

Oxymetholone Treatment for the Anemia of Bone Marrow Failure

By Raymond Alexanian, Judith Nadell, and Clarence Alfrey

Oxymetholone was given to 28 adults with chronic anemia from bone marrow disease. Changes in hematocrit and red cell mass were correlated with serial assessments of erythropoietin and erythropoiesis. Erythropoietin excretion was enhanced more than five-fold over the level expected for the hematocrit in 70% of the patients. Only 23% of the patients with an evaluable treatment trial increased their red cell mass by at least 20%. In all responders, the $T_{1/2}$ of ^{59}Fe disappearance ranged from 86–136 min and erythron iron turnover exceeded 0.25 mg/100 ml blood/day. A decline in serum iron concentration to the 50–100 $\mu\text{g}/100\text{ ml}$

range after 1 mo of oxymetholone was frequently associated with a subsequent response to therapy. Patients with severe bone marrow failure, for whom frequent red cell transfusions were required, did not improve. The failure of other patients to respond was attributed to complicating factors that either impaired maximal erythropoietin production or restricted iron supply to the bone marrow. Hepatic toxicity was detected in less than 10% of treated patients. Results support the use of oxymetholone in the treatment of patients with moderate degrees of bone marrow failure and symptomatic anemia.

STUDIES IN ANIMALS AND MAN have documented that androgenic hormones stimulate erythropoiesis,¹⁻⁴ an effect probably mediated by an increased production of erythropoietin.⁵⁻⁷ Even when basal levels of erythropoietin were elevated, as in most anemias resulting from bone marrow disease, further increments usually followed androgenic hormone therapy.^{8,9} Nevertheless, red cell mass improved infrequently, presumably because the bone marrow was unable to respond.^{3,9}

Oxymetholone is an oral androgen considered to be effective in many patients with chronic, refractory anemia.¹⁰⁻¹² The capacity of oxymetholone to stimulate erythropoietin production, and the clinical usefulness of this hormone in adults with anemia due to chronic marrow disease, has not been determined. These questions were clarified by serial erythropoietin and erythrokinetic studies before and after giving oxymetholone to 28 anemic adults with bone marrow failure. Results indicated a high frequency and degree of erythropoietin stimulation, but a low incidence of bone marrow improvement. Those patients most likely to benefit were those with a greater magnitude of marrow proliferation, with a marked degree of erythropoietin stimulation, and with an adequate iron supply.

From the Departments of Medicine, The University of Texas M. D. Anderson Hospital and Tumor Institute, and Baylor College of Medicine, Houston, Texas.

Submitted October 6, 1971; first revision March 1, 1972; second revision April 18, 1972; accepted April 27, 1972.

Supported by USPHS Grants AM 09155 and HE 05435

Raymond Alexanian, M.D.: Associate Professor of Medicine, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Judith Nadell, M.D.: Associate Medical Director, Syntex Research, Palo Alto, Calif. Clarence Alfrey, M.D.: Associate Professor of Medicine, Baylor College of Medicine, Houston, Texas.

Table 1. Response of 28 Patients to Oxymetholone

	No. Patients	No. Evaluable Trial	No. Responsive*
Idiopathic marrow failure			
Aplastic	7	6	0
Normal and hyperplastic	7	7	2
Myelofibrosis	3	3	0
Lymphoma	4	4	1
Myeloma	7	6	3
—	—	—	—
Total	28	26	6

* Response was defined by an increase in red cell mass of $> 20\%$ with elimination of transfusion requirements. In all responders, the hematocrit also increased by at least 5 vol/100 ml.

MATERIALS AND METHODS

Twenty-eight patients with chronic refractory anemia from bone marrow failure were studied before and during treatment with oxymetholone. The median age was 67, ranging from 20 to 78; 18 of our patients were male. Fourteen patients had idiopathic bone marrow failure; three had myelofibrosis; four had lymphoma with no marrow infiltration; and seven had multiple myeloma in a remission status (Table 1). Bone marrow hemosiderin was present in all, and no patient had marked marrow infiltration by malignant cells (i.e., $> 20\%$). Patients with a significant hemolytic component, or a serum iron concentration less than $60 \mu\text{g}/100 \text{ ml}$ before treatment were excluded. Six patients were included with normal pretreatment serum iron values, even though postoxymetholone values fell later to less than $60 \mu\text{g}/100 \text{ ml}$. The creatinine clearance exceeded $50 \text{ ml}/\text{min}$ in all but two patients whose clearances were between $35\text{--}50 \text{ ml}/\text{min}$; these two patients were included only after urinary erythropoietin excretion was found to be appropriate for the degree of anemia. Serum bilirubin, alkaline phosphatase, and transaminase were measured before treatment and at monthly intervals thereafter. Red cell transfusions (i.e., two or more per mo) were given to 14 patients when the hematocrit was less than 20 vol/100 ml. No patient received chemotherapy for malignant disease or corticosteroids during the treatment trial.

