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YEAR BOOK OF HEMATOLOGY® 1991

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1991

The Year Book of HEMATOLOGY®

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Journals Represented

Year Book Medical Publishers subscribes to and surveys nearly 850 U.S. and foreign medical and allied health journals. From these journals, the Editors select the articles to be abstracted. Journals represented in this YEAR BOOK are listed below.

American Journal of Clinical Pathology
American Journal of Hematology
American Journal of Medicine
American Journal of Obstetrics and Gynecology
American Journal of Pathology
American Journal of Pediatric Hematology/Oncology
American Journal of Physiology
American Journal of Surgery
Anesthesia and Analgesia
Anesthesiology
Annals of Internal Medicine
Annals of Surgery
Archives of Internal Medicine
Archives of Pathology and Laboratory Medicine
Arteriosclerosis
Blood
British Journal of Cancer
British Journal of Haematology
British Medical Journal
Cancer
Cancer Chemotherapy and Pharmacology
Cancer Research
Cell
Circulation
Diseases of the Colon and Rectum
European Journal of Cancer and Clinical Oncology
European Journal of Haematology
European Journal of Obstetrics, Gynecology and Reproductive Biology
International Journal of Cardiology
International Journal of Radiation, Oncology, Biology, and Physics
Investigative Radiology
Israel Journal of Medical Sciences
Journal of Biological Chemistry
Journal of Child Neurology
Journal of Clinical Investigation
Journal of Clinical Oncology
Journal of Emergency Medicine
Journal of Immunology
Journal of Pediatric Surgery
Journal of Pediatrics
Journal of Perinatology
Journal of Rheumatology
Journal of Surgical Research
Journal of Thoracic and Cardiovascular Surgery
Journal of Trauma
Journal of Urology
Journal of the American College of Cardiology

Journal of the American Medical Association
Lancet
Leukemia
Medicine
Modern Pathology
Nature
Nephron
Neurology
New England Journal of Medicine
Pediatric Research
Pediatrics
Pharmacotherapy
Proceedings of the National Academy of Sciences
Science
Seminars in Thrombosis and Hemostasis
Southern Medical Journal
Stroke
Surgery
Surgery, Gynecology and Obstetrics
Thrombosis and Haemostasis
Transfusion
Transplantation
Vox Sanguinis

Standard Abbreviations

The following terms are abbreviated in this edition: acquired immunodeficiency syndrome (AIDS), central nervous system (CNS), cerebrospinal fluid (CSF), computed tomography (CT), electrocardiography (ECG), and human immunodeficiency virus (HIV).

Introduction

The ancient philosophers were fond of stating, "There is nothing new under the sun." Unfortunately for them, that was probably true. If, however, they had had the opportunity to read the YEAR BOOK OF HEMATOLOGY, it is likely that they would have stated "nothing ever stays the same." I make these comments because, even though I have edited this volume for five years and should be acclimated, I am continually amazed at the quality and quantity of current clinical research. Just when I think I've read it all, excellent new studies appear, and this year is no exception. For example, as Paul Ness notes, the field of transfusion medicine has advanced from preoccupation with the adverse effects of transfusion practices to treatment options. For years, I, and I am sure many of you also, have faithfully transfused patients with paroxysmal nocturnal hemoglobinuria with washed packed red cells to avoid enhancing their hemolytic process. This practice now has been shown to be unnecessary in the absence of a previous febrile reaction as long as group-specific blood is used (Abstract 6–1).

Other similar pearls based on solid clinical data abound. For example, warming platelet concentrates stored at room temperature before transfusion improves the platelet count increment (Abstract 6–5), whereas ABO matching improves platelet recovery in multiply-transfused patients (Abstract 6–16). Using leukocyte-free blood components also protects against platelet transfusion refractoriness in this situation (Abstract 6–8), and an efficient filter for this purpose is now available (Abstract 6–6). Vancomycin, which is used so often in seriously ill, immunocompromised patients, also may be a factor in refractoriness to platelet transfusions caused by vancomycin-dependent antibodies that react with platelet-specific glycoproteins (Abstract 6–18). A new test for hepatitis C promises to improve the safety of the blood supply (Abstracts 6–47 and 6–48), and pasteurization of factor VIII concentrates eliminates the risk of not only hepatitis C but also HIV infection as well (Abstract 6–9).

