YEAR BOOK®

YEAR BOOK OF HEMATOLOGY® 1989

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The Year Book of HEMATOLOGY®

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Journals Represented

Year Book Medical Publishers subscribes to and surveys more than 700 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.

Acta Radiologica
American Heart Journal
American Journal of Clinical Pathology
American Journal of Diseases of Children
American Journal of Hematology
American Journal of Medicine
American Journal of Obstetrics and Gynecology
American Journal of Pathology
American Journal of Pediatric Hematology-Oncology
Anesthesia
Annals of Internal Medicine
Annals of Thoracic Surgery
Archives of Disease in Childhood
Archives of Internal Medicine
Archives of Pathology and Laboratory Medicine
Archives of Surgery
Arthritis and Rheumatism
Blood
British Journal of Haematology
British Journal of Surgery
British Medical Journal
Cancer
Cancer Research
Cancer Treatment Reports
Cell
Chinese Medical Journal
Circulation
Clinical and Laboratory Haematology
Clinical Pediatrics
Clinical Pharmacology and Therapeutics
Clinical Radiology
Critical Care Medicine
European Journal of Haematology
Fetal Therapy
Human Toxicology
International Journal of Sports Medicine
Journal of the American College of Cardiology
Journal of the American Medical Association
Journal of Clinical Investigation
Journal of Experimental Medicine
Journal of Immunology
Journal of Laboratory and Clinical Medicine
Journal of the National Cancer Institute
Journal of Obstetrics and Gynaecology
Journal of Pediatrics
Journal of Sports Medicine and Physical Fitness
Journal of Surgical Research
Klinische Wochenschrift

Lancet
Mayo Clinic Proceedings
Medical Oncology and Tumor Pharmacotherapy
Medicine
Nature
Neurology
New England Journal of Medicine
Oral Surgery, Oral Medicine, Oral Pathology
Pediatrics
Proceedings of the National Academy of Sciences
Radiology
Seminars in Hematology
Surgery
Thrombosis and Haemostasis
Tissue Antigens
Transfusion
Transplantation
Vox Sanguinis

Introduction

This is the third edition of the YEAR BOOK OF HEMATOLOGY, and naturally the following statement comes to mind: "Good things come in threes." Of course, it's just as obvious that next year I'm going to claim that good things come in fours, but that is an editor's prerogative.

This year there have been further interesting developments in erythropoietin research both at the clinical and the molecular levels, but clinicians must also be prepared to deal with other recombinant human hematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and interleukin 3. The interleukins also continue to multiply at a rapid rate: at the time of publication there were seven to contend with. Dr. Quesenberry has performed a real service in providing definition to this burgeoning area of leukocyte biology. Networking cannot be considered a "Y" word when applied to hematopoietic growth factors.

In the area of clinical coagulation, new therapeutic venues have also appeared. Desmopressin (DDAVP) may have a role in the management of hemorrhage after cardiac surgery, while ketoconazole can reverse the DIC associated with prostatic carcinoma.

Therapeutic advances also continue with respect to hematopoietic malignancies. Of particular interest are the application of cyclosporin A in Hodgkin's disease, pentostatin (2′-deoxycoformycin) in hairy cell leukemia, and mitoxantrone in the acute leukemias.

In the area of transfusion medicine, transfusion-related HTLV infection continues to be a major concern since acquisition of the HTLV-I can now be considered a potential complication of blood transfusion, but major progress is also being made in rendering blood products virus-free.

Finally, this year our state-of-the-art review covers the red cell cytoskeleton. I was prompted to offer this because of the rapidity with which knowledge about red cell structural proteins has grown. For the rest, I think that this volume will provide many winter nights of interesting reading to say nothing of its reference value.

Best wishes for the New Year.

Jerry L. Spivak, M.D.

Table of Contents

The material covered in this volume represents literature through February 1988.

1 Red Blood Cells

Introduction

This year in the section on red blood cells, we offer a potpourri of articles dealing with subjects as diverse as the erythrocyte sedimentation rate and R binder deficiency associated with neurologic abnormalities. Articles concerning recombinant human erythropoietin dominate the section, as well they should, since the development of this hormone as a recombinant protein was a major scientific and therapeutic milestone. However, the rapidity with which progress can be accomplished with recombinant DNA technology has created a serious paradox with respect to erythropoietin.

