

## COMMENTS &amp; OPINIONS

**Erythropoietin Resistance During Androgen Deficiency**

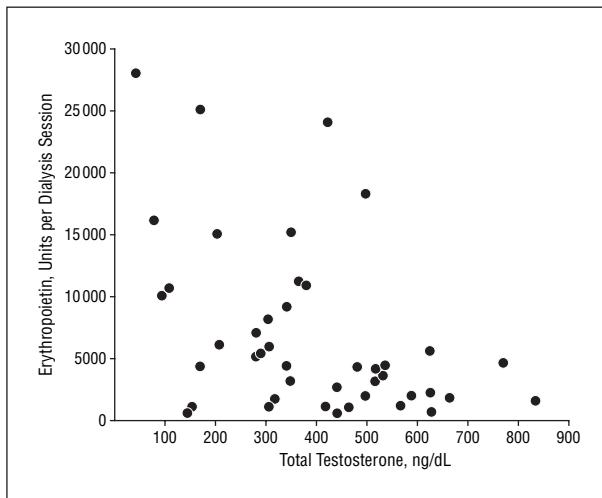
The discussion by Spivak<sup>1</sup> of chronic anemias in the elderly would have been more complete if it had included consideration of the potential contribution by hypogonadism to these anemias in older men.

Male hypogonadism characteristically is accompanied by decreasing red blood cell mass and develops frequently with advancing age, having been documented in 25% of men with chronic renal failure (CRF)<sup>2</sup> and many men with malignancies, including 80% of those receiving sustained-action opioids.<sup>3</sup> Hematocrit levels in hypogonadal men improve during replacement testosterone therapy because of a combination of androgen stimulation of erythropoietin (EPO) production and direct stimulation of androgen-dependent erythropoietic cells. Among older men, however, testosterone levels are rarely examined as a factor potentially contributing to anemia, even though the origin of these anemias remains unknown in a large percentage.

Before EPO therapy became available, androgens were widely used to treat many chronic anemias including the anemia of CRF, a condition in which it continues to be used extensively in countries other than the United States and where it has been documented to improve endurance, strength, mood, libido, and erectile function, while decreasing the cost of supplemental EPO therapy by as much as 80%.<sup>4</sup>

We have compared total testosterone levels with the median EPO requirements in 43 of the 52 men who had been treated in our small dialysis unit.<sup>5</sup> These values are presented in the **Figure**. In each subject, treatment with 3-times weekly EPO and appropriate iron therapy had been dictated by conventional protocols for the preceding year. The Spearman  $\rho$  analysis demonstrated a close inverse relationship between these 2 variables ( $P<.01$ ), which was independent of multiple other variables including the presence of iron deficiency or other disease states. The EPO requirements of hypogonadal men (total testosterone level  $<280$  ng/dL [ $<9.7$  nmol/L]) averaged over 3 times those of men with testosterone levels greater than 450 ng/dL ( $>15.6$  nmol/L).

We continue to see older hypogonadal men with a variety of anemias whose response to iron and/or EPO therapy is greatly enhanced following the recognition of their need for replacement testosterone therapy. Androgen therapy in these men is often accompanied by greatly diminished requirements for iron, EPO, and transfusions.



**Figure.** Median erythropoietin and total testosterone levels in men without polycystic renal disease receiving chronic dialysis for renal failure. To convert testosterone to nanomoles per liter, multiply by 0.0347.

Controlled studies evaluating cost, quality of life, and requirements for EPO, iron, and transfusion therapy in anemic hypogonadal men receiving conventional therapy compared with those also receiving androgens should receive high priority.

Harry W. Daniell, MD

**Correspondence:** Dr Daniell, 2626 Edith Ave, Suite A, Redding, CA 96001 (HWDaniell@aol.com).

**Financial Disclosure:** Dr Daniell has received grant support for a study examining the use of Androderm, a transdermal testosterone preparation in the treatment of OPIAD (opioid-induced androgen deficiency) as well as several speaking honoraria from Watson Pharmaceutical, which produces Androderm.

- Spivak JL. Anemia in the elderly. *Arch Intern Med.* 2005;165:2187-2189.
- Schmidt A, Luger A, Horl W. Sexual hormone abnormalities in male patients with renal failure. *Nephrol Dial Transplant.* 2002;17:368-371.
- Rajagopal A, Vassilopoulou-Selini R, Palmer JL, Kaur G, Bruera E. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. *Cancer.* 2004;100:851-858.
- Gacon A, Belvis J, Berisa F, Iglesias E, Estopinan V, Teruel J. Nandrolone decanoate is a good alternative for the treatment of anemia in elderly male patients on hemodialysis. *Geriatr Nephrol Urol.* 1999;9:67-72.
- Daniell H. Higher erythropoietin requirements in hypogonadal and iron-deficient men on hemodialysis. *Dial Transplant.* 2005;34:326-336.