Erythropoiesis was evaluated from measurements of plasma iron turnover, erythron iron turnover, and red cell mass. Plasma iron turnover was measured using ^{59}Fe after the intravenous injection of $5\text{--}10 \mu\text{Ci}$ of citrated ^{59}Fe previously incubated in normal plasma. Blood was collected at measured time intervals for 3 hr, the $T_{1/2}$ of plasma clearance was determined, and plasma iron turnover ($\text{mg}/100 \text{ ml blood}/\text{day}$) was calculated.¹³ Erythrocytic iron turnover (EIT) was derived by subtracting the calculated nonerythron turnover (serum iron $\times$ plasmacrit $\times 0.0035$) from the measured plasma iron turnover.¹⁴ Fixed red blood cell iron turnover (FRIT) was derived from the product of the plasma iron turnover and the per cent utilization of ^{59}Fe in the measured red cell mass. No patient with significant hemolytic anemia, defined by a FRIT ($\text{mg}/100 \text{ ml blood}/\text{day}$) more than 2% of the red cell iron content (mg) in 100 ml blood, was included in this study. Red cell iron content was derived by assuming that 1 ml of red cells contained 1 mg of iron. Using a FRIT/red cell iron index for those anemic patients not requiring red cell transfusions, the median rate of hemolysis was $1.5\%/ \text{day}$. Five patients were considered to have significant ineffective erythropoiesis when total erythropoiesis derived from the erythron iron turnover¹⁴ (plasma iron turnover minus nonerythron turnover) exceeded, by more than $0.60 \text{ mg}/100 \text{ ml blood}/\text{day}$, the rate of effective erythropoiesis derived from the fixed red cell iron turnover. This level of ineffective erythropoiesis was $1\frac{1}{2}$ times the total red cell production in normal man.¹⁵ A linear body scanner was used to define the distribution of ^{59}Fe in the body 1 day after the injection of ^{59}Fe .¹⁶ The fraction of administered isotope found over the pelvis and upper abdomen was calculated for each patient. Erythropoietin production

was determined from the urinary excretion by assay of urine or urine concentrates in polycythemic mice and expressed in standard B units/day as previously described.⁷ Since erythropoietin excretion reached maximum levels in man 1 mo after oral androgens,⁹ maximal erythropoietin production was evaluated after this duration of therapy.

Oxymetholone (Syntex Research) was initiated in a daily dose of 1.0 mg/kg for women and 5.0 mg/kg for men. The dose was increased in 50% increments at monthly intervals if side effects were not distressing (muscle cramps, virilization, nausea), but not to more than 100 mg/day for women or 450 mg/day for men. An evaluable treatment trial required at least 3 mo of therapy with a minimum total dose of 5.0 g of oxymetholone. The red cell mass was measured with ⁵¹Cr-tagged red cells before and after at least 3 mo of treatment; clinical response was defined as an increase of at least 20% with elimination of red cell transfusion requirements.

Table 2. Hematologic Status of 26 Evaluable Patients Treated With Oxymetholone

	Diag- nosis*	Hct (Vol/ 100 ml)	WBC Gran Platelets (× 10 ³ cu mm)			Bone Marrow Cellularity† Cytology‡	
Responsive patients							
D.H.	MM	32	2.6	1.6	124	N; 20% RBC; 10% PC	
R.C.‡	L	26	2.4	1.3	44	N; 20% RBC	
A.W.	IRA	29§	4.8	1.0	87	N; 40% RBC	
Z.G.‡	MM	18§	5.1	4.2	276	N; 30% RBC; 20% PC	
E.S.	MM	34	6.0	3.1	177	N; 30% RBC; 20% PC	
B.T.	IRA	26	2.3	0.7	92	N; 40% RBC	
Unresponsive patients							
Decreased marrow							
M.R.	AA	19§	2.4	0.7	70	D; < 5% RBC	
C.D.	MF	21§	4.6	1.7	554	I; 90% fibrosis	
B.M.	AA	27§	1.8	0.7	45	D; 10% RBC	
L.C.	AA	31§	3.3	1.4	105	N; < 5% RBC	
W.P.	MF	25§	1.1	0.9	308	I; 90% fibrosis	
J.M.	AA	18§	2.6	0.6	24	D; < 5% RBC	
T.S.	AA	30§	5.7	3.2	434	N; < 5% RBC	
L.L.	AA	29§	2.2	1.0	34	D; < 5% RBC	
Normal and increased marrow							
M.B.	MM	19	3.6	2.0	33	N; 20% RBC; 20% PC	
F.G.	IRA	22§	0.9	0.5	62	N; 20% RBC	
E.T.	L	33	3.3	1.6	171	N; 20% RBC	
E.P.	IRA	38	4.7	0.9	265	N; 40% RBC	
H.C.	L	39	28.8	3.5	86	N; 20% RBC	
N.G.	MM	31	3.3	2.6	183	N; 20% RBC; 20% PC	
J.G.	MM	35	5.0	3.9	211	N; 20% RBC; 20% PC	
R.M.	L	36	3.1	1.9	162	I; 60% RBC	
J.C.	MF	30§	3.4	1.2	40	I; 50% RBC	
F.L.	IRA	31§	2.6	1.1	245	I; 50% RBC	
S.C.	IRA	32	8.2	5.0	364	I; 30% RBC	
W.O.	IRA	34	2.1	1.3	211	I; 40% RBC	