This hormone, while long acknowledged as mandatory for erythropoiesis, has until recently essentially been a laboratory curiosity, since there was no acceptable clinical assay available for it and no preparation of the erythropoietin was suitable for human use. Indeed, as many of us can sadly testify, there were insufficient quantities of purified erythropoietin available for experimental purposes. Now, with the assistance of genetic engineering, adequate quantities of erythropoietin are available for both clinical and experimental studies, and the pace of investigation has been such that the hormone has been demonstrated to be clinically effective even before its physiology is completely understood. Furthermore, most clinicians are not familiar with erythropoietin, since until last year neither diagnostic nor therapeutic indications for it had been developed.

In this edition of the YEAR BOOK, we feature five articles dealing with erythropoietin and its recombinant derivative. An additional clinical trial in patients with end-stage renal disease is described as are the effects of the hormone on the bleeding time in such patients. The paradox of normal plasma erythropoietin levels in patients with cyanotic congenital heart disease is explained, and its biosynthesis in the kidney is explored. Based on in vitro clinical assays of erythroid progenitor cells, it now appears that the anemia of prematurity may be due to erythropoietin lack, and our own (unpublished) studies substantiate that contention, although the reason for this erythropoietin deficiency is unknown.

Excellent clinical investigation continues to be represented in these pages with articles on the clinical features of autoimmune hemolytic anemia, chronic lung disease in sickle cell anemia, sudden death in sickle trait patients, the neurologic implications of R binder deficiency, and the treatment of thalassemia major and pure red cell aplasia in children. AIDS is also represented, of course, and in this instance it is the pancytopenia associated with AZT therapy that merits attention. A superb article on the erythrocyte sedimentation rate (ESR) has also appeared, and while the ESR is more in the realm of internal medicine, I could not resist including it: I've also included a table on hematologic values in the very

old, which I hope will be a useful clinical reference. In lieu of our usual complement of articles on the red cell cytoskeleton this year, we offer a concise review by an expert in the field to provide both definition and perspective concerning this rapidly evolving area of erythrocyte physiology.

All in all, I think the section contains an interesting mixture of subjects that are worthy of your attention. Finally, I also want to be sure that you are aware of an editorial by Dr. Helen Ranney (*West J Med* 146:473, 1987) entitled "Clinical Evaluation of Anemia." The *Western Journal of Medicine* frequently contains hematologic gems, and Dr. Ranney's comments are a must for all clinical hematologists.

Jerry L. Spivak, M.D.

Erythropoietin

▶ The literature on the clinical application of recombinant erythropoietin continues to burgeon, and we will continue to document it here until there is sufficient understanding of how the hormone should be employed and of its attendant risks. The article by Dr. Casati et al. cited below confirms previously published observations (see the 1988 YEAR BOOK OF HEMATOLOGY, pp. 14–20) that erythropoietin is effective in correcting the anemia associated with end-stage renal disease.

Indeed, the results of a recent multicenter study of renal dialysis patients (*Kidney Int* 33:189a, 1988) indicate an overall response rate of 97.5% with alleviation of the transfusion requirement in 97.7% of those patients requiring transfusions before erythropoietin therapy. This is a remarkable record of effectiveness. In these renal dialysis patients, an increase in blood pressure was observed in some previously hypertensive patients as well as in some normotensive patients following erythropoietin therapy. In normal volunteers, the hormone does not cause hypertension. Consequently, it appears that the milieu of end-stage renal disease is indicatable here, particularly when there is prior elevation of the blood pressure.

Of interest in this regard is the study by Neff and colleagues (*Circulation* 43:876, 1971) which demonstrated that transfusing uremic patients to a normal hematocrit increased peripheral vascular resistance, elevated diastolic blood pressure, and reduced cardiac output. It is noteworthy that in these patients the elevation in hematocrit was associated with a reduction in plasma volume. The mechanism for this is unclear, and whether it is involved in the pathogenesis of the hypertension or its exacerbation remains to be determined. It is also worth noting that not all uremic patients respond in the same fashion and that, in some, elevation of the red cell mass is associated with an improvement in cardiac output. Dr. Raines (*Lancet* 1:97, 1988) has written a comprehensive review of the problem of hypertension and the hematocrit in renal failure.

Seizures represent another unresolved problem. They may be related to changes in blood viscosity, vascular resistance, or cardiac output associated with elevation of the red cell mass, but whether they are more frequent in

erythropoietin-treated patients than in controls or represent a risk associated solely with preexisting hypertension is unknown.

The study of Casati et al. also demonstrated that patients with aluminum intoxication responded to erythropoietin but required higher dosages. Other conditions which impair or prevent a response to erythropoietin include infection or iron deficiency.—J.L. Spivak, M.D.

