Oxymetholone Therapy in Aplastic Anemia

By Donald M. Allen, Morris H. Fine, Thomas F. Necheles and William Dameshek

The prognosis of children with aplastic anemia has substantially improved since the late 1950's when testosterone and its derivatives were found to have a stimulating effect on bone marrow regeneration. Despite this improvement, mortality remains at greater than 50 per cent with a significant number of children with aplastic anemia failing to respond to adequate courses of testosterone.

A synthetic derivative of testosterone, oxymetholone (2-hydroxymethylene-17 alpha-methyl-17B-hydroxy-3-androstanone), has been used extensively in the treatment of aplastic anemia by Sanchez-Medal and his co-workers. Their experience with this compound indicated that it might have a greater erythropoietic stimulating ability than testosterone. We have now used oxymetholone in the treatment of five consecutive children with aplastic anemia, including two who were apparently refractory to testosterone, and all have had a satisfactory bone marrow and clinical response.

Case Reports

Case 1-J.B.: This 7 1/2 year old boy with idiopathic aplastic anemia had a three week history of cough, fatigue, increasing pallor, easy bruising, and nosebleeds. A bone marrow biopsy was extremely hypocellular and fibrotic.

Initial treatment was sublingual testosterone propionate, 60 mg. (2.0 mg./Kg.) and prednisone, 60 mg. daily. The prednisone was tapered after three weeks to a maintenance dose of 15 mg. daily. Testosterone was continued for two months and then replaced with oral oxymetholone,* 100 mg. daily (3.6 mg./Kg.). During the first four months of therapy, he received seven 500 cc. units of blood with the last transfusion three months after therapy was begun. After one month of oxymetholone (three months of androgen) his white count had improved, and by two months he had a reticulocytosis of 6.5 per cent which was followed by a rise in hemoglobin to 12.8 Gm./100 ml. at four months (Fig. 1). Bruising and petechiae subsided during the second month associated with a platelet rise to 29,000/mm. at three months. After six months on

*Kindly supplied by Syntex Laboratories, Inc., Palo Alto, California, as Anadrol, 50 mg. tablets.

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oxymetholone (eight months of androgen) all treatment was discontinued. He has now remained well for twenty-four months off all medications and his most recent peripheral blood counts included a hemoglobin of 13.2 Gm./100 ml., platelets 158,000/cu. mm., and a white blood count of 7,900 with a normal differential. He has a slightly husky voice, pubic hair, and an enlarged penis, but his bone age and height age are the same as his chronologic age. No jaundice was observed and serial liver-function studies have remained normal.

Case 2—N.A.: This 8 year old girl with idiopathic aplastic anemia had a two-month history of generalized petechiae followed by easy bruising and progressive fatigue. A bone marrow biopsy was hypocellular with patchy areas of erythroid activity and minimal megaloblastic changes.

She was treated with folic acid and vitamin B₁₂ for one week and then placed on 20 mg. of prednisone daily. There was a progressive fall in her hemoglobin and after five weeks, oxymetholone, 100 mg. orally per day (2.5 mg./Kg.), was added.

A reticulocytosis of 3.5 per cent was present after one month (Fig. 1); by three months reticulocytes peaked at 7.9 per cent, and by five to six months her hemoglobin level was normal. Bruising diminished gradually by the second month with a slow rise in the platelet count to 30,000 to 50,000/mm.³ by the fifth month. Her total white count has remained in the 2,000 to 4,000/mm.³ range, but an absolute increase in neutrophils was evident by the third month and has persisted. Signs of virilization were minimal with only slight huskiness of her voice and the development of pubic hair. Her bone and height age have remained consistent with her chronologic age. After six months, both oxymetholone and prednisone were discontinued and her blood counts have now remained unchanged for twenty-one months. No jaundice was noted at any time and serial liver-function studies have all been normal.
Case 3—K.R.: This 9 year old girl with idiopathic aplastic anemia had been presumably well until the day of admission when she developed severe epistaxis. She had a peripheral pancytopenia and bone marrow aspirate was hypocellular with no megakaryocytes, few myeloid and erythroid elements, increased mast cells, and a relative lymphocytosis.

Initial treatment was oxymetholone, 100 mg. (4.0 mg./Kg.) and prednisone, 40 Mg. orally per day. She required three transfusions to maintain her hemoglobin over 6 Gm. per cent during the first two months, but at two months an early reticulocytosis of 3.0 per cent was present; by three months reticulocytes were 18 per cent; and by four months her hemoglobin level was normal (Fig. 2). The absolute neutrophil level was improved by the third month and was entirely normal at five months when treatment was stopped. Bleeding symptoms progressively diminished during the first two months with a definite improvement in the platelet level by five months, when oxymetholone and prednisone were discontinued. She has been followed for eighteen months off medications and has maintained a completely normal hemogram. Her bone age and height are equal to her chronologic age. No jaundice developed and liver-function studies have remained normal.