In 1988, we noted that recombinant tissue plasminogen activator (rtPA) was not behaving as predicted. Now, as Dr. Bell discusses, the accumulated evidence backing up this contention appears overwhelming. It seems that rtPA is not a more effective fibrinolytic agent than streptokinase or urokinase with respect to reperfusion or patency rates, and even more disturbing, the risk of bleeding, particularly intracranial hemorrhage (Abstract 5–69), appears to be greater with rtPA than with the other fibrinolytic agents. It is unfortunate that concurrent heparin therapy also does not augment the effect of rtPA (Abstract 5–70). This particular emperor continues to have no clothes.

Circulating anticoagulants can be a vexing clinical problem and sometimes an iatrogenic one as in the case of bovine thrombin used for intraoperative topical hemostasis, antibodies against which have caused spuriously prolonged thrombin times (Abstract 5–40). Several major articles now have appeared on the "lupus anticoagulant" in patients who do not have lupus (Abstracts 5–44 and 5–45), and, important for those who treat patients with factor VIII inhibitors, recombinant, activated factor VIII provides a promising new approach to therapy (Abstract 5–47). Porcine factor VIII is also a viable option in this situation (Abstract 5–48), although eventually subject to the same difficulty noted for bovine thrombin. For those interested in streptokinase antibodies and

their persistence, Abstract 5–76 is required reading. Finally, continuous infusion of factor VIII (first suggested by our coagulation group [*Blood* 67:969, 1986]) appears to be a more efficient method of administering this agent than intermittent bolus therapy (Abstract 4–26).

Dr. Quesenberry once again has performed a marvelous service in unraveling the complexities of the various (or should I say multifarious) myeloid growth factors and interleukins. My personal bias that G-CSF would be a more widely applicable growth factor than GM-CSF is being confirmed (Abstracts 2–1 through 2–3). Of course, it may be naive to focus on the use of myeloid growth factors as single agents because evidence is increasing that growth factors may be more effective when employed in combination (Abstract 2–29). Of particular note this year is the increasing recognition of the role of IL-6 in disease (Abstracts 2–24 through 2–26). Finally, for the vocabulary of many, the experimentalists have introduced a new word, *apoptosis*, which translates into programmed cell death (Abstract 2–8). This offering was not intended for Scrabble or Trivial Pursuit fans but rather to serve notice that for hematopoietic cells as well as other hormone-responsive cells, there is a physiologic nonrandom mechanism for DNA degradation which, at least in the case of IL-3 or erythropoietin-dependent cells, is triggered if these growth factors are removed from the environment. Thus, these growth factors act as survival factors as well as mitogens.

If anything, this year more than ever, Peter Wiernik has convinced me that specialization is not only very much alive but growing stronger. One only has to review the wealth of data presented on any given subject in chapter 3, Hematopoietic Malignancies, to be convinced of this. Certainly nothing is cut and dried in this area. For example, prognosis is not uniform in nodular sclerosing Hodgkin's disease (Abstracts 3–4 and 3–5), and the role of staging laparotomy in this disease has been further defined (Abstracts 3–11). New drugs such as fludarabine (Abstract 3–41) and pentostatin (Abstract 3–36) are improving the outlook for patients with chronic lymphocytic leukemia and hairy cell leukemia, and the tobacco lobby has been dealt another blow because it appears that cigarette smoking can affect adversely survival of patients with chronic myelogenous leukemia (Abstract 3–42). A new, relatively nontoxic treatment regimen—vincristine, doxorubicin, and high-dose dexamethasone—appears effective in multiple myeloma (Abstract 3–34), whereas idarubicin is highly active in acute myelogenous leukemia (Abstracts 3–68 and 3–69). In addition to the abstracts selected, Dr. Wiernik also has provided a formidable reading list with which to while away the winter.