Benefits and Risks of Protracted Treatment With Human Recombinant Erythropoietin in Patients Having Haemodialysis

Casati S, Passerini P, Campise MR, Graziani, G, Cesana B, Perisic M, Ponticelli C (Ospedale Maggiore Policlinico, Milan, Italy; Cilag Ltd, Schaffhausen, Switzerland)

Br Med J 295:1017–1020, October 1987 1–1

Inadequate secretion of erythropoietin is the main cause of uremic anemia. The authors describe the results of replacement therapy with human recombinant erythropoietin administered for 8–11 months to 14 uremic patients (Table 1).

Human recombinant erythropoietin was administered after dialysis three times per week. The initial dose was 24 units per kilogram of body weight and was increased until hemoglobin concentrations were 100–120 gm/L. One patient was dropped from the study because of recurrent thrombosis of the vascular access sites. All other patients responded, but

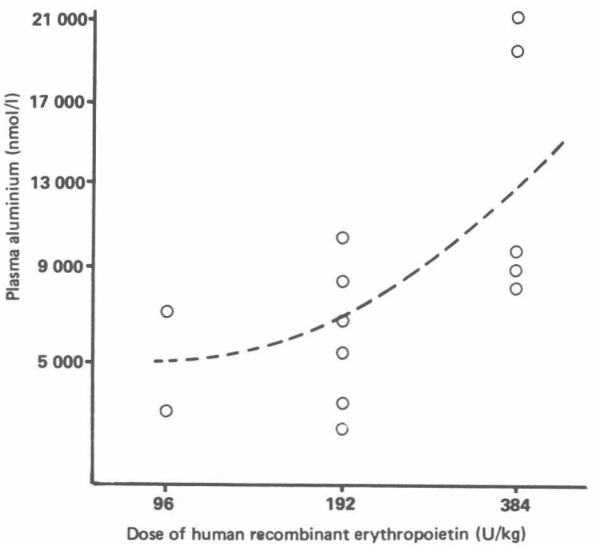

Fig 1–1.—Relationship between plasma aluminum concentrations after desferrioxamine test (40 mg/kg) and dose of human recombinant erythropoietin needed to increase hemoglobin concentration by 20 gm/L ($F_{1,11} = 10 \cdot 30$; $P = .0083$; regression equation $y = 123 \cdot 0952 + 1 \cdot 4554E - 03x^2$). (Courtesy of Casati S, Passerini P, Campise MR, et al: *Br Med J* 295:1017–1020, October 1987.)

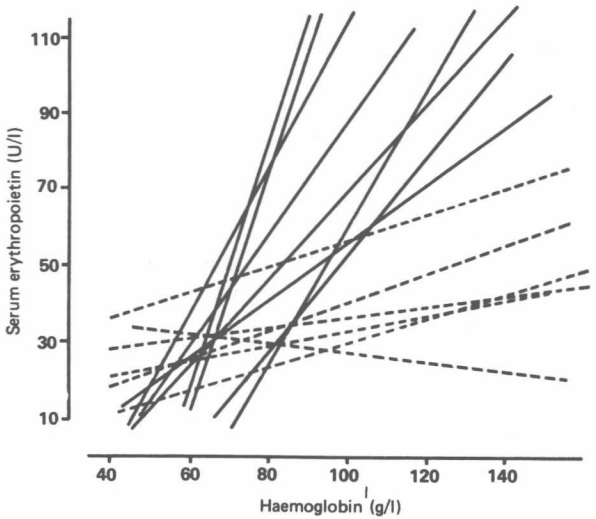

Fig 1–2.—Relationship between serum erythropoietin concentration and hemoglobin concentration in 14 patients given increasing doses of human recombinant erythropoietin. Relationship was significant in 8 patients (straight line; $P = .0012$ to $P = .0374$) and not significant in 6 (broken line). (Courtesy of Casati S, Passerini P, Campise MR, et al: *Br Med J* 295:1017–1020, October 1987.)