Case 4—J.L.: This 16 year old white male with aplastic anemia had been well until approximately eighteen months before admission when fatigue, pallor, petechiae and purpura developed following a relatively prolonged contact with model lacquer and putty. When first seen elsewhere, he had a pancytopenia and a markedly hypocellular bone marrow. After two and a half months he had not improved and was started on treatment of prednisone 45 mg. orally and testosterone propionate 90 mg. (2mg./Kg.) sublingually daily. He continued on this regimen for seven months during which he was transfused every two to three weeks. Because of lack of improvement, both testosterone and prednisone were then stopped. He was started on ACTH and thyroid extract, and then splenectomized. Postsplenectomy his platelets rose to 60,000 to 80,000/mm.³ for six weeks, then returned to the previous 0 to 10,000/mm.³ level. He continued to require biweekly transfusions and had intermittent hemorrhages prior to his first New England Medical Center Hospitals admission eighteen

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*This patient was studied through the cooperation and assistance of Dr. Herbert Haegele, Portsmouth Naval Hospital, Portsmouth, New Hampshire.
months after the onset of this aplasia. These admission findings included a marked peripheral pancytopenia and a very hypoplastic bone marrow biopsy. He was started on oral oxymetholone, 150 mg. per day (3.0/Kg.) and prednisone 10 mg. per day. Two weeks later the oxymetholone was increased to 200 mg. (4.0 mg./Kg.) Two months after initiation of oxymetholone therapy his platelet count had risen to a level of 30,000/mm.\(^3\), reticulocytes were 7 per cent, and his hemoglobin had stabilized at 6.7 Gm./100 ml. (Fig. 3). After seven months on this regimen his hemoglobin was 13.5 Gm./100 ml., white cell count 7,050/mm.\(^3\) with 46 per cent neutrophils, and platelets 30,000/mm.\(^3\). The dosages of oxymetholone and prednisone were gradually lowered and stopped completely after eight months of therapy. By two months off treatment he was again pancytopenic and he was restarted on oxymetholone 200 mg. per day (4 mg/Kg.), and prednisone 10 mg. per day. A second response was evident after two and a half months with 9 per cent reticulocytes and a hemoglobin increase to 7.5 Gm./100 ml. Despite a continued reticulocytosis of 4 to 8 per cent, during the next five months, his hemoglobin remains at 8 Gm./100 ml. His white cell count is 5,600 with 64 per cent neutrophils and platelets stable at 33,000/mm.\(^3\). He apparently has a very labile bone marrow and may require continuous therapy with androgen. He has continued to have completely normal liver-function studies while on high doses of oxymetholone for over twelve months.

Case 5—M.L.: This 5 year old boy with constitutional aplastic anemia was admitted for evaluation of short stature and anemia. He had a pancytopenia with a hemoglobin of 5.2 Gm./100 ml., hematocrit 17.5 per cent, reticulocytes 1.5 per cent, white blood cells 2,800/mm.\(^3\), and platelets 20,000/mm.\(^3\). Bone marrow aspiration and biopsy were hypocellular with rare megakaryocytes and diminished erythroid and myeloid precursors. Bone films of the hand revealed a retarded bone age of 2 years 6 months (chronologic age, 5 years).

Treatment with growth hormone, 4 mg. per day intramuscularly for six weeks was without effect. Therapy was changed to sublingual testosterone propionate in a dose of 30 mg. per day (2 mg./Kg.). When no effect was evident at six weeks, the dose was increased to 60 mg. per day (4 mg./Kg.) and prednisone 10 mg. per day was added. Both drugs were continued for a total of eight months without any improvement in his blood counts. Testosterone was
Fig. 4.—Hemoglobin and reticulocyte response in Case 5 related to therapy with testosterone and prednisone and then with oxymetholone and prednisone. Relapse occurred as oxymetholone dosage was lowered (not shown).

discontinued and he was started on oxymetholone, 100 mg. orally (6.5 mg./Kg.). After two months, his reticulocyte count had risen to 8.5 per cent and the hemoglobin to 9 Gm./100 ml. from a previously stable level of 5 to 6 Gm./100 ml. (Fig. 4). An absolute increase in neutrophils occurred during the second to third month. Platelet levels are unchanged, but bleeding problems, purpura, and petechiae have been minimal. During the eight months on oxymetholone, he has developed mild acne and pubic hair, deepening of his voice and definite penile growth. He has also had striking linear growth improving from well below the third percentile to the twenty-fifth percentile in height and to the tenth percentile in weight. During this growth spurt his bone age accelerated and is now at his chronologic age of six years.

When the dosage of oxymetholone was reduced to 25 mg./day (1.1 mg./Kg.), his blood counts remained stable for two months. He then had a progressive fall in hemoglobin and hematocrit necessitating a blood transfusion and reinstitution of the original dose of oxymetholone 100 mg./day (5 mg./Kg.). He has had good response to this second course of oxymetholone but appears to require continuous maintenance therapy.

DISCUSSION

Sanchez-Medal and co-workers\(^4\) have reported their use of oxymetholone and related derivatives in aplastic anemia in eight children and fifty-four adults. Responses were obtained in 46.7 per cent of the whole group and in 70 per cent of those treated for more than two months. Remission was evident in most patients during the second to fourth month of therapy, and a favorable response was unrelated to age, sex, etiology, degree of pancytopenia, or bone marrow cellularity.