I've said very little about red blood cells, but chapter 1 contains abundant new information about erythropoietin, which is now well established as a therapeutic agent for the anemia associated with renal disease. Multiple other uses for this hormone are, of course, under scrutiny; it undoubtedly will have widespread utility and not just for anemic patients.

If I were asked to choose the most important therapeutic technology of the past two decades, my choice would be bone marrow transplantation. In support of that choice, I asked an acknowledged leader in the field, Dr. George Santos, to write this year's state-of-the-art review, and I highly recommend it to you. To spotlight this area, I've also grouped together all the abstracts on bone marrow transplantation after Dr. Santos' article.

I think you would all agree that the past year has been an exciting one in which change has been the rule not the exception, and not just in the cloistered world of hematology. As in the past, I hope that you will enjoy reading what we offer here, and I wish you all a healthy and happy New Year.

Jerry L. Spivak, M.D.

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The material in this volume represents literature reviewed through February 1990.

1 Red Blood Cells

Introduction

After four years of clinical trials, I think that it is safe to state that recombinant human erythropoietin has come of age. Sufficient data have been collected on patients with anemia and end-stage renal disease to substantiate clinically what had been known from numerous animal studies: that exogenous erythropoietin can correct anemia caused by a lack of sufficient endogenous erythropoietin production. The record of efficacy as demonstrated in a large multicenter trial (Abstract 1–1) was remarkable. Ninety-seven percent of patients responded. Myelofibrosis, severe infection, iron deficiency, hypersplenism, and active blood loss are among the identified causes of treatment failure. This is not surprising, but what is still unclear is why approximately 20% of patients need much more hormone than the rest, a question that has important economic ramifications with respect to how the government intends to underwrite this useful agent.

Having observed that erythropoietin works, the next question that must be addressed is, "But is it worthwhile?" One answer is easy: it alleviates the need for blood transfusions. That alone would make it a worthwhile agent. A second answer would be that, contrary to a poorly controlled experimental study, acceleration of renal failure in predialysis patients has not been observed to date (Abstract 1–5), but the final word on this requires more precise measurements of renal function in these patients. Now, two quality-of-life studies have taken the issue even further, and on the basis of these studies (Abstracts 1–3 and 1–4), we can unequivocally say yes and do so with the knowledge that the patient population was a demanding one with respect to chronicity of disease. I suspect that institution of erythropoietin therapy at an earlier stage in chronic renal failure will prove even more successful in improving quality of life. In this regard, it is important to remember that anemia is only one complication of the uremic state and that erythropoietin cannot replace dialysis. Thus, quality-of-life issues related to ability to work, et cetera, must be viewed in terms of the total context of the patient's illness, not just the anemia.

It is important that the Canadian multicenter trial (Abstract 1–3) provided additional useful information because of its rigorous design. We now can state unequivocally that venous access thrombosis is a complication of therapy with recombinant human erythropoietin. We also can state now that hemoglobin levels in the range of 11.0 gm% to 13.0 gm% do not provide substantial subjective improvement over hemoglobin levels of 9.5 gm% to 11.0 gm%.

Now that erythropoietin has passed the test for the anemia of end-stage renal disease, its use is being explored in a wider number of venues. This year, we present several articles, both experimental (Abstracts 1–11 and 1–13) and clinical (Abstract 1–12), dealing with the use of recombinant erythropoietin in

the perioperative period. Our own data (*JAMA* 260:65, 1988, and 1990 YEAR BOOK, p 314) predicted that recombinant erythropoietin would be a useful adjunct for enhancing the collection of autologous blood. Now Goodnough and his colleagues have confirmed this in a controlled clinical trial. My fellow editor, Dr. Ness, is skeptical about the beneficial impact of erythropoietin therapy in autologous blood donors, but I am more enthusiastic, particularly because it was put to a severe test (phlebotomy twice weekly) in the Goodnough trial. I also think, based on our unpublished observations as well as those of Levine and colleagues (Abstract 1–11 and 1–13), that erythropoietin will have a role in the perioperative period. Obviously, more work still must be done with regard to this application of the hormone.