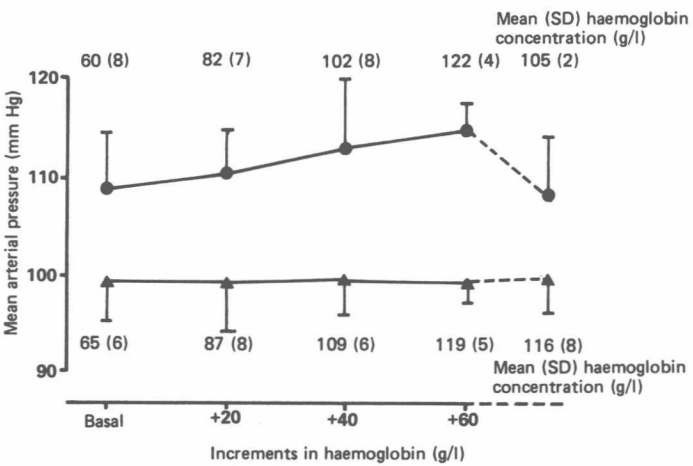

Fig 1–3.—Variations in mean arterial pressure at various increments of hemoglobin concentration during treatment with human recombinant erythropoietin. *Triangles* indicate patients with normal blood pressure before treatment with erythropoietin; *circles,* patients receiving antihypertensive agents before treatment with erythropoietin. After full correction, erythropoietin doses were adjusted to maintain stable hemoglobin values in normotensive patients and lower hemoglobin values in hypertensive patients *(broken line).* Significance of difference between groups: $F_{1,11}$, $= 22 \cdot 11$; $P = .0006$. No differences found within groups at different times of treatment. (Courtesy of Casati S, Passerini P, Campise, MR, et al: *Br Med J* 295:1017–1020, October 1987.)

TABLE 1.—Clinical and Hematologic Characteristics of Patients at Entry to Study

Case No	Sex	Age (years)	Years of haemodialysis	Original nephropathy	Pretreatment haemoglobin (g/l)	Serum erythropoietin (U/l)	Pretreatment mean arterial pressure (mm Hg)	Native kidneys
1	F	50	16	Chronic glomerulonephritis	51	32	98*	Absent
2	M	30	14	Alport's syndrome	65	20	90	Present
3	M	60	3	Chronic pyelonephritis	61	35	111*	Left nephrectomy
4	M	57	14	Chronic glomerulonephritis	65	42	101*	Present
5	M	46	12	Chronic glomerulonephritis	74	32	101*	Present
6	F	56	1	Chronic glomerulonephritis	70	24	98	Present
7	F	53	11	Chronic pyelonephritis	57	20	105*	Absent
8	M	50	14	Chronic glomerulonephritis	57	35	102	Absent†
9	F	26	14	Chronic glomerulonephritis	49	23	111*	Absent
10	F	59	4	Chronic glomerulonephritis	60	26	96*	Present
11	M	36	1	Nephrosclerosis	68	24	122*	Present
12	M	35	1	Chronic glomerulonephritis	67	40	98	Present
13	M	35	12	Chronic glomerulonephritis	58	25	105	Present
14	M	46	16	Chronic pyelonephritis	74	15	75	Absent†

*Receiving antihypertensive treatment.
†Previous splenectomy.
(Courtesy of Casari S, Passerini P, Campise MR, et al: *Br Med J* 295:1017–1020, October 1987.)

each required a different dose of erythropoietin. The dosage needed was higher in patients with higher concentrations of aluminum (Fig 1–1).

All 13 patients had full correction of anemia in 12–20 weeks (Table 2). In 8 patients, there was a significant correlation between serum erythropoietin concentration and hemoglobin concentration (Fig 1–2). Anti-

TABLE 2.—Effects of Human Recombinant Erythropoietin on Hemoglobin Concentrations and Reticulocyte Counts After 12–20 and 35–45-Weeks of Treatment*

Case No	Baseline haemoglobin (g/l)	Baseline reticulocyte count ($\times 10^9$/l)	Haemoglobin after 12-20 weeks (g/l)	Reticulocyte count after 12-20 weeks ($\times 10^9$/l)	Weekly dose of human recombinant erythropoietin (U/kg)	Haemoglobin after 35-40 weeks (g/l)	Reticulocyte count after 35-40 weeks ($\times 10^9$/l)	Weekly dose of human recombinant erythropoietin (U/kg)
1	51	14·0	131	39·0	1224	100	85·6	720
2	65	28·8	145	56·7	1296	107	46·3	288
3	61	18·1	136	48·4	864	105	25·1	288
4	65	10·9	124	55·4	1296	104	38·7	720
5	74	17·5	127	68·4	1224	116	50·3	624
6	70	28·7	121	34·3	720	115	25·8	240
7	57	13·5	127	46·4	1296	102	21·4	312
8	57	10·7	108	44·8	796	113	15·3	66
9	49	57·5	104	19·9	720	80	14·6	432
10†	60	7·5	79	32·6	1296		Dropped out	
11	68	13·2	128	26·3	432	106	26·5	120
12	67	21·9	115	58·3	504	108	48·8	168
13	58	18·7	107	19·9	648	107	22·3	108
14	74	7·9	108	23·8	648	114	15·9	108
Mean	62	20·1	121	41·6	897	105	33·6	322
SD	8	12·9	12	15·9	324	9	20·1	23

*Quadratic trends for hemoglobin concentration and reticulocyte count (analysis of variance): $F_{1, 12} = 94 \cdot 67$, $P < .000001$; and $F_{1, 12} = 10 \cdot 29$, $P = .0076$. Cases 8–14 entered into study after decision to reduce correction of anemia to hemoglobin concentrations of 100–120 gm/L.