* AA, aplastic anemia; IRA, idiopathic refractory anemia; MF, myelofibrosis; MM, multiple myeloma; L, lymphoma.

† Marrow cellularity on clot section. N, normal; I, increased; D, decreased; RBC, erythroid cells; PC, plasma cells; WBC, white blood cells; Gran, granulocytes.

‡ Creatinine clearance 35–50 ml/min.

§ Required red cell transfusions.

Table 3. Ferrokinetic Studies in 28 Patients Treated With Oxymetholone

	Hct (Vol/ 100 ml)	Serum Iron $\mu\text{g}/100\text{ ml}$		Basal Iron Turnover Data (mg/100 ml blood/day)			Organ Scans		
		Basal	Post Therapy	uFe $T_{1/2}$ (min)	Total Erythron	Fixed Red Cell	% uFe Uptake in Red Cells	% Pelvis	% Upper Abdomen
Normal ranges	44-50	86-137	—	69-122	0.30-0.50	0.30-0.50	64-79	23-35	26-33
Responsive patients									
D.H.	32	103	63	136	0.27	0.27	52	Pelvis XRT 22	31
R.C.	26	162	82	112	0.65	0.61	57	23	30
A.W.	29*	197	156	128	0.60	0.26	24	Pelvis XRT 28	25
Z.G.	18*	148	58	118	0.61	0.34	33	27	18
E.S.	34	105	60	86	0.57	0.46	57	25	28
B.T.	26	137	74	136	0.40	0.40	53		
Median values	28†	143	69	123	0.59	0.37	53		
Unresponsive patients									
Decreased marrow									
M.R.	19*	253	220	260	0.07	0.06	7	6	66
C.D.	21*	249	150	228	0.17	0.08	9	22	41
B.M.	27*	185	142	190	0.24	0.24	34	24	51
L.C.	31*	220	184	220	0.16	0.03	4	16	47
W.P.	25*	95	63	150	0.23	0.01	1	14	41
J.M.	18*	182	150	249	0.08	0.08	13	12	53
T.S.	30*	176	167	210	0.16	0.05	9	14	57
L.L.	29*	249	245	226	0.16	0.16	21	16	41
Median values	< 20†	203	159	223	0.16	0.07	9	14	49

Normal marrow (Effective erythropoiesis)								
M.B.	19	111	147	0.30	0.30	49	19	28
F.G.	22*	221	158	0.49	0.21	19	23	39
E.T.	33	92	80	0.55	0.52	67	33	21
E.P.	38	80	83	0.43	0.43	72	30	20
H.C.	39	108	93	0.48	0.48	68	20	28
N.G.	31	78	84	0.45	0.43	67	20	27
J.G.	35	60	72	0.40	0.40	73	20	30
Median values	33†	92	84	0.45	0.43	67	20	28
Increased marrow (Ineffective erythropoiesis)								
R.M.	36	68	29	1.35	0.56	37	24	37
J.C.	30*	291	106	1.21	0.12	6	30	30
F.L.	31*	161	55	1.63	0.02	1	31	27
S.C.	32	122	50	1.37	0.37	22	27	18
W.O.	34	273	101	1.15	0.53	30	25	29
Median values	32†	161	55	1.35	0.37	22	27	29
Early death								
H.S.	25*	234	154	0.53	0.21	18	22	33
R.B.	29	85	64	0.73	0.62	66	22	39

* Required red cell transfusions.

† Assumes Hct < 20 for transfused patients.