Continuing the erythropoietin motif, we bring you an important study on the objective improvement in cardiovascular function that occurs in patients with end-stage renal disease after correction of their anemia with recombinant erythropoietin (Abstract 1–5). Indeed, its use appears to ameliorate myocardial ischemia rather than exacerbate it. Four excellent studies dealing with erythropoietin production have now appeared. Abstract 1–8 describes changes in erythropoietin production after renal transplantation. Abstract 1–7 defines the pathophysiology of erythropoietin production in autosomal dominant polycystic kidney disease. The authors confirm the interstitial location of erythropoietin-producing cells and demonstrate that the cysts don't produce erythropoietin. Abstract 1–10 describes the unusual behavior of erythropoietin after chemotherapy. Finally, Abstract 1–6 clearly defines the behavior of renal erythropoietin-producing cells during the induction and correction of anemia.

Erythropoietin, of course, was not the only topic on my mind this year, and we're happy to bring you the following: an article (Abstract 1–21) suggesting that α-interferon might be useful in managing cold agglutinin disease; an article (Abstract 1–20) describing the successful use of intravenous gamma globulin for parvovirus B19-associated red cell aplasia in an immunocompromised patient; an article (Abstract 1–18) on the natural history of sickle cell anemia with respect to causes of death in patients aged less than 20 years; an article (Abstract 1–19) on another troublesome aspect of sickle cell anemia, leg ulcers; an article (Abstract 1–3) that usefully reevaluates that great diagnostic wastebasket, the anemia of chronic disease; an article (Abstract 1–16) proposing a new molecular defect in polycythemia vera; and finally, a nice clinical study (Abstract 1–2) reemphasizing that autoimmune disorders such as hemolytic anemia or thrombocytopenia do not occur as isolated phenomena but rather as part of a constellation of immunologic abnormalities that are also expressed by relatives, indicating the presence of a genetic predisposition. A bibliography of other interesting articles, not abstracted because of space limitations, follows.

Jerry L. Spivak, M.D.

Erythropoietin

Recombinant Human Erythropoietin in Anemic Patients With End-Stage Renal Disease: Results of a Phase III Multicenter Clinical Trial

Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, Evans RW, Friedman EA, Graber SE, Haley NR, Korbet S, Krantz SB, Lundin AP, Nissenson

AR, Ogden DA, Paganini EP, Rader B, Rutsky EA, Stivelman J, Stone WJ, Teschan P, Van Stone JC, Van Wyck DB, Zuckerman K, Adamson JW (Univ of Alabama, Birmingham; Univ of Arizona, Tucson; The Cleveland Clinic; Downstate Med Ctr, New York; Univ of Missouri, Columbia; et al)
Ann Intern Med 111:992–1000, 1989 1–1

Severe anemia is a major problem in rehabilitating patients with end-stage renal disease. A phase III multicenter trial of recombinant human erythropoietin (rHuEpo) was undertaken with 333 hemodialysis patients having uncomplicated anemia, with hematocrits less than 0.30. Patients received rHuEpo intravenously in doses of 150 or 300 units/kg 3 times weekly. Dosages later were reduced to maintain hematocrits at 0.35.

Treatment with rHuEpo led to a dose-related rise in hematocrit (Fig 1–1). Transfusion requirements declined at the same time. The median dose needed to maintain hematocrit in the target range was 75 units/kg (Fig 1–2). Most patients described improved quality of life, with better exercise tolerance, more energy, improved sleep and appetite, and a perception of better health in general (Table 1). Fifteen patients had myalgias or a flulike syndrome. Significant increases in predialysis levels of serum creatinine and potassium accompanied the rise in hematocrit (Table 2). The rate of thrombotic events was 0.3 per patient-year.

Recombinant human erythropoietin is effective for and well tolerated by patients with end stage renal disease and anemia. It should become standard treatment for such patients because it enhances rehabilitation and improves general health substantially.