The favorable response to oxymetholone of the five consecutive children with aplastic anemia reported here is additional evidence that this anabolic hormone...
has potent erythropoietic-stimulating activity. Two of the responding patients can be considered as testosterone failures. Case 4, who improved on oxymetholone after eighteen months of aplasia, had been initially treated with the recommended dose of testosterone propionate for seven months with no signs of improvement. Case 5 had received testosterone propionate for eight months including six months on twice the usual dose.

The characteristic hematologic response in all of the patients in this series is similar to that reported by Sanchez-Medal. During the second to third months of treatment, a reticulocytosis developed followed by a gradual rise in hemoglobin. At about the same time, an absolute increase in circulating polymorphonuclears was noted and this was followed by a definite and clinically significant rise in the platelet count usually to the 30,000 to 50,000/mm$^3$ range. Although platelet counts have remained subnormal in three of the five patients, all have had a marked decrease in clinical bleeding problems.

The total duration of oxymetholone treatment for those with acquired aplasia was five to eight months. Oxymetholone and prednisone were discontinued when there was a stable hemoglobin of greater than 10 Gm./100 ml. Bone marrow examinations at this time all had normal to increased cellularity, numerous megakaryocytes, and normal erythroid and myeloid precursors.

Three of the patients with acquired aplasia have now been followed for twenty-four, twenty-one, and eighteen months off all medications with two of the three now having normal hemograms. The third has asymptomatic leukopenia (2,000 to 3,000/mm$^3$ with 20 to 30 per cent neutrophils) and thrombocytopenia (30,000 to 50,000/mm$^3$).

The fourth patient with acquired aplasia, J. L., relapsed during the third month off all treatment. He was restarted on oxymetholone plus a low dosage of prednisone and has had a fair second response although his hemoglobin and platelets are subnormal. He may require continuous maintenance therapy.

Patient M. L., with congenital or constitutional aplastic anemia, has continued to require oxymetholone therapy, as is the general experience with this form of aplasia.

No serious or even minor changes in liver function, as reported by Sanchez-Medal, were seen in any of the five patients at any time during treatment or later. It is possible that some of the reported cases of liver dysfunction following oxymetholone represent pre-existing hepatitis of the type followed by aplastic anemia as reported by Levy et al. and Schwarz et al. In any event, the incidence of severe liver dysfunction following oxymetholone is not great enough to limit its use in children with aplastic anemia.

Mild virilization, consisting of lowering of the pitch of the voice, pubic hair, enlargement of the phallus, and acne, were seen to some degree in all the prepubertal children.

Bone age measurements in the three prepubertal patients with acquired aplastic anemia have remained synchronous with chronologic ages. These findings confirm those of Sanchez-Medal, who found no changes in growth maturation. The boy with congenital aplastic anemia, who had both retarded bone age and linear growth, has had an acceleration of both, with his bone age afars now equal to his chronologic age and his height age improved
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from 2½ years (chronologic age = 5 4/12) to 6 years (chronologic age = 7 years) in twenty months of therapy.

It appears from the experience with these children and from the observations of Sanchez-Medal\(^5,\,6\) that oxymetholone has hematopoietic-stimulating properties which in some patients may be greater than that observed with testosterone derivatives. It is difficult to compare the effect of two compounds on a milligram for milligram basis, but it is apparent from these results that the dosages used of oral oxymetholone (2 to 6.5 mg./Kg./day) appear to have more effect than 2 to 4 mg./Kg./day of sublingual testosterone propionate. Whether this hematopoietic stimulus is the result of higher doses, better absorption, or a true enhancement of erythropoietic stimulation is a matter of speculation and can only be satisfactorily resolved by further investigation. In our hands, oxymetholone has proven useful in the treatment of aplastic anemia, and further trials, particularly in patients with refractory aplasia, are indicated.

### SUMMARY

Four consecutive children with acquired aplastic anemia, including one refractory to prolonged testosterone treatment, have responded to the synthetic anabolic drug oxymetholone. Three of these four are now off all medication and have remained well for eighteen to twenty-four months. A fifth child, with constitutional aplastic anemia refractory to testosterone therapy, has also improved while on oxymetholone. Mild virilization was the only side effect noted. Significant improvement in peripheral blood was noted in all five children during the second and third month of treatment. Oxymetholone appears to be a potent bone marrow stimulant.

### SUMMARIO IN INTERLINGUA

Quatro consecutive juveniles con acquirite anemia aplastic—incluse un qui esseva refractori a un prolongate therapia a testosterona—respondeva al anabolico synthetic oxymetholona. Tres del quatro require a iste tempore nulle medication e se trova ben depot inter dece-octo e vinti-quatro menses. Un quinte patiente pediatric con anemia aplastic constitutional refractori a testosterona ha etiam manifestate melioration clinic sub le tractamento con oxyrnetholona. Leve grados de virilisation esseva le sol adverse effecto lateral notate. Significative grados de melioration esseva constatate in omne el cinque juveniles durante le secunde e le tertie mense del tractamento. Il pare que oxymetholona es un potente stimulante del medulla ossee.

### REFERENCES

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