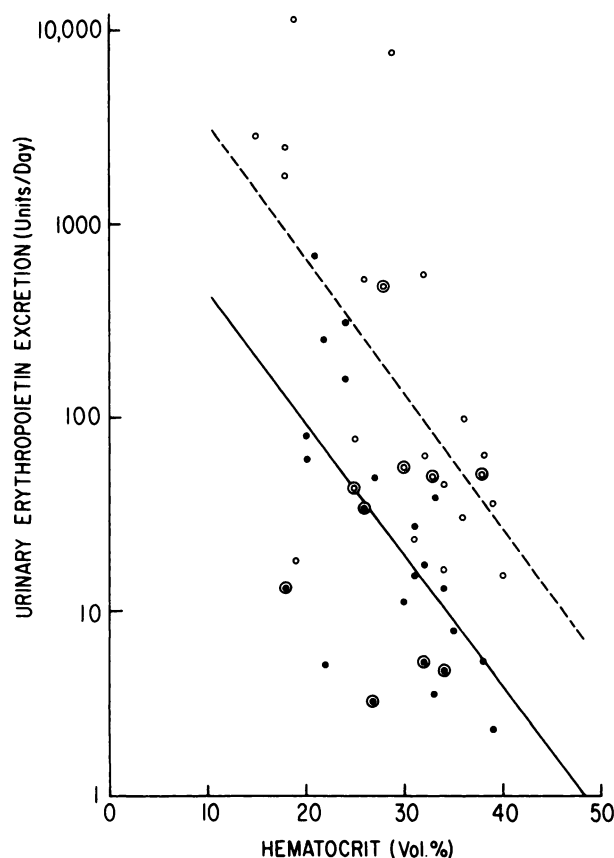


Fig. 1. Relationship of urinary erythropoietin excretion to hematocrit. Studies before androgens (solid circles) are compared with studies after 1 mo of treatment (open circles) in 23 patients with evaluable erythropoietin assays. The solid line was calculated from basal measurements and the dashed line from studies after 1 mo of treatment. Values for responsive patients are circled.

RESULTS

Erythropoietin and erythropoiesis were assessed before and during therapy in the 26 patients with an evaluable treatment trial of at least 3 mo. Only six patients (23%) increased their red cell mass by more than 20%, and five were women. In these responders, the median increment in hematocrit was 9 vol/100 ml (range 5 to 20), and in red cell mass 260 ml/sq m (range, 130-380). This elevation was recognized within 3 mo of treatment, and was equivalent to about 25% of the red cell mass in normal man.¹⁵ Only two of the 13 evaluable patients who had been dependent on red cell transfusions eliminated this requirement after oxymetholone (Table 2). Within 2 mo after the cessation of androgen treatment, the hematocrit declined by at least 5 vol/100 ml in all responding patients.

Erythropoietin

Oxymetholone produced an increment in urinary erythropoietin excretion of at least five times the value expected for the hematocrit in 16 of the 23 patients (70%) with evaluable studies before and after treatment. Seven patients showed less than a fivefold enhancement and all were unresponsive to

oxymetholone. Figure 1 compares urinary erythropoietin values after 1 mo of treatment with control measurements in relation to the hematocrit.

Erythrokinetics

The clinical response to oxymetholone was correlated with the degree of bone marrow activity in each patient (Tables 2 and 3). In responding patients, bone marrow erythroid cellularity was normal, the $T_{1/2}$ for ^{59}Fe disappearance ranged between 86–136 min, and the erythron iron turnover exceeded 0.25 mg/100 ml blood/day (normal range 0.30–0.50). The serum iron concentration was between 100–170 $\mu\text{g}/100$ ml before treatment in all but one; within 1 mo after institution of oxymetholone, the serum iron declined by at least 40 $\mu\text{g}/100$ ml, but not to a concentration less than 50 $\mu\text{g}/100$ ml (Table 3). Figure 2 contrasts the relationship between erythropoietin and erythropoiesis in the six responding patients with identical studies in the 20 unresponsive patients.