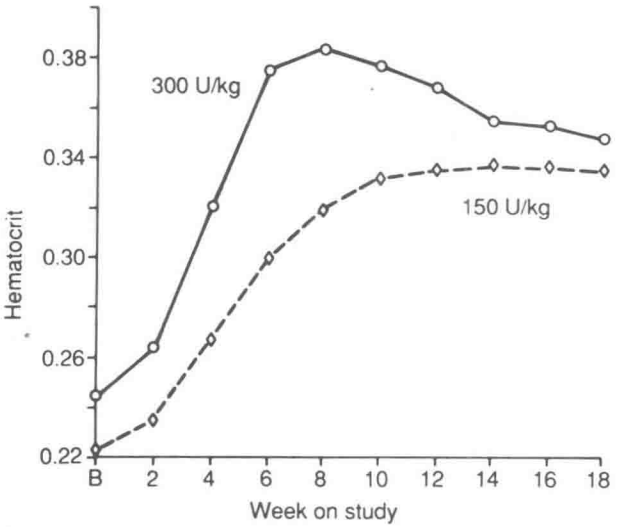

Fig 1–1.—The mean hematocrit values at biweekly intervals for 35 patients receiving 300 units of rHuEpo/kg *(circles)* or 201 patients receiving 150 units *(diamonds)* rHuEpo/kg. The rHuEpo was given intravenously 3 times per week. (Courtesy of Eschbach JW, Abdulhadi MH, Browne JK, et al: *Ann Intern Med* 111:992–1000, 1989.)

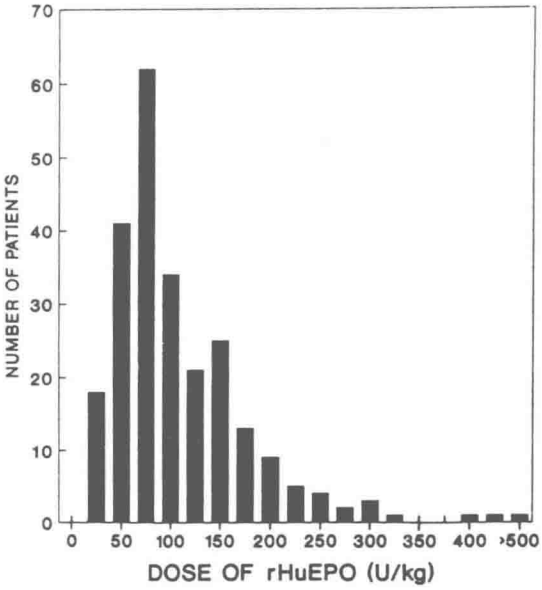

Fig 1–2.—The distribution of maintenance doses of rHuEpo required to maintain the hematocrit between 0.32 and 0.38. The dose level refers to the upper value within each 25 units (U)/kg dose range. The rHuEpo was given intravenously 3 times per week. (Courtesy of Eschbach JW, Abdulhadi MH, Browne JK, et al: *Ann Intern Med* 111:992–1000, 1989.)

TABLE 1.—Effect of rHuEpo on Levels of Functional Impairment, Energy, and Activity in 130 Patients

	Baseline	Second Evaluation*	Third Evaluation†
Hematocrit, mean	0.237	0.342	0.339
Functional impairment			
Normal, no complaints; able to carry on normal activity (Karnofsky), *% of patients*	25.9	44.5‡	43.5‡
Activity level			
Very or mostly active, *% of patients*	19.8	37.3‡	35.5‡
Energy level			
Patient reporting very full of energy or fairly energetic most of the time, %	25.9	45.4‡	48.1‡
Patients reporting low energy or no energy at all, %	46.2	23.2‡	22.2‡
Nottingham Health Profile score§	47.0	31.5‡	27.7‡

*Approximately 6 months after initiation of rHuEpo therapy.
†Approximately 10 months after initiation of rHuEpo therapy.
‡$P \leq .01$ compared with baseline.
§Scores: 100 = complete limitation; 0 = no physical limitation.
(Courtesy of Eschbach JW, Abdulhadi MH, Browne JK, et al: *Ann Intern Med* 111:992–1000, 1989.)

