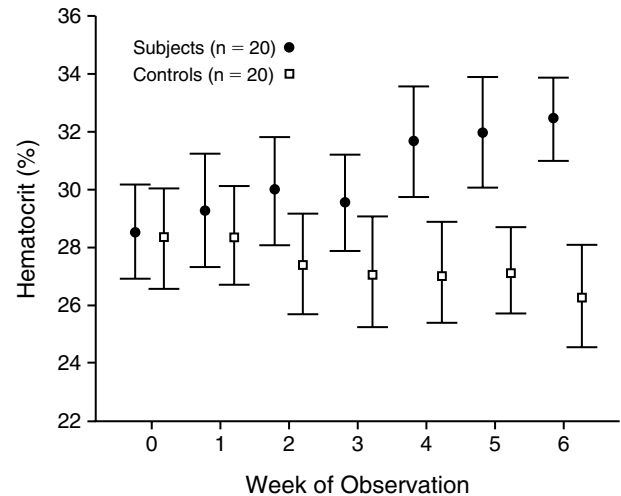


Figure 3. Effect of an Increased Level of Dialysis on the Hematocrit.

A multivariate analysis of variance was used to compare hematocrit values at base line with those in subsequent weeks. Bars represent 95 percent confidence intervals for the weekly mean hematocrit values. In the 20 patients who underwent dialysis at increased intensity the mean (\pm SE) hematocrit rose from 28.4 ± 0.78 percent at base line to 32.3 ± 0.71 percent after six weeks ($P=0.002$). The level of dialysis was increased from a mean urea-reduction value of 60.7 percent to one of 72.0 percent. In the 20 controls, the level of dialysis was not altered. There was no significant change in the hematocrit: at base line it was 28.2 ± 0.84 percent, and after six weeks it was 26.3 ± 0.85 percent ($P=0.175$).

thyroidism or aluminum toxicity.^{30,31} To identify these patients, a bone marrow biopsy is required.

We do not question the potential of erythropoietin to expand red-cell mass in patients with end-stage renal disease. The enhanced correction of anemia resulting from an increased level of dialysis in patients with end-stage renal disease who are treated with erythropoietin may reduce the cardiovascular morbidity and poor functional status associated with anemia and prolong survival.

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