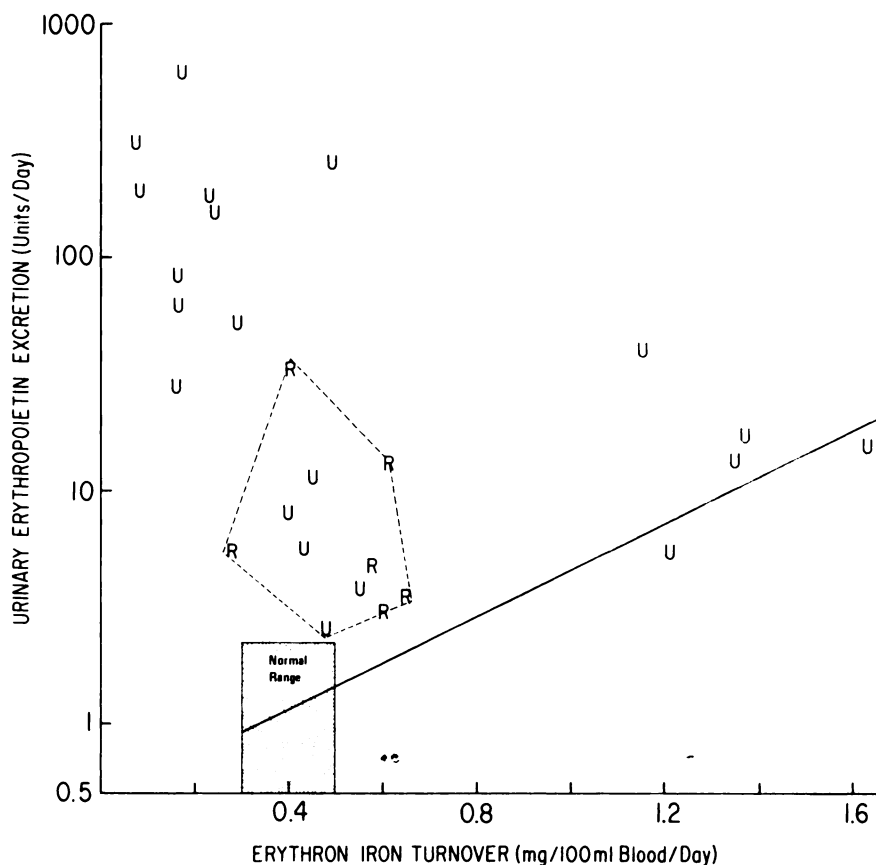


Fig. 2. Relationship between erythropoietin excretion and erythron iron turnover in 26 patients with an evaluable oxymetholone treatment trial. R indicates values for responsive patients (all of whom fell within the dashed lines), and U for patients unresponsive to oxymetholone. The stippled area includes the range for normal man and the solid line was calculated from previous studies before and/or after bleeding 13 normal volunteers.¹⁵

Patients failing to improve red cell production with oxymetholone were analyzed in three different groups (Table 3). In one group (8 patients), bone marrow function was depressed and erythron iron turnover was less than 0.25 mg/100 ml blood/day (median 0.16). All were markedly anemic and dependent on frequent red cell transfusions (two or more units/mo). Erythroid marrow cellularity was depressed and some patients also had severe granulocytopenia and thrombocytopenia (Table 2). Serum iron levels were high (median 203 μ g/100 ml) and usually remained elevated after oxymetholone. The $T_{1/2}$ of ^{59}Fe disappearance was markedly prolonged in all (median 223 min) (Table 3). Although basal erythropoietin excretion was appropriately high for the degree of anemia oxymetholone produced further marked elevations to more than 500 units/day in all.

The second group of unresponsive patients (7 patients) had a calculated erythron iron turnover within the normal range. Anemia was less severe, marrow erythroid cellularity was normal, and there was no evidence of significant ineffective erythropoiesis. The third group of unresponsive patients (5 patients) showed an erythron iron turnover greater than twice normal, increased marrow erythroid cellularity, and significant ineffective erythropoiesis (Table 3). Two of the four patients in this group who had bone marrow culture studies showed major cytogenetic abnormalities (courtesy of Dr. J. Trujillo).

While the maximum erythropoietin excretion after 1 mo of oxymetholone was stimulated to more than 5 times control to more than 40 units/day (i.e., > 20 times normal) in all "responsive" patients with evaluable studies, this occurred in only 6 of 13 "unresponsive" patients with normal or increased marrow function (Fig. 1). Four of the seven patients with "impaired" erythropoietin stimulation also had a marked fall in serum iron concentration to less than 30 μ g/100 ml (Table 3). Serum iron values remained low, in association with an iron binding capacity less than 300 μ g/100 ml, despite oral iron supplements for at least 2 mo. Only two of these four patients had overt clinical evidence of infection (pneumonia and urinary tract infection). When the analysis was limited to the eleven patients with an erythron iron turnover greater than 0.25 mg/100 ml blood/day without ineffective erythropoiesis, in whom the serum iron exceeded 50 μ g/100 ml after 1 mo of treatment, six showed a significant elevation in red cell volume after oxymetholone (Table 3).

Organ Scanning

Linear body scanning of ^{59}Fe distribution demonstrated other differences between patients responsive and unresponsive to oxymetholone. Figure 3 correlates ^{59}Fe uptake in the pelvis and upper abdomen with different levels of red cell production. Only patients with serum iron levels above 60 μ g/100 ml and without irradiation therapy to the pelvis were included in this analysis. Subjects with normal marrow function had a radioiron uptake in the pelvis of at least 20% of the injected dose (median 28%). The per cent uptake remained constant with increased red cell production, but declined with subnormal levels of erythropoiesis (i.e., EIT < 0.30 mg/100 ml blood/day). Radioiron uptake in the upper abdomen was less than 40% of the injected

dose with normal and increased erythropoiesis, but increased with declining red cell production (Fig. 3). None of the eight patients with markedly depressed radioiron uptake in the pelvis (< 18% of injected dose) or increased uptake in the upper abdomen (> 40% of injected dose) responded to oxy-metholone (Table 3). In contrast, four of nine patients without ineffective