TABLE 2—Effect of rHuEpo on Biochemical Values

Solutes	Baseline (± SE)	Number of Patients	P Value*	6 Months (± SE)	Number of Patients	10 Months (± SE)	Number of Patients	Baseline (± SE)	Maintenance Number of Patients	P Value*
			Maintenance							
Creatinine, *μmol/L*	1167 (13.2)	298	0.0013	1246 (14.1)	224	1299 (14.7)	99	1220 (13.8)	298	0.04
(mg/dL)	18 (0.2)			27 (0.3)		35 (0.4)		27 (0.3)		
Blood urea nitrogen, *mmol/L*	28.8 (80.8)	298	NS	29.4 (82.4)	224	31.1 (87.0)	99	27.7 (77.5)	298	NS
(mg/dL)	0.4 (1.2)			0.5 (1.5)		0.8 (2.3)		0.5 (1.4)		
Potassium, *mmol/L*	5.1 (5.1)	297	0.003	5.2 (5.2)	225	5.4 (5.4)	99	5.2 (5.2)	297	0.001
(mEq/L)	0.04 (0.04)			0.05 (0.05)		.08 (0.08)		0.06 (.06)		
Bicarbonate, *mmol/L*	20.7 (20.7)	296	<0.0005	18.7 (18.7)	222	18.4 (18.4)	99	19.0 (19.0)	296	<0.0005
(mEq/L)	0.2 (0.2)			0.3 (0.3)		0.3 (0.3)		0.2 (0.2)		
Uric acid, *μmol/L*	393 (6.6)	241	<0.0005	428 (7.2)	177	410 (6.9)	81	434 (7.3)	241	<0.0005
(mg/dL)	0.59 (0.1)			0.43 (0.1)		0.41 (0.2)		0.43 (0.1)		
Albumin, *g/L*	38.0 (3.8)	260	0.009	39.0 (3.9)	189	40.0 (4.0)	74	39.0 (3.9)	260	0.002
(g/dL)	0.3 (0.03)			0.3 (0.03)		0.4 (0.04)		0.3 (0.03)		
Phosphorus, *mmol/L*	1.78 (5.5)	292	NS	1.91 (5.9)	220	1.91 (5.9)	98	2.03 (6.3)	292	NS
(mg/dL)	0.03 (0.1)			0.03 (0.1)		0.03 (0.2)		0.06 (0.2)		
			Maintenance							
Creatinine, *μmol/L*	1167 (13.2)	298	<0.0005	1246 (14.1)	224	1299 (14.7)	99	1220 (13.8)	298	0.04
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Potassium, *mmol/L*	5.1 (5.1)	297	0.012	5.2 (5.2)	225	5.4 (5.4)	99	5.2 (5.2)	297	0.001
(mEq/L)	0.04 (0.04)			0.05 (0.05)		.08 (0.08)		0.06 (.06)		
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Creatinine, *μmol/L*	1167 (13.2)	298	0.0013	1246 (14.1)	224	1299 (14.7)	99	1220 (13.8)	298	0.04
(mg/dL)	18 (0.2)			27 (0.3)		35 (0.4)		27 (0.3)		
Blood urea nitrogen, *mmol/L*	28.8 (80.8)	298	NS	29.4 (82.4)	224	31.1 (87.0)	99	27.7 (77.5)	298	NS
(mg/dL)	0.4 (1.2)			0.5 (1.5)		0.8 (2.3)		0.5 (1.4)		
Potassium, *mmol/L*	5.1 (5.1)	297	0.003	5.2 (5.2)	225	5.4 (5.4)	99	5.2 (5.2)	297	0.001
(mEq/L)	0.04 (0.04)			0.05 (0.05)		.08 (0.08)		0.06 (.06)		
Bicarbonate, *mmol/L*	20.7 (20.7)	296	<0.0005	18.7 (18.7)	222	18.4 (18.4)	99	19.0 (19.0)	296	<0.0005
(mEq/L)	0.2 (0.2)			0.3 (0.3)		0.3 (0.3)		0.2 (0.2)		
Uric acid, *μmol/L*	393 (6.6)	241	<0.0005	428 (7.2)	177	410 (6.9)	81	434 (7.3)	241	<0.0005
(mg/dL)	0.59 (0.1)			0.43 (0.1)		0.41 (0.2)		0.43 (0.1)		
Albumin, *g/L*	38.0 (3.8)	260	0.009	39.0 (3.9)	189	40.0 (4.0)	74	39.0 (3.9)	260	0.002