## In reply

I thank Daniell for his interest in my editorial, but I cannot endorse his assertions. My editorial was not about the differential diagnosis of anemia in the elderly. Rather, it was about the impact of aging on red blood cell production within the context of 4 articles published simultaneously in the

**Table. Plasma Volume Contraction Caused by Androgen Replacement Therapy in a 52-Year-Old Man (Hematocrit Level, 56.4%)**

Variable	Expected*	Observed*	% Change
Red blood cell mass, mL	2370	2661	+12
Plasma volume, mL	3393	1824	-46
Total blood volume, mL	5763	4485	NA

Abbreviation: NA, not applicable.

\*The observed values are from Spivak<sup>6</sup>; the expected values were derived from the formulas in Pearson et al.<sup>7</sup>

ARCHIVES. As discussed in the editorial, aging *per se* does not result in anemia, but the associated age-related fall in male androgen production is probably responsible for the mild decline in hemoglobin and hematocrit levels observed in otherwise healthy elderly men.<sup>1</sup> Unfortunately, Daniell has conflated this age-related process with the syndrome of hypogonadism, when in fact the two have never been demonstrated to be synonymous. As a corollary, there is no proof for his assertion that hypogonadism “develops frequently with advancing age.” Daniell’s assertion that androgen therapy has a useful role in the management of anemia in end-stage renal disease also contradicts the known physiology of erythropoiesis. Androgens are neither necessary nor sufficient to sustain erythropoiesis and are not primarily involved in the elegant mechanism for oxygen sensing that regulates EPO production.<sup>2</sup> Indeed, chemical castration, which reduces serum testosterone to zero, has no effect on the serum erythropoietin level.<sup>3</sup>

It is axiomatic that anemia in adults is always secondary to some other disorder, and it is equally axiomatic that correction of the underlying disorder is the most effective means for alleviating the anemia. When hypogonadism is present, androgen replacement is appropriate; when erythropoietin production is impaired, recombinant EPO is the physiologic means for anemia correction. The assertion that androgen supplementation has a useful role in the latter situation in the absence of clinical hypogonadism is unproved, and Daniell’s own data (his Figure) support this. The statistical analysis he used was inappropriate to his data, which actually constitutes not 1 but 4 different patient cohorts: patients with a normal testosterone level who were EPO re-

sponsive; those with a normal testosterone level who were EPO unresponsive; those with a low testosterone level who were EPO responsive; and those with a low testosterone level who were EPO unresponsive. Thus, contrary to Daniell’s claim, the data actually demonstrate that EPO responsiveness was independent of the serum testosterone level. In this regard, equating a serum testosterone level alone with hypogonadism is inappropriate, and the 280 ng/dL (9.7 nmol/L) threshold that Daniell chose without age-specific referencing is higher than the value (196 ng/dL [6.8 nmol/L]) derived from a large healthy male population older than 60 years.<sup>4</sup>

Furthermore, the assumption that androgen therapy simply elevates red blood cell mass is untrue. As shown in the Table, androgen replacement therapy in a hypogonadal man caused only minimal red blood cell mass elevation but a substantial reduction in plasma volume. Because recombinant EPO also reduces the plasma volume, using both agents together needs a solid rationale. Finally, Daniell makes no mention of the many potential risks of androgens,<sup>5</sup> most of which are particularly relevant in the elderly. The role of androgen supplementation in anemia correction requires a physiologic rationale; recombinant EPO already has one.

Jerry L. Spivak, MD

**Correspondence:** Dr Spivak, Johns Hopkins University School of Medicine, Traylor 924, 720 Rutland Ave, Baltimore, MD 21205 (jlspivak@jhmi.edu).

**Financial Disclosure:** Dr Spivak is a consultant for Novartis, Celgene, Shire, and Roche.

- Nilsson-Ehle H, Jagenburg R, Landahl S, Svanborg A. Blood haemoglobin declines in the elderly: implications for reference intervals from age 70 to 88. *Eur J Haematol*. 2000;65:297-305.
- Semenza GL. HIF-1, O<sub>2</sub>, and the 3 PHDs: how animal cells signal hypoxia to the nucleus. *Cell*. 2001;107:1-3.
- Weber JP, Walsh PC, Peters CA, Spivak JL. Effect of reversible androgen deprivation on hemoglobin and serum immunoreactive erythropoietin in men. *Am J Hematol*. 1991;36:190-194.
- Mohr BA, Guay AT, O’Donnell AB, McKinlay JB. Normal, bound and non-bound testosterone levels in normally ageing men: results from the Massachusetts Male Ageing Study. *Clin Endocrinol (Oxf)*. 2005;62:64-73.
- Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med*. 2004;350:482-492.
- Spivak JL. Polycythemia vera: myths, mechanisms, and management. *Blood*. 2002;100:4272-4290.
- Pearson TC, Guthrie DL, Simpson J, et al; Expert Panel on Radionuclides of the International Council for Standardization in Haematology. Interpretation of measured red cell mass and plasma volume in adults. *Br J Haematol*. 1995;89:748-756.