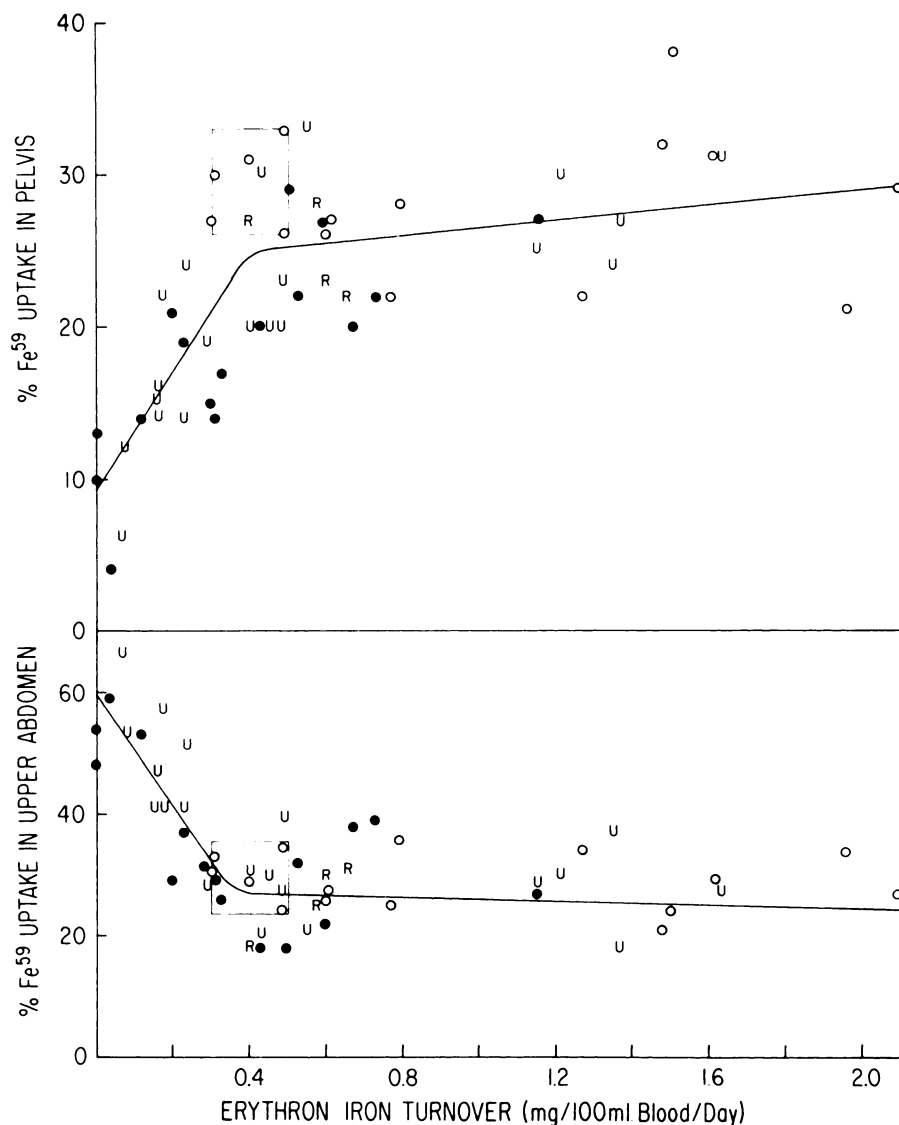


Fig. 3. Relationship between pelvis and upper abdominal uptake of ^{59}Fe and erythron iron turnover. R indicates four responsive patients, and U shows 20 unresponsive patients with evaluable scanning studies. Solid circles indicate other anemic patients not treated with androgens. Open circles show values for normal man before and after phlebotomy, and for four patients with secondary polycythemia. Boxes include ranges for normal man.

erythropoiesis and with an approximately normal ^{59}Fe distribution in the pelvis ($> 19\%$) and upper abdomen ($< 35\%$) elevated their red cell mass after oxymetholone (Fig. 3).

Clinical Effects

The doses of oxymetholone used in this study were well tolerated in most patients. The minimum 3 mo treatment trial was not completed by two patients because of death from progressive bone marrow disease (myeloma and aplastic anemia). Side effects from oxymetholone were frequent, but mild and reversible. Most patients complained of intermittent cramping muscle pain, but this never interfered with normal activities. Four women showed slight virilizing changes. Mild fluid retention developed in ten patients, four of whom had preexisting heart disease, but symptoms abated when the daily dose was reduced or an oral diuretic was added. No patient received less than 50 mg/day of oxymetholone. Two patients developed hepatic insufficiency as their treatment trial was completed (total doses 9 and 30 g). In one, the bilirubin increased to 17 mg/100 ml, the alkaline phosphatase to 15 Bessey-Lowry units (normal < 3 units), and the serum glutamic-oxaloacetic transaminase (SGOT) to 110 mU/ml. In the second patient, the bilirubin increased to 2.7 mg/100 ml, the SGOT to 155 mU/ml, while the alkaline phosphatase remained normal. Values returned to normal in both within 2 mo after the cessation of oxymetholone.

