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# This Week's Citation Classic®

**Shahidi N T & Diamond L K.** Testosterone-induced remission in aplastic anemia of both acquired and congenital types: further observations in 24 cases.
*N. Engl. J. Med.* **264**:953-67, 1961.
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A preliminary report of the first five cases treated with a combination of testosterone and corticosteroids was extended to cover 24 patients. [The *SCI*® indicates that this paper has been cited in over 215 publications since 1961.]

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Stimulation of hemopoiesis in aregenerative anemias has been the subject of investigations for many years. Agents such as cobalt, batyl alcohol, and semipurified erythropoietin had been tried on numerous occasions but were soon abandoned as the result of either their extreme toxicity or their ineffectiveness. The need for a hemopoietic stimulant, particularly for patients with aplastic anemia, was obvious. This condition, which still remains one of the most serious hematological problems, was almost uniformly fatal at that time. For instance, the review of the records at the Children's Hospital in Boston revealed that of 40 patients with aplastic anemia only 2 had spontaneous remissions; the remainder had died from complications of pancytopenia.

Early investigations had already demonstrated that the administration of androgens to a variety of mammals and fowl increases the reticulocyte count, hemoglobin, and bone-marrow erythropoietic activity.[1] Conversely, castration of the adult male in the same species resulted in a definite decrease in the peripheral blood red-cell count and hemoglobin concentration. The anemia in castrated male mammals was restored to normal by administration of androgens. In humans, repeated observations had shown that the adult male has a higher hemoglobin, hematocrit, and red-cell count than the adult female. These differences are not caused by iron deficiency, pregnancy, or blood loss in the female and are not present before puberty. On clinical grounds we knew that in conditions associated with excess androgen production, such as Cushing syndrome and congenital adrenal hyperplasia, the hemoglobin concentration and red-cell count exceed normal values. Conversely, an appreciable decrease in the number of circulating erythrocytes and the hemoglobin concentration has been noted in patients with hypogonadism.

Perhaps the most impressive evidence in support of androgen-induced erythropoiesis emerged from the observation by B.J. Kennedy and associates,[2] who were using testosterone to treat women with breast cancer. It was of interest to find that a marked rise in hemoglobin concentration occurred in these patients despite advanced metastases within the bone-marrow cavity. These observations led Gardner and Pringle[3] to use androgens in patients with myeloid metaplasia.

In an attempt to stimulate bone-marrow recovery in patients with aplastic anemia, we initiated androgen therapy in children with this condition. Fortunately, our first patient responded.[4] The most dramatic response was obtained in a young boy with constitutional aplastic anemia referred to us from Canada. This boy's reticulocytes rose from 1 percent to 15 percent within a month of therapy and his hemoglobin began to rise. When I mentioned this dramatic event to L.K. Diamond, then the chief of our service, he asked, with some skepticism, to see the reticulocyte smear himself. When I asked him on the following day what he thought of the smear, he replied, "They were the reticulocytes all right and they were dancing in my head all night." Our publication resulted in a surge of clinical and biochemical interest. The clinical papers described successful use of androgens in patients with aplastic anemia and other refractory anemias such as that seen in chronic renal failure. Biologists and biochemists began to investigate the mechanism whereby androgens stimulate erythropoiesis. It was soon discovered that androgens increased the synthesis of erythropoietin,[5] triggered hemopoietic stem cells into DNA synthesis,[6] and increased the level of erythrocyte 2,3-diphosphoglycerate,[7] which is known to facilitate the release of oxygen to the tissues.

1. **Shahidi N T.** Androgens and erythropoiesis: medical progress. *N. Engl. J. Med.* **289**:72-80, 1973. (Cited 95 times.)
2. **Kennedy B J & Gilbertsen A S.** Increased erythropoiesis induced by androgen-hormone therapy. *N. Engl. J. Med.* **256**:719-26, 1957. (Cited 115 times.)
3. **Gardner F H & Pringle J C, Jr.** Androgens and erythropoiesis. I. Preliminary clinical observations. *Arch. Intern. Med.* **107**:846-62, 1961. (Cited 90 times.)
4. **Shahidi N T & Diamond L K.** Testosterone-induced remission in aplastic anemia. *Amer. J. Dis. Child.* **98**:293-302, 1959. (Cited 115 times.)
5. **Fried W & Gurney C W.** Use of mild plethora to demonstrate an erythropoietic effect from small amounts of androgens. *Proc. Soc. Exp. Biol. Med.* **120**:519-23, 1965.
6. **Byron J W.** Effect of steroids on the cycling of haemopoietic stem cells. *Nature* **228**:1204, 1970. (Cited 100 times.)
7. **Parker J P, Beirne G J, Desai J N, Raich P C & Shahidi N T.** Androgen-induced increase in red-cell 2,3-diphosphoglycerate. *N. Engl. J. Med.* **287**:381-3, 1972. (Cited 60 times.)

 