†Case 10 excluded from calculations of mean and SD.

(Courtesy of Casati S, Passerini P, Campise MR, et al: *Br Med J* 295:1017–1020, October 1987.)

TABLE 3.—Serum Iron and Ferritin Concentrations at Start of Recombinant Erythropoietin Treatment and at Full Correction of Anemia*

Case No	Before treatment (haemoglobin 62 (SD 8) g/l) Iron (μmol/l)	Ferritin (μg/l)	At correction of anaemia (haemoglobin 121 (SD 12) g/l) Iron (μmol/l)	Ferritin (μg/l)	Cumulative intravenous iron supplementation (mg)
1	14·1	850	11·1	850	1126·8
2	23·1	305	15·7	292	876·4
3	16·4	314	10·7	160	1439·8
4	12·3	96	10·0	60	1064·2
5	13·9	104	12·7	42	1808·4
6	13·4	34	9·8	63	2367·4
7	12·3	108	11·1	75	1878·0
8	17·2	94	12·7	169	1247·8
9	20·0	628	10·5	269	
10	11·1	30	Dropped out		503·4
11	13·4	480	9·1	115	1061·2
12	13·8	71	13·6	95	1306·2
13	12·9	73	13·4	22	2982·6
14	14·1	94	8·6	58	3250·4

*Pretreatment ferritin concentration vs. concentration at correction of anemia: $F_{1, 12} = 3 \cdot 88$; $P = .075$.

(Courtesy of Casati S, Passerini P, Campise MR, et al: *Br Med J* 295:1017–1020, October 1987.)

bodies to erythropoietin were not detected in any of these patients. All patients reported great improvement in their condition. Although blood pressure was not affected in normotensive patients, hypertensive patients required increased antihypertensive therapy (Fig 1–3). Potassium concentrations increased with increasing hemoglobin. Iron supplementation was required in 13 patients (Table 3). One patient had a thrombosis of an arteriovenous fistula during erythropoietin therapy.

Human recombinant erythropoietin can correct anemia in uremic patients, improving their quality of life. However, side effects do occur, including hyperkalemia, an increase in hypertension, and vascular thrombosis. Erythropoietin therapy should thus be initiated in small doses, and hemoglobin concentrations should be kept at 100 gm/L. This is sufficient to reverse anemia symptoms without the risk of serious side effects.

Improvement in the Haemostatic Defect of Uraemia After Treatment With Recombinant Human Erythropoietin

Moia M, Mannucci PM, Vizzotto L, Casati S, Cattaneo M, Ponticelli C (State Univ and Maggiore Hosp, Milan, Italy)

Lancet 2:1227–1229, Nov 28, 1987 1–2

In the pathogenesis of hemostatic defects in uremia, red blood cells (RBCs) seem to be important because there is an inverse relation between the hematocrit and the bleeding time. In one study, when transfused, washed RBC concentrates were given to uremic patients with long bleed-

Changes in Hematocrit, Bleeding Time, and Platelet Adhesion to Human Artery Subendothelium During Treatment

	Haematocrit (%)			Bleeding time (min)			Platelet adhesion (% coverage)	
Patient	Before	D50	D100	Before	D50	D100	Before	D100
1	21	32	41	20	7	6	12	49
2	19	28	40	> 30	6	9	14	35
3	18	28	35	25	12	5	7	43
4	20	27	36	> 30	12	8	11	57
5	22	30	40	> 30	13	9	9	39
6	19	31	34	> 30	7	8	11	49
7	14	28	33	> 30	> 30	19	8	21
Mean (SD)	19 (2·6)	29 (1·9)	37 (3·3)	> 30 (20–> 30)*	12 (6–> 30)*	8 (5–19)*	10 (2·4)	42 (11·7)

*Median and range.
(Courtesy of Moia M, Mannucci PM, Vizzotto L, et al: *Lancet* 2:1227–1229, Nov 28, 1987.

ing times, improvement in the anemia was correlated with shortening of the bleeding time and improvement in bleeding symptoms. In this study, seven consecutive patients with chronic renal failure, severe anemia, long bleeding times, and mild bleeding symptoms were evaluated to determine whether the rise in autologous RBCs induced by recombinant human erythropoietin (RHE) would have the same effect as that of transfusion in improving hemostasis.

A bolus of RHE starting with 24 units/kg body weight three times a