DISCUSSION

This study was designed to evaluate the utility of oxymetholone in the treatment of adults with chronic refractory anemia resulting from bone marrow failure. Emphasis was placed on a systematic evaluation before and during therapy of those factors of major importance in the maintenance of normal erythropoiesis. These included erythropoietin production, iron supply, and the level of bone marrow activity. In order to provide a clear appraisal of the effect of androgens on patients with bone marrow disease, patients with renal disease, hemolytic anemia, or extensive marrow infiltration by malignant cells were excluded from this study. Erythropoietin production was evaluated from measurements of the daily urinary excretion. Previous studies had ruled out the likelihood of an indirect stimulation of endogenous erythropoiesis in assay animals by androgens.⁷ Iron supply to the bone marrow was assessed from the serum iron concentration, and was considered depressed when the level fell to less than 60 $\mu\text{g}/100\text{ ml}$.¹³ Because assessments of erythropoiesis from measurements of iron turnover are probably invalid with iron deficiency,¹⁷ patients with serum iron values less than 60 $\mu\text{g}/100\text{ ml}$ before treatment were considered ineligible for this study. The body distribution of radioiron was evaluated with a linear body scanner, and primary emphasis was placed on the per cent uptake over the pelvis and upper abdomen. Pelvis uptake of ^{59}Fe provided an index of red cell production in a major bone marrow segment; upper abdominal uptake reflected the incorporation of radioiron in liver parenchymal cells.¹⁶

Oxymetholone was used because of the convenience of oral administration, the high frequency of clinical benefit reported by others,¹⁰⁻¹² and our desire to evaluate the capacity of this drug to stimulate erythropoietin production in man. Maximal doses were given in order to achieve maximal erythropoietin stimulation and a more adequate opportunity for enhanced bone marrow activity. Thus, only treatment trials of more than 3 mo duration with a total dose of at least 5.0 g were considered evaluable. Despite the high doses used, side effects from oxymetholone were usually mild and reversible. Marked elevations in urinary erythropoietin to more than five times the value expected for the hematocrit were produced in 70% of the patients with evaluable studies. This degree of urinary erythropoietin stimulation after oxymetholone was comparable to previous studies using fluoxymesterone.⁹ When erythropoietin values failed to increase markedly, red cell production did not improve despite an "adequate level" of bone marrow activity. These observations support the conclusion that marked elevations in erythropoietin constitute the principal mechanism for the occasional efficacy of androgens in patients with anemia due to bone marrow disease. Whether oxymetholone also affects red cell production by other mechanisms, such as by a direct marrow stimulation independent of erythropoietin, was not evaluated in this study.

Significant elevation in red cell mass was observed in about one-fourth of our patients with an evaluable treatment trial. Benefit occurred only when patients had levels of erythropoiesis close to or within the normal range. Even in these patients, the increment in red cell production (i.e., change in red cell mass) was only about 10% of the elevation (i.e., change in erythron iron turnover) induced in normal man following a comparable degree of erythropoietin stimulation by phlebotomy.¹⁵ Improvements in erythropoiesis occurred only in patients with a normal or slightly prolonged $T_{1/2}$ of plasma ^{59}Fe disappearance, an almost normal distribution of radioiron to the pelvis and liver, and moderate declines in serum iron concentration after 1 mo of treatment.

Patients with more severe depression of bone marrow function, who required frequent red cell transfusions, did not benefit from oxymetholone. These patients usually had elevated serum iron values unaffected by treatment, markedly prolonged disappearance half-times of radioiron, and diminished red cell precursors in the bone marrow. Decreased pelvis and increased abdominal uptake of radioiron provided further evidence for the severe bone marrow damage in these patients. Even when marrow erythropoiesis appeared to be well preserved, oxymetholone failed to increase the red cell mass of many anemic patients. Some of these patients did not show a marked degree of erythropoietin stimulation, while others demonstrated substantial rates of ineffective erythropoiesis. In some unresponsive patients, the serum iron concentration fell with oxymetholone to very low levels ($< 30 \mu\text{g}/100 \text{ ml}$) despite adequate marrow iron stores and oral iron supplements. These patients were considered to have additional complications, such as the "anemia of chronic disease,"¹⁸ that restricted iron supply to the bone marrow and prevented an opportunity for further enhancement of erythropoiesis. The ineffectiveness of androgens in this clinical setting differs from the experience of Haurani who

reported improved iron reutilization and increased red cell mass with testosterone in patients with hypoferremia.¹⁹