(g/dL)	0.3 (0.03)			0.3 (0.03)		0.4 (0.04)		0.3 (0.03)		
Phosphorus, *mmol/L*	1.78 (5.5)	292	NS	1.91 (5.9)	220	1.91 (5.9)	98	2.03 (6.3)	292	NS
(mg/dL)	0.03 (0.1)			0.03 (0.1)		0.03 (0.2)		0.06 (0.2)		
			Maintenance							
Creatinine, *μmol/L*	1167 (13.2)	298	<0.0005	1246 (14.1)	224	1299 (14.7)	99	1220 (13.8)	298	0.04
(mg/dL)	18 (0.2)			27 (0.3)		35 (0.4)		27 (0.3)		
Blood urea nitrogen, *mmol/L*	28.8 (80.8)	298	0.014	29.4 (82.4)	224	31.1 (87.0)	99	27.7 (77.5)	298	NS
(mg/dL)	0.4 (1.2)			0.5 (1.5)		0.8 (2.3)		0.5 (1.4)		
Potassium, *mmol/L*	5.1 (5.1)	297	0.012	5.2 (5.2)	225	5.4 (5.4)	99	5.2 (5.2)	297	0.001
(mEq/L)	0.04 (0.04)			0.05 (0.05)		.08 (0.08)		0.06 (.06)		
Bicarbonate, *mmol/L*	20.7 (20.7)	296	<0.0005	18.7 (18.7)	222	18.4 (18.4)	99	19.0 (19.0)	296	<0.0005
(mEq/L)	0.2 (0.2)			0.3 (0.3)		0.3 (0.3)		0.2 (0.2)		
Uric acid, *μmol/L*	393 (6.6)	241	<0.0005	428 (7.2)	177	410 (6.9)	81	434 (7.3)	241	<0.0005
(mg/dL)	0.59 (0.1)			0.43 (0.1)		0.41 (0.2)		0.43 (0.1)		
Albumin, *g/L*	38.0 (3.8)	260	0.009	39.0 (3.9)	189	40.0 (4.0)	74	39.0 (3.9)	260	0.002
(g/dL)	0.3 (0.03)			0.3 (0.03)		0.4 (0.04)		0.3 (0.03)		
Phosphorus, *mmol/L*	1.78 (5.5)	292	NS	1.91 (5.9)	220	1.91 (5.9)	98	2.03 (6.3)	292	NS
(mg/dL)	0.03 (0.1)			0.03 (0.1)		0.03 (0.2)		0.06 (0.2)		

*Compared with baseline, using paired *t*-test. *NS*, not significant.
(Courtesy of Eschbach JW, Abdulhadi MH, Browne JK, et al: *Ann Intern Med* 111:992–1000, 1989.)

➤ This study is the phase III companion to the smaller uncontrolled phase I and II clinical trials that were reported in the 1988 YEAR BOOK OF HEMATOLOGY. In this multicenter trial, 333 patients were studied and the remarkable clinical effectiveness of erythropoietin (97.4%) was reaffirmed. Treatment failures were confined to the following situations: myelofibrosis, osteomyelitis, thalassemia minor, and active blood loss. It is interesting that, although the median effective dose was 75 units/kg, 17% of patients needed more than 150 units/kg. Why a fraction of patients need large doses of erythropoietin is unknown, but to date, no one has had resistance to recombinant erythropoietin or produced antibodies to it. Common adverse effects continue to be myalgias, conjunctival injection, and a flulike syndrome, which are not persistent. The incidence of de novo hypertension and exacerbation of preexisting hypertension were similar, and neither was dose-related. Seizures (5.4%) did not