Other investigations have defined changes in the "erythropoietin-sensitive stem cell population" from the relationship between the rates of erythropoiesis in irradiated and unirradiated polycythemic mice following a standardized dose of erythropoietin.^{20,21} Using similar assumptions, the erythropoietin-sensitive bone marrow capacity of each of our anemic patients was calculated as a percent of normal. This was derived from the ratio between the erythron iron turnover of each patient and the measured turnover of normal man for the urinary erythropoietin excretion of each anemic patient. In all patients responding to oxymetholone, the rate of erythropoiesis exceeded 20% of the level found in normal human beings after phlebotomy. No patient with a more depressed erythropoietin-sensitive marrow capacity, in whom frequent red cell transfusions were required, improved with oxymetholone. Thus, those patients with the greatest need for more red cell production seldom derived any benefit. These observations are in conformance with those of others who found that enhanced red cell production from androgens occurred more frequently in anemic patients with some evidence of marrow erythropoiesis, as in children with idiopathic refractory anemia⁴ and adults with myelofibrosis.²² Therapeutic trials with oxymetholone are justified primarily in those patients with symptomatic levels of chronic anemia who have moderate levels of residual erythropoiesis and who sustain an adequate iron supply to the bone marrow.

REFERENCES

1. Steinglass, P., Gordon, A. S., and Charipper, H. A.: Effect of castration and sex hormones on the blood of rats. *Proc. Soc. Exp. Biol. Med.* 48:169, 1941.
2. Kennedy, B. J., and Gilbertson, A. S.: Increased erythropoiesis induced by androgenic-hormone therapy. *New Eng. J. Med.* 256:719, 1957.
3. Gardner, F. H., and Pringle, J. C.: Androgens and erythropoiesis. *Arch. Intern. Med. (Chicago)* 107:112, 1961.
4. Shahidi, N. T., and Diamond, L. K.: Testosterone-induced remission in aplastic anemia of both acquired and congenital types. *New Eng. J. Med.* 264:953, 1961.
5. Mirand, E. A., Gordon, A. S., and Wenig, J.: Mechanism of testosterone action in erythropoiesis. *Nature (London)* 206:270, 1965.
6. Fried, W., and Gurney, C. W.: Erythropoietin effect of plasma from mice receiving testosterone. *Nature (London)* 206:1170, 1965.
7. Alexanian, R., Vaughn, W. K., and Ruchelman, M. W.: Erythropoietin excretion in man following androgens. *J. Lab. Clin. Med.* 70:777, 1967.
8. Rishpon-Meyerstein, N., Kilbridge, T., Simone, J., and Fried, W.: The effect of testosterone on erythropoietin levels in anemic patients. *Blood* 31:453, 1968.
9. Alexanian, R.: Erythropoietin and erythropoiesis in anemic man following androgens. *Blood* 33:564, 1969.
10. Sanchez-Medal, L., Gomez-Leal, A., Duarte, L., and Rico, M. G.: Anabolic androgenic steroids in the treatment of acquired aplastic anemia. *Blood* 34:283, 1969.
11. Allen, D. M., Fine, M. H., Necheles, T. F., and Dameshek, W.: Oxymetholone therapy in aplastic anemia. *Blood* 32:83, 1968.
12. Silink, S. J., and Firkin, B. G.: An analysis of hypoplastic anemia with special reference to the use of oxymetholone in its therapy. *Aust. Ann. Med.* 17:224, 1968.
13. Finch, C. A., et al.: Ferrokines in man. *Medicine* 49:17, 1970.
14. Cook, J. D., Marsaglia, G., Eschbach, J. W., Funk, D. D., and Finch, C. A.: Ferro-

kinetics: A biologic model for plasma iron exchange in man. *J. Clin. Invest.* 49:197, 1970.

15. Alexanian, R., and Alfrey, C.: Erythropoiesis in the anemia of bone marrow failure. *J. Clin. Invest.* 49:1986, 1970.

16. Alfrey, C. P., Jr., Lynch, E. C., and Hettig, R. A.: Studies of iron kinetics using a linear scanner. *J. Lab. Clin. Med.* 73:405, 1969.

17. Hillman, R. S., and Henderson, P. A.: Control of marrow production by the level of iron supply. *J. Clin. Invest.* 48:454, 1969.

18. Cartwright, G. E.: The anemia of

chronic disorders. *Seminars Hemat.* 3:351, 1966.

19. Haurani, F. I., and Green, D.: Primary defective iron reutilization. *Amer. J. Med.* 42:151, 1967.

20. Gurney, C.W., Lajtha, L.G., and Oliver, R.: A method for investigation of stem-cell kinetics. *Brit. J. Haemat.* 8:461, 1962.

21. Alexanian, R., Porteous, D. D., and Lajtha, L. G.: Stem cell kinetics after irradiation. *Int. J. Radiat. Biol.* 7:87, 1963.

22. Gardner, F. H., and Nathan, D. G.: Androgens and erythropoiesis. *New Eng. J. Med.* 274:420, 1966.